HUTCHMED (China) Limited
和黃醫藥（中國）有限公司

(Incorporated in the Cayman Islands with limited liability)
(Stock Code: 13)

OVERSEAS REGULATORY ANNOUNCEMENT

This announcement is issued pursuant to Rule 13.10B of the Rules Governing the Listing of Securities on The Stock Exchange of Hong Kong Limited.

Please refer to the attached Form 20-F which was filed with the U.S. Securities and Exchange Commission on March 3, 2022 by the Company.

By Order of the Board

Edith Shih
Non-executive Director and Company Secretary

Hong Kong, March 3, 2022

As at the date of this announcement, the Directors of the Company are:

Executive Directors:
Mr TO Chi Keung, Simon
(Chairman)
Mr Christian Lawrence HOGG
(Chief Executive Officer)
Mr CHENG Chig Fung, Johnny
(Chief Financial Officer)
Dr Weiguo SU
(Chief Scientific Officer)

Non-executive Directors:
Dr Dan ELDAR
Ms Edith SHIH

Independent Non-executive Directors:
Mr Paul Rutherford CARTER
(Senior Independent Director)
Dr Karen Jean FERRANTE
Mr Graeme Allan JACK
Professor MOK Shu Kam, Tony

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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549
FORM 20-F

(Mark one)

☐ **REGISTRATION STATEMENT PURSUANT TO SECTION 12(b) OR (g) OF THE SECURITIES EXCHANGE ACT OF 1934**

OR

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the fiscal year ended December 31, 2021

OR

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the transition period from to

OR

☐ **SHELL COMPANY REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

Date of event requiring this shell company report

Commission file number 001-37710

HUTCHMED (CHINA) LIMITED

(Exact name of Registrant as specified in its charter)
N/A

(Translation of Registrant's name into English)

Cayman Islands

(Jurisdiction of incorporation or organization)

48th Floor, Cheung Kong Center
2 Queen's Road Central
Hong Kong
+852 2121 8200

(Address of principal executive offices)

Christian Lawrence Hogg
Chief Executive Officer
Level 18, The Metropolis Tower
10 Metropolis Drive
Hunghom, Kowloon
Hong Kong
Telephone: +852 2121 8200
Facsimile: +852 2121 8281

(Name, telephone, email and/or facsimile number and address of Company contact person)

Securities registered or to be registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
American depositary shares, each representing five ordinary shares, par value $0.10 per share	HCM	Nasdaq Global Select Market
Ordinary shares, par value $0.10 per share*		Nasdaq Global Select Market*
Ordinary shares, par value $0.10 per share	0013	The Stock Exchange of Hong Kong Limited
Ordinary shares, par value $0.10 per share	HCM	The AIM Market of the London Stock Exchange

*Not for trading, but only in connection with the listing of American depositary shares on the Nasdaq Global Select Market

Securities registered or to be registered pursuant to Section 12(g) of the Act:

None
(Title of Class)

Securities for which there is a reporting obligation pursuant to Section 15(d) of the Act:

None
(Title of Class)

Indicate the number of outstanding shares of each of the issuer's classes of capital or common stock as of the close of the period covered by the Annual Report:
864,530,850 ordinary shares were issued and outstanding as of December 31, 2021.

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act.

☒ Yes ☐ No

If this report is an annual or transition report, indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934. Note

☐ Yes ☒ No

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days.

☒ Yes ☐ No

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files).

☒ Yes ☐ No

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or an emerging growth company. See definition of "large accelerated filer," "accelerated filer," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer ☒ | Accelerated filer ☐ | Non-accelerated filer ☐ | Emerging growth company ☐

If an emerging growth company that prepares its financial statements in accordance with U.S. GAAP, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards† provided pursuant to Section 13(a) of the Exchange Act. ☐

†The term "new or revised financial accounting standard" refers to any update issued by the Financial Accounting Standards Board to its Accounting Standards Codification after April 5, 2012.

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepare or issued its audit report. ☒

Indicate by check mark which basis of accounting the registrant has used to prepare the financial statements included in this filing:

U.S. GAAP ☒ | International Financial Reporting Standards as issued by the International Accounting Standards Board ☐ | Other ☐

If "Other" has been checked in response to the previous question, indicate by check mark which financial statement item the registrant has elected to follow.

☐ Item 17 ☐ Item 18

If this is an Annual Report, indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act).

☐ Yes ☒ No

(APPLICABLE ONLY TO ISSUERS INVOLVED IN BANKRUPTCY PROCEEDINGS DURING THE PAST FIVE YEARS)
Indicate by check mark whether the registrant has filed all documents and reports required to be filed by Sections 12, 13 or 15(d) of the Securities Exchange Act of 1934 subsequent to the distribution of securities under a plan confirmed by a court.

☐ Yes ☐ No

HUTCHMED (China) Limited
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INTRODUCTION

This annual report on Form 20-F contains our audited consolidated statements of operations data for the years ended December 31, 2021, 2020 and 2019 and our audited consolidated balance sheet data as of December 31, 2021 and 2020. Our consolidated financial statements have been prepared in accordance with U.S. generally accepted accounting principles, or U.S. GAAP.

This annual report also includes audited consolidated income statement data for the years ended December 31, 2021, 2020 and 2019 and the audited consolidated statements of financial position data as of December 31, 2021 and 2020 for our non-consolidated joint venture, Shanghai Hutchison Pharmaceuticals, and audited consolidated income statement data for the period from January 1, 2021 to September 28, 2021 and the years ended December 31, 2020 and 2019 and the audited consolidated statements of financial position data as of September 28, 2021 and December 31, 2020 of Hutchison Baiyunshan when it was our non-consolidated joint venture. On September 28, 2021, we completed the disposal of our entire interest in Hutchison Baiyunshan, which was our non-core and over-the-counter drug joint venture business. The financial statements of each of Shanghai Hutchison Pharmaceuticals and Hutchison Baiyunshan have been prepared in accordance with International Financial Reporting Standards, or IFRS, as issued by the International Accounting Standard Board, or IASB.

Unless the context requires otherwise, references herein to the "company," "HUTCHMED," "we," "us" and "our" refer to HUTCHMED (China) Limited (formerly Hutchison China MediTech Limited) and its consolidated subsidiaries and joint ventures.

Conventions Used in this Annual Report

Unless otherwise indicated, references in this annual report to:

- "ADRs" are to the American depositary receipts, which evidence our ADSs;
- "ADSs" are to our American depositary shares, each of which represents five ordinary shares;
- "China" or "PRC" are to the People's Republic of China, excluding, for the purposes of this annual report only, Taiwan and the special administrative regions of Hong Kong and Macau;
- "CK Hutchison" are to CK Hutchison Holdings Limited, a company incorporated in the Cayman Islands and listed on The Stock Exchange of Hong Kong Limited, or the Hong Kong Stock Exchange, and the ultimate parent company of our largest shareholder, Hutchison Healthcare Holdings Limited;
- "E.U." are to the European Union;
- "Guangzhou Baiyunshan" are to Guangzhou Baiyunshan Pharmaceutical Holdings Company Limited, a leading China-based pharmaceutical company listed on the Shanghai Stock Exchange and the Hong Kong Stock Exchange;
- "Hain Celestial" are to The Hain Celestial Group, Inc., a Nasdaq-listed, natural and organic food and personal care products company;
- "HK$" or "HK dollar" are to the legal currency of the Hong Kong Special Administrative Region;
- "Hutchison Baiyunshan" are to Hutchison Whampoa Guangzhou Baiyunshan Chinese Medicine Company Limited, which was our non-consolidated joint venture with Guangzhou Baiyunshan in which we indirectly held a 50% interest through a holding company until our disposal of such interest on September 28, 2021 (this interest was previously held through a holding company in which we have a 80% interest);
- "HUTCHMED Science Nutrition" (formerly Hutchison Consumer Products Limited) are to HUTCHMED Science Nutrition Limited, our wholly owned subsidiary;
- "Hutchison Hain Organic" are to Hutchison Hain Organic Holdings Limited, our joint venture with Hain Celestial in which we have a 50% interest;

- "Hutchison Healthcare" are to Hutchison Healthcare Limited, our wholly owned subsidiary;
- "HUTCHMED Limited" (formerly Hutchison MediPharma Limited), our subsidiary through which we operate our Oncology/Immunology operations in which we have a 99.8% interest;
- "HUTCHMED Holdings" are to HUTCHMED Holdings Limited (formerly Hutchison MediPharma Holdings Limited), our subsidiary in which we have a 99.8% interest and which is the indirect holding company of HUTCHMED Limited;
- "Hutchison Sinopharm" are to Hutchison Whampoa Sinopharm Pharmaceuticals (Shanghai) Company Limited, our joint venture with Sinopharm in which we have a 50.9% interest;
- "ordinary shares" or "shares" are to our ordinary shares, par value $0.10 per share;
- "RMB" or "renminbi" are to the legal currency of the PRC;
- "SEHK" are to The Stock Exchange of Hong Kong;
- "Shanghai Hutchison Pharmaceuticals" are to Shanghai Hutchison Pharmaceuticals Limited, our non-consolidated joint venture with Shanghai Pharmaceuticals in which we have a 50% interest;
- "Shanghai Pharmaceuticals" are to Shanghai Pharmaceuticals Holding Co., Ltd., a leading pharmaceutical company in China listed on the Shanghai Stock Exchange and the Hong Kong Stock Exchange;
- "Sinopharm" are to Sinopharm Group Co. Ltd., a leading distributor of pharmaceutical and healthcare products and a leading supply chain service provider in China listed on the Hong Kong Stock Exchange;
- "U.S." or "United States" are to the United States of America;
- "$" or "U.S. dollars" are to the legal currency of the United States; and
- "£" or "pound sterling" are to the legal currency of the United Kingdom.

References in this annual report to our "Oncology/Immunology" operations are to all activities related to oncology/immunology, including sales, marketing, manufacturing and research and development with respect to our drugs and drug candidates, and references to our "Other Ventures" are to all of our other businesses.

Our reporting currency is the U.S. dollar. In addition, this annual report also contains translations of certain foreign currency amounts into dollars for the convenience of the reader. Unless otherwise stated, all translations of pound sterling into U.S. dollars were made at £1.00 to $1.33, all translations of RMB into U.S. dollars were made at RMB6.39 to $1.00 and all translations of HK dollars into U.S. dollars were made at HK$7.80 to $1.00, which are the exchange rates used in our audited consolidated financial statements as of December 31, 2021. We make no representation that the pound sterling, HK dollar or U.S. dollar amounts referred to in this annual report could have been or could be converted into U.S. dollars, pounds sterling or HK dollars, as the case may be, at any particular rate or at all.

Trademarks and Service Marks

We own or have been licensed rights to trademarks, service marks and trade names for use in connection with the operation of our business, including, but not limited to, the trademarks "Hutchison", "Chi-Med", "Hutchison China MediTech", "HUTCHMED", "Elunate", "Sulanda", "Orpathys", "Tazverik" and the logos used by HUTCHMED Limited. All other trademarks, service marks or trade names appearing in this annual report that are not identified as marks owned by us are the property of their respective owners.

Solely for convenience, the trademarks, service marks and trade names referred to in this annual report are listed without the ®, ™ and (sm) symbols, but we will assert, to the fullest extent under applicable law, our applicable rights in these trademarks, service marks and trade names.

CAUTIONARY STATEMENT REGARDING FORWARD-LOOKING STATEMENTS

This annual report contains forward-looking statements made under the "safe harbor" provisions of the U.S. Private Securities Litigation Reform Act of 1995. These statements relate to future events or to our future financial performance and involve known and unknown risks, uncertainties and other factors which may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. The words "anticipate," "assume," "believe," "contemplate," "continue," "could," "estimate," "expect," "goal," "intend," "may," "might," "objective," "plan," "potential," "predict," "project," "positioned," "seek," "should," "target," "will," "would," or the negative of these terms or other similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. These forward-looking statements are based on current expectations, estimates, forecasts and projections about our business and the industry in which we operate and management's beliefs and assumptions, are not guarantees of future performance or development and involve known and unknown risks, uncertainties and other factors. These forward-looking statements include statements regarding:

- the initiation, timing, progress and results of our or our collaboration partners' pre-clinical and clinical studies, and our research and development programs;
- our or our collaboration partners' ability to advance our drug candidates into, and/or successfully complete, clinical studies;
- the timing of regulatory filings and the likelihood of favorable regulatory outcomes and approvals;
- regulatory developments in China, the United States and other countries;
- the expansion of our oncology drug sales team to support the marketing and sales of our approved drug candidates and the ability of this team to effectively develop and execute promotional and marketing activities;
- the timing, progress and results of our commercial launches, the rate and degree of market acceptance and potential market for any of our approved drug candidates;
- the pricing and reimbursement of our and our joint ventures' products and our approved drug candidates;
- our ability to contract on commercially reasonable terms with contract research organizations, or CROs, third-party suppliers and manufacturers;
- the scope of protection we are able to establish and maintain for intellectual property rights covering our or our joint ventures' products and our drug candidates;
- the ability of third parties with whom we contract to successfully conduct, supervise and monitor clinical studies for our drug candidates;
- estimates of our expenses, future revenues, capital requirements and our needs for additional financing;
- our ability to obtain additional funding for our operations;
- the potential benefits of our collaborations and our ability to enter into future collaboration arrangements;
- the ability and willingness of our collaborators to actively pursue development activities under our collaboration agreements;
- our receipt of milestone or royalty payments, service payments and manufacturing costs pursuant to our strategic alliances with AstraZeneca AB (publ), or AstraZeneca, and Lilly (Shanghai) Management Company Limited, or Eli Lilly;
- our financial performance;

- our ability to attract and retain key scientific and management personnel;
- our relationship with our joint venture and collaboration partners;
- developments relating to our competitors and our industry, including competing drug products;
- changes in our tax status or the tax laws in the jurisdictions that we operate;
- developments in our business strategies and business plans; and
- the extent of the impact of the COVID-19 pandemic, including the duration, spread, severity, and any recurrence of the COVID-19 pandemic, the duration and scope of related government orders and restrictions and the extent of the impact of the COVID-19 pandemic on the global economy.

Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. As a result, any or all of our forward-looking statements in this annual report may turn out to be inaccurate. We have included important factors in the cautionary statements included in this annual report on Form 20-F, particularly in the section of this annual report on Form 20-F titled "Risk Factors," that we believe could cause actual results or events to differ materially from the forward-looking statements that we make. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Moreover, we operate in a highly competitive and rapidly changing environment in which new risks often emerge. It is not possible for our management to predict all risks, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements we may make.

You should read this annual report and the documents that we reference herein and have filed as exhibits hereto completely and with the understanding that our actual future results may be materially different from what we expect. The forward-looking statements contained herein are made as of the date of the filing of this annual report, and we do not assume any obligation to update any forward-looking statements except as required by applicable law.

In addition, this annual report contains statistical data and estimates that we have obtained from industry publications and reports generated by third-party market research firms. Although we believe that the publications, reports and surveys are reliable, we have not independently verified the data and cannot guarantee the accuracy or completeness of such data. You are cautioned not to give undue weight to this data. Such data involves risks and uncertainties and are subject to change based on various factors, including those discussed above.

PART I

ITEM 1. IDENTITY OF DIRECTORS, SENIOR MANAGEMENT AND ADVISERS

Not applicable.

ITEM 2. OFFER STATISTICS AND EXPECTED TIMETABLE

Not applicable.

ITEM 3. KEY INFORMATION

A. Reserved.

B. Capitalization and Indebtedness.

Not applicable.

C. Reasons for the Offer and Use of Proceeds.

Not applicable.

D. Risk Factors.

HUTCHMED (China) Limited is a Cayman Islands holding company which conducts its operations in China through its PRC subsidiaries (our corporate group does not include any variable interest entities). We face various legal and operational risks and uncertainties as a company with substantial operations in China. The PRC government has significant authority to exert influence on the ability of a company with substantial operations in China, like us, to conduct its business, accept foreign investments or be listed on a U.S. stock exchange. For example, we face risks associated with regulatory approvals of offshore offerings, anti-monopoly regulatory actions, cybersecurity and data privacy, as well as the lack of inspection from the U.S. Public Company Accounting Oversight Board, or PCAOB, on our auditors. The PRC government may also intervene with or influence our operations as the government deems appropriate to further regulatory, political and societal goals. The PRC government publishes from time to time new policies that can significantly affect our industry in which we operate and we cannot rule out the possibility that it will in the future further release regulations or policies regarding our industry that could adversely affect our business, financial condition and results of operations. Any such action, once taken by the PRC government, could cause the value of our ADSs and ordinary shares to significantly decline or in extreme cases, become worthless.

You should carefully consider all of the information in this annual report before making an investment in the ADSs. Below please find a summary of the principal risks and uncertainties we face, organized under relevant headings. In particular, as we are a China-based company incorporated in the Cayman Islands, you should pay special attention to subsections headed "Item 3. Key Information-3.D. Risk Factors-Other Risks and Risks Related to Doing Business in China."

The following summarizes some, but not all, of the risks provided below. Please carefully consider all of the information discussed in this Item 3.D. "Risk Factors" in this annual report for a more thorough description of these and other risks.

Risks Relating to Our Financial Position and Need for Capital

- Risks relating to our need for additional funding
- Risks relating to our existing and future indebtedness

Risks Relating to Our Oncology/Immunology Operations and Development of Our Drug Candidates

- Risks relating to our approach to the discovery and development of drug candidates and the lengthy, expensive and uncertain clinical development process

- Risks relating to expediting regulatory review, obtaining and maintaining regulatory approval and ongoing regulatory review for our drug candidates
- Risks relating to the commercialization of our drug candidates
- Risks relating to undesirable side effects of our drug candidates
- Risks relating to competition in discovering, developing and commercializing drugs
- Risks relating to our collaboration partners with respect to clinical trials, marketing and distribution
- Risks relating to the expansion of our international operations

Risks Relating to Sales of Our Internally Developed Drugs and Other Drugs

- Risks relating to obtaining and maintaining permits and licenses for our and our joint ventures' pharmaceutical operations in China
- Risks relating to leveraging our Other Ventures' prescription drug business to commercialize our internally developed drug candidates
- Risks relating to competition in selling our approved, internally developed drugs and drugs of our Other Ventures
- Risks relating to maintaining and enhancing the brand recognition of our drugs
- Risks relating to the availability of reimbursement of our drugs, the lack of which could diminish our sales or profitability
- Risks relating to counterfeit products in China
- Risks relating to rapid changes in the pharmaceutical industry rendering our products obsolete
- Risks relating to cultivating or sourcing raw materials
- Risks relating to adverse publicity of us, our joint ventures or our products

Risks Relating to Our Dependence on Third Parties

- Risks relating to disagreements with current or future collaboration partners which we rely on for certain drug development activities including the conducting of clinical trials
- Risks relating to relying on third party suppliers for the active pharmaceutical ingredients in our drug candidate and drug products
- Risks relating to our collaboration partners or our CROs' failure to comply with regulatory requirements pertaining to clinical trials
- Risks relating to our collaboration partners, principal investigators, CROs and other third-party contractors and consultants engaging in misconduct or other improper activities
- Risks relating to relying on third parties to construct our new manufacturing facility in Shanghai
- Risks relating to relying on distributors for logistics and distributions services

- Risks relating to the availability of benefits currently enjoyed by virtue of our association with CK Hutchison

Other Risks and Risks Relating to Doing Business in China

- Risks relating to COVID-19
- Risks relating to compliance with privacy laws, information security policies and contractual obligations related to data privacy and security and any information technology or data security failures
- Risks relating to product liability claims or lawsuits
- Risks relating to liabilities under anti-corruption laws, environmental, health and safety laws and laws relating to equity incentive plans
- Risks relating to uncertainties with respect to the PRC legal system, China's currency exchange limits and PRC government tax incentives or treatment

Risks Relating to Intellectual Property

- Risks relating to our, our joint ventures and our collaboration partners' abilities to protect and enforce intellectual property rights and maintain confidentiality of trade secrets
- Risks relating to infringing upon third parties' intellectual property rights

Risks Relating to our ADSs

- Risks relating to being delisted from the Nasdaq if the PCAOB continues to be unable to inspect our independent registered public accounting firm
- Risks relating to our largest shareholder which may limit the ability of other shareholders to influence corporate matters

You should carefully consider the following risk factors in addition to the other information set forth in this annual report. If any of the following risks were actually to occur, our company's business, financial condition and results of operations prospects could be adversely affected and the value of our ADSs would likely suffer.

Risks Relating to Our Financial Position and Need for Capital

We may need substantial additional funding for our product development programs and commercialization efforts. If we are unable to raise capital on acceptable terms when needed, we could incur losses and be forced to delay, reduce or eliminate such efforts.

We expect our expenses to increase significantly in connection with our ongoing activities, particularly as we or our collaboration partners advance the clinical development of our clinical drug candidates which are currently in active or completed clinical studies in various countries. We will incur significant expenses as we continue research and development and initiate additional clinical trials of, and seek regulatory approval for, these and other future drug candidates. In addition, we have incurred and expect to continue to incur significant commercialization expenses related to product manufacturing, marketing, sales and distribution in China and the United States for Sulanda (surufatinib), our unpartnered drug product approved in China in December 2020, and any of our other unpartnered drug candidates that may be approved in the future. In particular, the costs that may be required for the manufacture of any drug candidate that receives regulatory approval may be substantial as we may have to modify or increase the production capacity at our current manufacturing facilities or contract with third-party manufacturers. We may also incur expenses as we create additional infrastructure, such as our new manufacturing facility under construction in Shanghai, and expand our U.S.-based clinical and commercial team to support our operations at our U.S. subsidiaries, HUTCHMED International Corporation (formerly Hutchison MediPharma International Inc. and Hutchison MediPharma (US), Inc.) and HUTCHMED US Corporation. Accordingly, we may need to obtain substantial funding in connection with our continuing operations through public or private equity offerings, debt financings, collaborations or licensing arrangements or other sources. If we are unable to raise capital when needed or on attractive terms, we could incur losses and be forced to delay, reduce or eliminate our research and development programs or any future commercialization efforts.

Our net cash used in operating activities was $80.9 million, $62.1 million and $204.2 million for the years ended December 31, 2019, 2020 and 2021, respectively. We believe, however, that our expected cash flow from operations, including dividends from our Other Ventures and milestone and other payments from our collaboration partners, our cash and cash equivalents and short-term investments as well as our unutilized bank facilities as of December 31, 2021, will enable us to fund our operating expenses, debt service and capital expenditure requirements for at least the next 12 months. We have based this estimate on assumptions that may prove to be wrong, and we could use our capital resources sooner than we currently expect. Our future capital requirements will depend on many factors, including:

- the number and development requirements of the drug candidates we pursue;
- the scope, progress, timing, results and costs of researching and developing our drug candidates, and conducting pre-clinical and clinical trials;
- the cost, timing and outcome of regulatory review of our drug candidates;
- the cost and timing of commercialization activities, including product manufacturing, marketing, sales and distribution, for our drug candidates for which we have received regulatory approval;
- the amount and timing of any milestone or royalty payments, service payments and reimbursement of manufacturing costs from our collaboration partners, with whom we cooperate with respect to the development and potential commercialization of certain of our drug candidates;
- the cash received from commercial sales of drug candidates for which we have received regulatory approval;
- our ability to establish and maintain strategic partnerships, collaboration, licensing or other arrangements and the financial terms of such agreements;
- the cost, timing and outcome of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending any intellectual property-related claims;
- our headcount growth and associated costs, particularly as we expand our clinical and commercialization activities in the United States and Europe; and

- the costs of operating as a public company listed in Hong Kong, the United States and United Kingdom.

Identifying potential drug candidates and conducting pre-clinical testing and clinical trials is a time-consuming, expensive and uncertain process that may take years to complete, and our commercial revenue will be derived from sales of products that will not be commercially available unless and until we receive regulatory approval. We may never generate the necessary data or results required for certain drug candidates to obtain regulatory approval, and even if approved, they may not achieve commercial success. Accordingly, we will need to continue to rely on financing to achieve our business objectives. Adequate financing may not be available to us on acceptable terms, or at all.

Raising capital may cause dilution to our shareholders, restrict our operations or require us to relinquish rights to technologies or drug candidates.

We expect to finance our cash needs in part through cash flow from our operations, including dividends from our Other Ventures, and we may also rely on raising capital through a combination of public or private equity offerings, debt financings and/or license and development agreements with collaboration partners. In addition, we may seek capital due to favorable market conditions or strategic considerations, even if we believe we have sufficient funds for our current or future operating plans. To the extent that we raise capital through the sale of equity or convertible debt securities (including potential further listings on other stock exchanges), the ownership interest of our shareholders may be materially diluted, and the terms of such securities could include liquidation or other preferences that adversely affect the rights of our existing shareholders. Debt financing and preferred equity financing, if available, may involve agreements that include restrictive covenants that limit our ability to take specified actions, such as incurring additional debt, making capital expenditures or declaring dividends. Additional debt financing would also result in increased fixed payment obligations.

In addition, if we raise funds through collaborations, strategic partnerships or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or drug candidates or grant licenses on terms that may not be favorable to us. We may also lose control of the development of drug candidates, such as the pace and scope of clinical trials, as a result of such third-party arrangements. If we are unable to raise funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market drug candidates that we would otherwise prefer to develop and market ourselves.

Our existing and any future indebtedness could adversely affect our ability to operate our business.

Our outstanding indebtedness combined with current and future financial obligations and contractual commitments, including any additional indebtedness beyond our current facilities with HSBC, Deutsche Bank AG and Bank of China could have significant adverse consequences, including:

- requiring us to dedicate a portion of our cash resources to the payment of interest and principal, and prepayment and repayment fees and penalties, thereby reducing money available to fund working capital, capital expenditures, product development and other general corporate purposes;

- increasing our vulnerability to adverse changes in general economic, industry and market conditions;

- subjecting us to restrictive covenants that may reduce our ability to take certain corporate actions or obtain further debt or equity financing;

- limiting our flexibility in planning for, or reacting to, changes in our business and the industry in which we compete; and

- placing us at a competitive disadvantage compared to our competitors that have less debt or better debt servicing options.

We intend to satisfy our current and future debt service obligations with our existing cash and cash equivalents and short-term investments. Nevertheless, we may not have sufficient funds, and may be unable to arrange for financing, to pay the amounts due under our existing debt. Failure to make payments or comply with other covenants under our existing debt instruments could result in an event of default and acceleration of amounts due.

We have historically incurred significant net operating cash outflows, and may continue to experience net cash outflow from operating activities.

Investment in biopharmaceutical drug development is highly speculative. It entails substantial upfront expenditures and significant risk that a drug candidate might fail to gain regulatory approval or become commercially viable. We continue to incur significant expenses related to our ongoing operations. For a detailed discussion of our net cash used in operating activities, see Item 5.B. "Operating and Financial Review and Prospects", "Liquidity and Capital Resources." We expect to incur significant expenses, particularly research and development expenses, for the foreseeable future as we expand our development of, and seek regulatory approvals for, our drug candidates. Typically, it takes many years to develop one new drug from the drug discovery stage to the time it is available for treating patients. Our ability to improve our cash flow depends on a number of variables, including the number and scope of our drug development programs and the associated costs of those programs, the cost of commercializing any approved products, our ability to generate revenues and the timing and amount of milestones and other payments we make or receive through arrangements with third parties. Our failure to generate positive cash flow from operations may adversely affect our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations. There is no assurance that we will be able to generate sufficient net cash inflows from operating activities, which could have adverse effects on our long-term viability.

We face risks with our short-term investments and in collecting our accounts receivables.

Our short-term investments are bank deposits with maturities of more than three months but less than one year. Our short-term investments were $199.5 million and $634.2 million as of December 31, 2020 and 2021, respectively, and are placed with major financial institutions. These investments may earn yields substantially lower than expected. Failure to realize the benefits we expected from these investments may materially and adversely affect our business and financial results. To date, we have experienced no loss or lack of access to our invested cash or cash equivalents; however, we can provide no assurance that access to our invested cash and cash equivalents will not be impacted by adverse conditions in the financial and credit markets.

Our accounts receivable balance, net of allowance for credit losses, totaled $47.9 million and $83.6 million as of December 31, 2020 and 2021, respectively. We have policies and procedures in place to ensure that sales are made to customers with an appropriate credit history. We perform periodic credit evaluations of our customers and monitor risk factors and forward-looking information, such as country risk, when determining credit limits for customers. However, there can be no assurance such policies and procedures will effectively limit our credit risk and enable us to avoid losses, which could adversely affect our financial condition and results of operations. In addition, amounts due to us are not covered by collateral or credit insurance. If we fail to collect all or part of such accounts receivable in a timely manner, or at all, our financial condition may be materially and adversely affected.

Risks Relating to Our Oncology/Immunology Operations and Development of Our Drug Candidates

Historically, our in-house research and development division, which is included in our Oncology/Immunology operations, has not generated significant profits or has operated at a net loss. Our future profitability is dependent on the successful commercialization of our drug candidates.

To date, fruquintinib, surufatinib and savolitinib (marketed as Elunate, Sulanda and Orpathys, respectively) are our only drug candidates that have been approved for sale. We do not expect our Oncology/Immunology operations to be significantly profitable unless and until we generate substantial revenues from Elunate, Sulanda and Orpathys and can successfully commercialize our other drug products. We expect to incur significant sales and marketing costs as we prepare to commercialize our drug candidates.

Successful commercialization of our drug candidates is subject to many risks. Elunate is marketed in collaboration with our partner, Eli Lilly. Beginning in October 2020, we assumed responsibility for the development and execution of all on-the-ground medical detailing, promotion and local and regional marketing activities for Elunate in China. Sulanda is marketed by us without the support of a collaboration partner. Orpathys is marketed in collaboration with our partner, AstraZeneca. Elunate, Sulanda and Orpathys are the first innovative oncology drugs we, as an organization, have commercialized, and there is no guarantee that we will be able to successfully commercialize them or any of our other drug candidates for their approved indications. There are numerous examples of failures to meet expectations of market potential, including by pharmaceutical companies with more experience and resources than us. There are many factors that could cause the commercialization of Elunate, Sulanda, Orpathys or our other drug products to be unsuccessful, including a number of factors that are outside our control. In the case of Elunate, for example, the third-line metastatic colorectal cancer, or mCRC, patient population in China may be smaller than we estimate or physicians may be unwilling to prescribe, or patients may be unwilling to take, Elunate for a variety of reasons. Additionally, any negative development for fruquintinib, surufatinib or savolitinib in clinical development in additional indications, or in regulatory processes in other jurisdictions, may adversely impact the commercial results and potential of Elunate, Sulanda or Orpathys in China and globally. Thus, significant uncertainty remains regarding the commercial potential of Elunate, Sulanda and Orpathys.

We may not achieve profitability after generating revenues from Elunate, Sulanda and/or Orpathys or our other drug candidates, if ever. If the commercialization of Elunate, Sulanda, Orpathys and/or our other drug candidates is unsuccessful or perceived as disappointing, our stock price could decline significantly and the long-term success of the product and our company could be harmed.

All of our drug candidates, other than fruquintinib, surufatinib and savolitinib for approved indications in China, are still in development. If we are unable to obtain regulatory approval and ultimately commercialize our drug candidates, or if we experience significant delays in doing so, our business will be materially harmed.

All of our drug candidates are still in development, including fruquintinib, surufatinib and savolitinib which have been approved in China for the treatment of third-line mCRC, non-pancreatic neuroendocrine tumors (NETs) and advanced pancreatic NETs, and non-small cell lung cancer, or NSCLC, respectively, but are still in development in the United States and other jurisdictions for these and other indications.

Although we receive certain payments from our collaboration partners, including upfront payments and payments for achieving certain development, regulatory or commercial milestones, for certain of our drug candidates, our ability to generate revenue from our drug candidates is dependent on their receipt of regulatory approval for and successful commercialization of such products, which may never occur. Each of our drug candidates in development will require additional pre-clinical and/or clinical trials, regulatory approval in multiple jurisdictions, manufacturing supply, substantial investment and significant marketing efforts before we generate any revenue from product sales. The success of our drug candidates will depend on several factors, including the following:

- successful completion of pre-clinical and/or clinical trials;
- successful enrollment in, and completion of, clinical trials;
- receipt of regulatory approvals from applicable regulatory authorities for planned clinical trials, future clinical trials, drug registrations or post-approval trials;
- successful completion of all safety studies required to obtain regulatory approval and/or fulfillment of post-approval requirements in the United States, China and other jurisdictions for our drug candidates;
- adapting our commercial manufacturing capabilities to the specifications for our drug candidates for clinical supply and commercial manufacturing;
- obtaining and maintaining patent and trade secret protection or regulatory exclusivity for our drug candidates;
- launching commercial sales of our drug candidates, if and when approved, whether alone or in collaboration with others;
- acceptance of the drug candidates, if and when approved, by patients, the medical community and third-party payors;

- effectively competing with other therapies;
- obtaining and maintaining healthcare coverage and adequate reimbursement;
- enforcing and defending intellectual property rights and claims; and
- maintaining a continued acceptable safety profile of the drug candidates following approval.

If we do not achieve one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize our drug candidates, which would materially harm our business.

Our primary approach to the discovery and development of drug candidates focuses on the inhibition of kinases, some of which are unproven.

A primary focus of our research and development efforts is on identifying kinase targets for which drug compounds previously developed by others affecting those targets have been unsuccessful due to limited selectivity, off-target toxicity and other problems. We then work to engineer drug candidates which have the potential to have superior efficacy, safety and other features as compared to such prior drug compounds. We also focus on developing drug compounds with the potential to be global best-in-class/next-generation therapies for validated kinase targets.

Even if we are able to develop compounds that successfully target the relevant kinases in pre-clinical studies, we may not succeed in demonstrating safety and efficacy of the drug candidates in clinical trials. Even if we are able to demonstrate safety and efficacy of compounds in certain indications in certain jurisdictions, we may not succeed in demonstrating the same in other indications or same indications in other jurisdictions. As a result, our efforts may not result in the discovery or development of drugs that are commercially viable or are superior to existing drugs or other therapies on the market. While the results of pre-clinical studies, early-stage clinical trials as well as clinical trials in certain indications have suggested that certain of our drug candidates may successfully inhibit kinases and may have significant utility in several cancer indications, potentially in combination with other cancer drugs, chemotherapy and immunotherapies, we have not yet demonstrated efficacy and safety for many of our drug candidates in later stage clinical trials.

We may expend our limited resources to pursue a particular drug candidate or indication and fail to capitalize on drug candidates or indications that may be more profitable or for which there is a greater likelihood of success.

Because we have limited financial and managerial resources, we must limit our research programs to specific drug candidates that we identify for specific indications. As a result, we may forego or delay pursuit of opportunities with other drug candidates or for other indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial drugs or profitable market opportunities. In addition, if we do not accurately evaluate the commercial potential or target market for a particular drug candidate, we may relinquish valuable rights to that drug candidate through collaboration, licensing or other royalty arrangements when it would have been more advantageous for us to retain sole development and commercialization rights to such drug candidate.

The regulatory approval processes of the U.S. Food and Drug Administration, or FDA, National Medical Products Administration of China, or NMPA, and comparable authorities are lengthy, time consuming and inherently unpredictable, and if we are ultimately unable to obtain regulatory approval for our drug candidates, our ability to generate revenue will be materially impaired.

Our drug candidates and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale, distribution, import and export, are subject to comprehensive regulation by the FDA, NMPA and other regulatory agencies in the United States and China and by comparable regulatory authorities in other countries. Securing regulatory approval requires the submission of extensive pre-clinical and clinical data and supporting information to the various regulatory authorities for each therapeutic indication to establish the drug candidate's safety and efficacy. Securing regulatory approval also requires the submission of information about the drug manufacturing process to, and inspection of manufacturing facilities by, the relevant regulatory authority. Our drug candidates may not be effective, may be only moderately effective or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining regulatory approval or prevent or limit commercial use.

The process of obtaining regulatory approvals in the United States, China and other countries is expensive, may take many years if additional clinical trials are required, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the drug candidates involved. Changes in regulatory approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted New Drug Application, or NDA, pre-market approval or equivalent application types, may cause delays in the approval or rejection of an application. The FDA, NMPA and comparable regulatory authorities in other countries have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional pre-clinical, clinical or other studies. Our drug candidates could be delayed in receiving, or fail to receive, regulatory approval for many reasons, including the following:

- the FDA, NMPA or comparable regulatory authorities may disagree with the number, design, size, conduct or implementation of our clinical trials;
- we may be unable to demonstrate to the satisfaction of the FDA, NMPA or comparable regulatory authorities that a drug candidate is safe and effective for its proposed indication;
- the results of clinical trials may not meet the level of statistical significance required by the FDA, NMPA or comparable regulatory authorities for approval;
- we may be unable to demonstrate that a drug candidate's clinical and other benefits outweigh its safety risks;
- the FDA, NMPA or comparable regulatory authorities may disagree with our interpretation of data from pre-clinical studies or clinical trials;
- the data collected from clinical trials of our drug candidates may not be sufficient to support the submission of an NDA or other submission or to obtain regulatory approval in the United States or elsewhere;
- the FDA, NMPA or comparable regulatory authorities may fail to approve the manufacturing processes for our clinical and commercial supplies;
- the approval policies or regulations of the FDA, NMPA or comparable regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval;
- the FDA, NMPA or comparable regulatory authority may prioritize treatments for emerging health crises, such as COVID-19, resulting in delays for our drug candidates;
- the FDA, NMPA or comparable regulatory authorities may restrict the use of our products to a narrow population; and
- our collaboration partners or CROs that are retained to conduct the clinical trials of our drug candidates may take actions that materially and adversely impact the clinical trials.

In addition, even if we were to obtain approval, regulatory authorities may approve any of our drug candidates for fewer or more limited indications than we request, may not approve the price we intend to charge for our drugs, may grant approval contingent on the performance of costly post-marketing clinical trials, or may approve a drug candidate with a label that does not include the labeling claims necessary or desirable for the successful commercialization of that drug candidate. Any of the foregoing scenarios could materially harm the commercial prospects for our drug candidates.

Furthermore, even though the NMPA has granted approval for fruquintinib and surufatinib for use in third-line mCRC and NET patients, respectively, and approval for savolitinib for lung cancer with Met exon 14 skipping alterations, we are still subject to substantial, ongoing regulatory requirements. See "—Even if we receive regulatory approval for our drug candidates, we are subject to ongoing obligations and continued regulatory review, which may result in significant additional expense."

If the FDA, NMPA or another regulatory agency revokes its approval of, or if safety, efficacy, manufacturing or supply issues arise with, any therapeutic that we use in combination with our drug candidates, we may be unable to market such drug candidate or may experience significant regulatory delays or supply shortages, and our business could be materially harmed.

We are currently developing combination therapies using our savolitinib, fruquintinib, surufatinib and other drug candidates with various immunotherapies, targeted therapies and/or other therapies. For example, we are currently developing savolitinib in combination with immunotherapy (Imfinzi) and targeted therapy (Tagrisso). However, we did not develop and we do not manufacture or sell Imfinzi, Tagrisso or any other therapeutic we use in combination with our drug candidates. We may also seek to develop our drug candidates in combination with other therapeutics in the future.

If the FDA, NMPA or another regulatory agency revokes its approval, or does not grant approval, of any of these and other therapeutics we use in combination with our drug candidates, we will not be able to market our drug candidates in combination with such therapeutics. If safety or efficacy issues arise with these or other therapeutics that we seek to combine with our drug candidates in the future, we may experience significant regulatory delays, and we may be required to redesign or terminate the applicable clinical trials. In addition, if manufacturing or other issues result in a supply shortage of these or any other combination therapeutics, we may not be able to complete clinical development of savolitinib, fruquintinib, surufatinib and/or any other of our drug candidates on our current timeline or at all.

Even if one or more of our drug candidates were to receive regulatory approval for use in combination with a therapeutic, we would continue to be subject to the risk that the FDA, NMPA or another regulatory agency could revoke its approval of the combination therapeutic, or that safety, efficacy, manufacturing or supply issues could arise with one of these combination therapeutics. This could result in Orpathys, Elunate, Sulanda or one of our other products being removed from the market or being less successful commercially.

We face substantial competition, which may result in others discovering, developing or commercializing drugs before or more successfully than we do.

The development and commercialization of new drugs is highly competitive. We face competition with respect to our current drug candidates, and will face competition with respect to any drug candidates that we may seek to develop or commercialize in the future, from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide. There are a number of large pharmaceutical and biotechnology companies that currently market drugs or are pursuing the development of therapies in the field of kinase inhibition for cancer and other diseases. Some of these competitive drugs and therapies are based on scientific approaches that are the same as or similar to our approach, and others are based on entirely different approaches. Potential competitors also include academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for research, development, manufacturing and commercialization. Specifically, there are a large number of companies developing or marketing treatments for cancer and immunological diseases, including many major pharmaceutical and biotechnology companies.

Many of the companies against which we are competing or against which we may compete in the future have significantly greater financial resources and expertise in research and development, manufacturing, pre-clinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved drugs than we do. Mergers and acquisitions in the pharmaceutical, biotechnology and diagnostic industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize drugs that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any drugs that we or our collaborators may develop. Our competitors also may obtain FDA, NMPA or other regulatory approval for their drugs more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we or our collaborators are able to enter the market. The key competitive factors affecting the success of all of our drug candidates, if approved, are likely to be their efficacy, safety, convenience, price, the level of generic competition and the availability of reimbursement from government and other third-party payors.

Clinical development involves a lengthy and expensive process with an uncertain outcome.

There is a risk of failure for each of our drug candidates. It is difficult to predict when or if any of our drug candidates will prove effective and safe in humans or will receive regulatory approval. Before obtaining regulatory approval from regulatory authorities for the sale of any drug candidate, we or our collaboration partners must complete pre-clinical studies and then conduct extensive clinical trials to demonstrate the safety and efficacy of our drug candidates in humans. Clinical testing is expensive, difficult to design and implement and can take many years to complete. The outcomes of pre-clinical development testing and early clinical trials may not be predictive of the success of later clinical trials, and interim results of a clinical trial do not necessarily predict final results. Moreover, pre-clinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their drug candidates performed satisfactorily in pre-clinical studies and clinical trials have nonetheless failed to obtain regulatory approval of their drug candidates. Our current or future clinical trials may not be successful.

Commencing each of our clinical trials is subject to finalizing the trial design based on ongoing discussions with the FDA, NMPA or other regulatory authorities. The FDA, NMPA and other regulatory authorities could change their position on the acceptability of our trial designs or clinical endpoints, which could require us to complete additional clinical trials or impose approval conditions that we do not currently expect. Successful completion of our clinical trials is a prerequisite to submitting an NDA or analogous filing to the FDA, NMPA or other regulatory authorities for each drug candidate and, consequently, the ultimate approval and commercial marketing of our drug candidates. We do not know whether any of our clinical trials will begin or be completed on schedule, if at all.

We and our collaboration partners may incur additional costs or experience delays in completing our pre-clinical or clinical trials, or ultimately be unable to complete the development and commercialization of our drug candidates.

We and our collaboration partners, including AstraZeneca, Eli Lilly, BeiGene Ltd., or BeiGene, Inmagene Biopharmaceuticals Co. Ltd., or Inmagene, Innovent Biologics (Suzhou) Co., Inc., or Innovent, Genor Biopharma Co. Ltd., or Genor, Shanghai Junshi Biosciences Co. Ltd., or Junshi and Epizyme, Inc., or Epizyme, may experience delays in completing our pre-clinical or clinical trials, and numerous unforeseen events could arise during, or as a result of, future clinical trials, which could delay or prevent us from receiving regulatory approval, including:

- regulators, institutional review boards, or IRBs, ethics committees or the China Human Genetic Resources Administration Office may not authorize us or our investigators to commence or conduct a clinical trial at a prospective trial site;
- we may experience delays in reaching, or we may fail to reach, agreement on acceptable terms with prospective trial sites and prospective CROs, who conduct clinical trials on behalf of us and our collaboration partners, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- clinical trials may produce negative or inconclusive results, and we or our collaboration partners may decide, or regulators may require us or them, to conduct additional clinical trials or we may decide to abandon drug development programs;
- the number of patients required for clinical trials of our drug candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate or participants may drop out of these clinical trials or fail to return for post-treatment follow-up at a higher rate than we anticipate;
- third-party contractors used in our clinical trials may fail to comply with regulatory requirements or meet their contractual obligations in a timely manner, or at all, or may deviate from the clinical trial protocol or drop out of the trial, which may require that we or our collaboration partners add new clinical trial sites or investigators;

- we or our collaboration partners may elect to, or regulators, IRBs or ethics committees may require that we or our investigators, suspend or terminate clinical research for various reasons, including non-compliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks;

- the cost of clinical trials of our drug candidates may be greater than we anticipate;

- the supply or quality of our drug candidates, companion diagnostics, if any, or other materials necessary to conduct clinical trials of our drug candidates may be insufficient or inadequate; and

- our drug candidates may have undesirable side effects or unexpected characteristics, causing us or our investigators, regulators, IRBs or ethics committees to suspend or terminate the trials, or reports may arise from pre-clinical or clinical testing of other cancer therapies that raise safety or efficacy concerns about our drug candidates.

We could encounter regulatory delays if a clinical trial is suspended or terminated by us or our collaboration partners, by, as applicable, the IRBs of the institutions in which such trials are being conducted, by the Data Safety Monitoring Board, which is an independent group of experts that is formed to monitor clinical trials while ongoing, or by the FDA, NMPA or other regulatory authorities. Such authorities may impose a suspension or termination due to a number of factors, including: a failure to conduct the clinical trial in accordance with regulatory requirements or the applicable clinical protocols, inspection of the clinical trial operations or trial site by the FDA, NMPA or other regulatory authorities that results in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a drug, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. Many of the factors that cause a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our drug candidates. Further, the FDA, NMPA or other regulatory authorities may disagree with our clinical trial design and our interpretation of data from clinical trials, or may change the requirements for approval even after it has reviewed and commented on the design for our clinical trials.

If we or our collaboration partners are required to conduct additional clinical trials or other testing of our drug candidates beyond those that are currently contemplated, if we or our collaboration partners are unable to successfully complete clinical trials of our drug candidates or other testing, if the results of these trials or tests are not positive or are only modestly positive or if there are safety concerns, we may:

- be delayed in obtaining regulatory approval for our drug candidates;

- not obtain regulatory approval at all;

- obtain approval for indications or patient populations that are not as broad as intended or desired;

- be subject to post-marketing testing requirements; or

- have the drug removed from the market after obtaining regulatory approval.

Our drug development costs will also increase if we experience delays in testing or regulatory approvals. We do not know whether any of our clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. Significant pre-clinical study or clinical trial delays also could allow our competitors to bring products to market before we do and impair our ability to successfully commercialize our drug candidates and may harm our business and results of operations. Any delays in our clinical development programs may harm our business, financial condition and prospects significantly.

If we or our collaboration partners experience delays or difficulties in the enrollment of patients in clinical trials, the progress of such clinical trials and our receipt of necessary regulatory approvals could be delayed or prevented.

We or our collaboration partners may not be able to initiate or continue clinical trials for our drug candidates if we or our collaboration partners are unable to locate and enroll a sufficient number of eligible patients to participate in these trials as required by the FDA, NMPA or similar regulatory authorities. In particular, we and our collaboration partners have designed many of our clinical trials, and expect to design future trials, to include some patients with the applicable genomic alteration that causes the disease with a view to assessing possible early evidence of potential therapeutic effect. Genomically defined diseases, however, may have relatively low prevalence, and it may be difficult to identify patients with the applicable genomic alteration. In addition, for many of our trials, we focus on enrolling patients who have failed their first or second-line treatments, which limits the total size of the patient population available for such trials. The inability to enroll a sufficient number of patients with the applicable genomic alteration or that meet other applicable criteria for our clinical trials would result in significant delays and could require us or our collaboration partners to abandon one or more clinical trials altogether.

In addition, some of our competitors have ongoing clinical trials for drug candidates that treat the same indications as our drug candidates, and patients who would otherwise be eligible for our clinical trials may instead enroll in clinical trials of our competitors' drug candidates.

Patient enrollment may be affected by other factors including:

- the severity of the disease under investigation;
- the total size and nature of the relevant patient population;
- the design and eligibility criteria for the clinical trial in question;
- the availability of an appropriate genomic screening test/companion diagnostic;
- the perceived risks and benefits of the drug candidate under study;
- the efforts to facilitate timely enrollment in clinical trials;
- the patient referral practices of physicians;
- the availability of competing therapies which are undergoing clinical trials;
- the ability to monitor patients adequately during and after treatment;
- the proximity and availability of clinical trial sites for prospective patients ; and
- the impact of the COVID-19 pandemic, including but not limited to the duration and scope of related government orders and restrictions.

Enrollment delays in our clinical trials may result in increased development costs for our drug candidates, which could cause the value of our company to decline and limit our ability to obtain financing.

Our drug candidates may cause undesirable side effects that could delay or prevent their regulatory approval, limit the commercial profile of an approved label, or result in significant negative consequences following regulatory approval, if any.

Undesirable side effects caused by our drug candidates could cause us or our collaboration partners to interrupt, delay or halt clinical trials or could cause regulatory authorities to interrupt, delay or halt our clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA, NMPA or other regulatory authorities. In particular, as is the case with all oncology drugs, it is likely that there may be side effects, for example, hand-foot syndrome, associated with the use of certain of our drug candidates. Results of our trials could reveal a high and unacceptable severity and prevalence of these or other side effects. In such an event, our trials could be suspended or terminated and the FDA, NMPA or comparable regulatory authorities could order us to cease further development of or deny approval of our drug candidates for some or all targeted indications. The drug-related side effects could affect patient recruitment or the ability of enrolled patients to complete the trial or result in potential product liability claims. Any of these occurrences may harm our business, financial condition and prospects significantly.

Further, our drug candidates could cause undesirable side effects related to off-target toxicity. Many of the currently approved tyrosine kinase inhibitors or TKIs have been associated with off-target toxicities because they affect multiple kinases. While we believe that the kinase selectivity of our drug candidates has the potential to significantly improve the unfavorable adverse off-target toxicity issues, if patients were to experience off-target toxicity, we may not be able to achieve an effective dosage level, receive approval to market, or achieve the commercial success we anticipate with respect to any of our drug candidates, which could prevent us from ever generating revenue or achieving profitability. Many compounds that initially showed promise in early-stage testing for treating cancer have later been found to cause side effects that prevented further development of the compound.

Clinical trials assess a sample of the potential patient population. With a limited number of patients and duration of exposure, rare and severe side effects of our drug candidates may only be uncovered with a significantly larger number of patients exposed to the drug candidate. If our drug candidates receive regulatory approval and we or others identify undesirable side effects caused by such drug candidates (or any other similar drugs) after such approval, a number of potentially significant negative consequences could result, including:

- regulatory authorities may withdraw or limit their approval of such drug candidates;
- regulatory authorities may require the addition of labeling statements, such as a “boxed” warning or a contra-indication;
- we may be required to create a medication guide outlining the risks of such side effects for distribution to patients;
- we may be required to change the way such drug candidates are distributed or administered, conduct additional clinical trials or change the labeling of the drug candidates;
- regulatory authorities may require a Risk Evaluation and Mitigation Strategy, or REMS, plan to mitigate risks, which could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools;
- we may be subject to regulatory investigations and government enforcement actions;
- we may decide to remove such drug candidates from the marketplace;
- we could be sued and held liable for injury caused to individuals exposed to or taking our drug candidates; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of the affected drug candidates and could substantially increase the costs of commercializing our drug candidates, if approved, and significantly impact our ability to successfully commercialize our drug candidates and generate revenue.

We and our collaboration partners have conducted and intend to conduct additional clinical trials for certain of our drug candidates at sites outside the United States, and the FDA may not accept data from trials conducted in such locations or may require additional U.S.-based trials.

We and our collaboration partners have conducted, currently are conducting and intend in the future to conduct, clinical trials outside the United States, particularly in China where our Oncology/Immunology operations are headquartered as well as in other jurisdictions such as Australia, Japan, South Korea, the U.K, and various European countries.

Although the FDA may accept data from clinical trials conducted outside the United States, acceptance of these data is subject to certain conditions imposed by the FDA. For example, the clinical trial must be well designed and conducted by qualified investigators in accordance with current good clinical practices, or GCPs, including review and approval by an independent ethics committee and receipt of informed consent from trial patients. The trial population must also adequately represent the U.S. population, and the data must be applicable to the U.S. population and U.S. medical practice in ways that the FDA deems clinically meaningful. Generally, the patient population for any clinical trial conducted outside of the United States must be representative of the population for which we intend to seek approval in the United States. In addition, while these clinical trials are subject to applicable local laws, FDA acceptance of the data will be dependent upon its determination that the trials also comply with all applicable U.S. laws and regulations. There can be no assurance that the FDA will accept data from trials conducted outside of the United States. If the FDA does not accept the data from our clinical trials conducted outside the United States, it would likely result in the need for additional clinical trials, which would be costly and time-consuming and delay or permanently halt our ability to develop and market these or other drug candidates in the United States.

In addition, there are risks inherent in conducting clinical trials in jurisdictions outside the United States including:

- regulatory and administrative requirements of the jurisdiction where the trial is conducted that could burden or limit our ability to conduct our clinical trials;
- foreign exchange fluctuations;
- manufacturing, customs, shipment and storage requirements;
- cultural differences in medical practice and clinical research; and
- the risk that patient populations in such trials are not considered representative as compared to patient populations in the United States and other markets.

If we are unable to obtain and/or maintain priority review by the NMPA, fast track designation by the FDA, or another expedited registration pathway for our drug candidates, the time and cost we incur to obtain regulatory approvals may increase. Even if we receive such approvals, they may not lead to a faster development, review or approval process.

Under the Opinions on Priority Review and Approval for Encouraging Drug Innovation, the NMPA may grant priority review approval to (i) certain drugs with distinctive clinical value, including innovative drugs not sold within or outside China, (ii) new drugs with clinical treatment advantages for AIDS and other rare diseases, and (iii) drugs which have been concurrently filed with the competent drug approval authorities in the United States or E.U. for marketing authorization and passed such authorities' onsite inspections and are manufactured using the same production line in China. Priority review provides a fast track process for drug registration. We have received priority review status for a number of our drug candidates, including for example fruquintinib for the treatment of advanced colorectal cancer, or CRC, savolitinib for the treatment of NSCLC and surufatinib for the treatment of advanced NET. We anticipate that we may seek priority review for certain of our other drug candidates in the future.

In the United States, if a drug is intended for the treatment of a serious or life-threatening condition and the drug demonstrates the potential to address unmet medical needs for this condition, we may apply for fast track designation by the FDA. The FDA has broad discretion whether or not to grant this designation, so even if we believe a particular drug candidate is eligible for this designation, we cannot be sure that the FDA would decide to grant it. We have sought and will likely continue to seek fast track designation for some of our drug candidates. For example, in April 2020, the FDA granted fast track designation to surufatinib for both the non-pancreatic and pancreatic neuroendocrine tumor development programs. Even if we receive fast track designation for a drug candidate, we may not experience a faster development process, review or approval compared to conventional FDA procedures. The FDA may withdraw fast track designation if it believes that the designation is no longer supported by data from our clinical development program.

A failure to obtain and/or maintain priority review, fast track designation or any other form of expedited development, review or approval for our drug candidates would result in a longer time period to commercialization of such drug candidate, could increase the cost of development of such drug candidate and could harm our competitive position in the marketplace. In addition, even if we obtain priority review, there is no guarantee that we will experience a faster review or approval compared to non-accelerated registration pathways or that a drug candidate will ultimately be approved for sale.

Although we have obtained orphan drug designation for surufatinib for the treatment of pancreatic NETs in the United States, we may not be able to obtain or maintain the benefits associated with orphan drug status, including market exclusivity.

Under the Orphan Drug Act, the FDA may designate a drug as an orphan drug if it is intended to treat a rare disease or condition, which is generally defined as affecting fewer than 200,000 individuals in the United States. We have obtained orphan drug designation from the FDA for surufatinib for the treatment of pancreatic NETs. Generally, if a drug with an orphan drug designation subsequently receives the first marketing approval for the indication for which it has such designation, the drug may be entitled to a seven-year period of marketing exclusivity, which precludes the FDA from approving another marketing application for the same molecule for the same indication for that time period. We can provide no assurance that another drug will not receive marketing approval prior to our product candidates. Orphan drug exclusivity may be lost if the FDA determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the drug to meet the needs of patients with the rare disease or condition. In addition, even after a drug is granted orphan exclusivity and approved, the FDA can subsequently approve another drug for the same condition before the expiration of the seven-year exclusivity period if the FDA concludes that the later drug is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care.

Even if we receive regulatory approval for our drug candidates, we are subject to ongoing obligations and continued regulatory review, which may result in significant additional expense.

If the FDA, NMPA or a comparable regulatory authority approves any of our drug candidates, we will continue to be subject to extensive and ongoing regulatory requirements. For example, even though the NMPA has granted approval of fruquintinib, the manufacturing processes, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion and recordkeeping for fruquintinib continue to be subject to the NMPA's oversight. These requirements include submissions of safety and other post-marketing information and reports, registration, as well as continued compliance with current good manufacturing processes.

Any regulatory approvals that we receive for our drug candidates may also be subject to limitations on the approved indicated uses for which the drug may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including post-approval testing, sometimes referred to as Phase IV clinical trials, and surveillance to monitor the safety and efficacy of the drug. In addition, regulatory policies may change or additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our drug candidates. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any regulatory approval that we may have obtained, which would adversely affect our business, prospects and ability to achieve or sustain profitability.

We may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with any of our drugs that receive regulatory approval.

Once a drug is approved by the FDA, NMPA or a comparable regulatory authority for marketing, it is possible that there could be a subsequent discovery of previously unknown problems with the drug, including problems with third-party manufacturers or manufacturing processes, or failure to comply with regulatory requirements. If any of the foregoing occurs with respect to our drug products, it may result in, among other things:

- restrictions on the marketing or manufacturing of the drug, withdrawal of the drug from the market, or drug recalls;
- fines, warning letters or holds on clinical trials;
- refusal by the FDA, NMPA or comparable regulatory authority to approve pending applications or supplements to approved applications filed by us, or suspension or revocation of drug license approvals;
- drug seizure or detention, or refusal to permit the import or export of drugs; and
- injunctions or the imposition of civil or criminal penalties.

Any government investigation of alleged violations of law could require us to expend significant time and resources and could generate negative publicity. If we or our collaborators are not able to maintain regulatory compliance, regulatory approval that has been obtained may be lost and we may not achieve or sustain profitability, which would adversely affect our business, prospects, financial condition and results of operations.

The incidence and prevalence for target patient populations of our drug candidates are based on estimates and third-party sources. If the market opportunities for our drug candidates are smaller than we estimate or if any approval that we obtain is based on a narrower definition of the patient population, our revenue and ability to achieve profitability will be adversely affected, possibly materially.

Periodically, we make estimates regarding the incidence and prevalence of target patient populations for particular diseases based on various third-party sources and internally generated analysis and use such estimates in making decisions regarding our drug development strategy, including determining indications on which to focus in pre-clinical or clinical trials.

These estimates may be inaccurate or based on imprecise data. For example, the total addressable market opportunity will depend on, among other things, their acceptance by the medical community and patient access, drug pricing and reimbursement. The number of patients in the addressable markets may turn out to be lower than expected, patients may not be otherwise amenable to treatment with our drugs, or new patients may become increasingly difficult to identify or gain access to, all of which would adversely affect our results of operations and our business.

Our future success depends on our ability to retain key executives and to attract, retain and motivate qualified personnel.

We are highly dependent on the expertise of the members of our research and development team, as well as the other principal members of our management, including Christian Lawrence Hogg, our Chief Executive Officer and director, and Weiguo Su, Ph.D., our Chief Scientific Officer and director. Although we have entered into employment agreements with our executive officers, each of them may terminate their employment with us at any time with three months' prior written notice. We do not maintain "key person" insurance for any of our executives or other employees.

Recruiting and retaining qualified management, scientific, clinical, manufacturing and sales and marketing personnel will also be critical to our success. The loss of the services of our executive officers or other key employees could impede the achievement of our research, development and commercialization objectives and seriously harm our ability to successfully implement our business strategy. Furthermore, replacing executive officers and key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to successfully develop, gain regulatory approval of and commercialize drugs. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these key personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. Failure to succeed in clinical trials may make it more challenging to recruit and retain qualified scientific personnel.

We have expanded our footprint and operations in the United States, and we intend to expand our international operations further in the future, but we may not achieve the results that we expect.

In early 2018, we opened our first office in the United States. While we have been involved in clinical and non-clinical development in North America and Europe for over a decade, the activities conducted by our U.S. office will significantly broaden and scale our non-Asian clinical development and international operations. We have significantly expanded, and intend to continue to expand, our U.S. clinical team to support our increasing clinical activities in the United States, Europe, Japan and Australia. In preparation for a potential approval of Sulanda in the United States in 2022, we have built a team of more than 30 personnel covering supply chain, market access, marketing, sales and commercial operation activities. Conducting our business in multiple countries subjects us to a variety of risks and complexities that may materially and adversely affect our business, results of operations, financial condition and growth prospects, including, among other things:

- the increased complexity and costs inherent in managing international operations;
- diverse regulatory, financial and legal requirements, and any future changes to such requirements, in one or more countries where we are located or do business;
- country-specific tax, labor and employment laws and regulations;
- applicable trade laws, tariffs, export quotas, custom duties or other trade restrictions and any changes to them;
- challenges inherent in efficiently managing employees in diverse geographies, including the need to adapt systems, policies, benefits and compliance programs to differing labor and other regulations;
- changes in currency rates; and
- regulations relating to data security and the unauthorized use of, or access to, commercial and personal information.

As a result of our growth, our business and corporate structure has become more complex. There can be no assurance that we will effectively manage the increased complexity without experiencing operating inefficiencies or control deficiencies. Significant management time and effort is required to effectively manage the increased complexity of our company, and our failure to successfully do so could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

We may be restricted from transferring our scientific data abroad.

On March 17, 2018, the General Office of the State Council promulgated the Measures for the Management of Scientific Data, or the Scientific Data Measures, which provides a broad definition of scientific data and relevant rules for the management of scientific data. According to the Scientific Data Measures, enterprises in China must seek governmental approval before any scientific data involving a state secret may be transferred abroad or to foreign parties. Further, any researcher conducting research funded at least in part by the Chinese government is required to submit relevant scientific data for management by the entity to which such researcher is affiliated before such data may be published in any foreign academic journal. Given that the term state secret is not clearly defined in the Scientific Data Measures, if and to the extent our research and development of drug candidates will be subject to the Scientific Data Measures and any subsequent laws as required by the relevant government authorities, we cannot assure you that we can always obtain relevant approvals for sending scientific data (such as the results of our pre-clinical studies or clinical trials conducted within China) abroad or to our foreign partners in China. The PRC Personal Information Protection Law, effective November 2021, provides that where a personal information processor needs to provide personal information outside the territory of the PRC due to business or other needs, it shall meet any of the following conditions: (i) it shall pass the security evaluation organized by the Cyberspace Administration of China ("CAC") in accordance with the provisions of Article 40 thereof, (ii) it shall have been certified by a specialized agency for protection of personal information in accordance with the provisions of the CAC, (iii) it shall enter into a contract with the overseas recipient under the standard contract formulated by the CAC, specifying the rights and obligations of both parties, or (iv) it shall meet other conditions prescribed by laws, administrative regulations or the CAC. If we are unable to obtain necessary approvals or meet the necessary requirements in a timely manner, or at all, our research and development of drug candidates may be hindered, which may materially and adversely affect our business, results of operations, financial conditions and prospects. If the relevant government authorities consider the transmission of our scientific data to be in violation of the requirements under the Scientific Data Measures, we may be subject to fines and other administrative penalties imposed by those government authorities.

If we expand our existing compassionate-use program or participate in additional compassionate-use programs, discrepancies among the regulations in different countries may lead to increased risk of adverse drug reactions and serious adverse events arising from the use of our drug candidates.

Compassionate-use programs are regulatory programs that facilitate access to investigational drugs for the treatment of patients with serious or immediately life-threatening diseases or conditions that lack therapeutic alternatives. Currently, there is no unified approach or standard practice to regulate compassionate-use programs or access to investigational drugs across countries. In China, the PRC Drug Administration Law provides that drugs in clinical trials intended for the treatment of serious life-threatening diseases without existing effective treatments may, upon review and informed consent, be administered to patients with the same conditions within the institution conducting the clinical trials, provided that such drugs may be beneficial as indicated by medical observation and such practice is in conformity with ethical principles. In the United States, compassionate-use programs are limited to patients who have a life-threatening disease or serious disease or condition, who may gain access to an investigational medical product for treatment outside of clinical trials when no comparable or satisfactory alternative therapy options are available. Additionally, the U.S. Right to Try Act provides a separate pathway for patients with a life-threatening disease or condition who have exhausted all other treatment options and who are unable to participate in clinical trials to access investigational drugs that have passed Phase I clinical trials under a more expedited process.

The regulatory discrepancy for compassionate-use programs among countries may lead to uneven patient entry criteria and protocols for compassionate use programs. This may create increased risk of serious adverse events because of enrolled patients' advanced disease or comorbidities. In addition, because the products in compassionate-use programs are investigational drugs, many of which are still in experimental stages, patients in compassionate-use program may exhibit adverse drug reactions from using these products. We currently have named patient programs in Hong Kong for compassionate use of fruquintinib and surufatinib and an expanded access program in the United States for compassionate use of surufatinib. Although we have enrolled a limited number of patients in each of our current programs, we may be subject to the risk of enrolled patients exhibiting adverse drug reactions or serious adverse events being produced from the use of our drug products, particularly if we expand such programs or establish or participate in additional compassionate-use programs. Such occurrences can potentially lead to clinical holds of our ongoing clinical trials or complicate the determination of the safety profile of a drug candidate under regulatory review for commercial marketing, or expose us to tort liability.

Risks Relating to Sales of Our Internally Developed Drugs and Other Drugs

Pharmaceutical companies in China are required to comply with extensive regulations and hold a number of permits and licenses to carry on their business. Our and our joint ventures' ability to obtain and maintain these regulatory approvals is uncertain, and future government regulation may impose additional burdens on our operations.

The pharmaceutical industry in China is subject to extensive government regulation and supervision. The regulatory framework addresses all aspects of operations in the pharmaceutical industry, including approval, production, distribution, advertising, licensing and certification requirements and procedures, periodic renewal and reassessment processes, registration of new drugs and environmental protection. Violation of applicable laws and regulations may materially and adversely affect our business. In order to manufacture and distribute pharmaceutical products in China, we and our joint ventures are required to, among other things:

- obtain a pharmaceutical manufacturing permit for each production facility from the NMPA;
- obtain a drug registration certificate, which includes a drug approval number, from the NMPA for each drug manufactured by us;
- obtain a pharmaceutical distribution permit from the NMPA; and
- renew the pharmaceutical manufacturing permits, the pharmaceutical distribution permits, drug registration certificates, among other requirements.

If we or our joint ventures are unable to obtain or renew such permits or any other permits or licenses required for our or their operations, we will not be able to engage in the manufacture and distribution of our products and our business may be adversely affected.

The regulatory framework regarding the pharmaceutical industry in China is subject to change and amendment from time to time. Any such change or amendment could materially and adversely impact our business, financial condition and results of operations. The PRC government has introduced various reforms to the Chinese healthcare system in recent years and may continue to do so, with an overall objective to expand basic medical insurance coverage and improve the quality and reliability of healthcare services. Specific upcoming regulatory and policy changes remain uncertain. The implementing measures to be issued may not be sufficiently effective to achieve the stated goals and, as a result, we may not be able to benefit from such reform to the level we expect, if at all. Moreover, the reform could give rise to regulatory developments, such as more burdensome administrative procedures, which may have an adverse effect on our business and prospects.

For further information regarding government regulation in China and other jurisdictions, see Item 4.B. "Business Overview—Regulation—Government Regulation of Pharmaceutical Product Development and Approval," "Business Overview—Regulation—Coverage and Reimbursement" and "Business Overview—Regulation—Other Healthcare Laws."

As a significant portion of the operations of our Other Ventures is conducted through joint ventures, we are dependent on the success of our joint ventures, our receipt of dividends or other payments from our joint ventures for cash to fund our operations, and our investments in our joint ventures are subject to liquidity risk.

We are party to a joint venture agreement with Shanghai Pharmaceuticals, relating to our non-consolidated joint venture namely, Shanghai Hutchison Pharmaceuticals, which forms part of the operations of our Other Ventures. Our equity in earnings of such non-consolidated joint venture, net of tax, was $30.7 million, $33.5 million and $44.7 million for the years ended December 31, 2019, 2020 and 2021, respectively, as recorded in our consolidated financial statements. As such, our results of operations and financial performance have been, and will continue to be, affected by the financial performance of such joint venture as well as any other equity investees we have or may have in the future. We may also be required to recognize an impairment charge in our consolidated financial statements if there is a decline in the fair market value of our investments in such businesses below their carrying amounts for whatever reason that is determined to be other-than-temporary. Furthermore, we have consolidated joint ventures with each of Sinopharm and Hain Celestial which accounted for substantially all of our Other Ventures' consolidated revenue for the years ended December 31, 2019, 2020 and 2021.

As a result, our ability to fund our operations and pay our expenses or to make future dividend payments, if any, is largely dependent on the earnings of our joint ventures and the payment of those earnings to us in the form of dividends. Payments to us by our joint ventures will be contingent upon our joint ventures' earnings and other business considerations and may be subject to statutory or contractual restrictions. Each joint venture's ability to distribute dividends to us is subject to approval by their respective boards of directors, which in the case of Shanghai Hutchison Pharmaceuticals is comprised of an equal number of representatives from each party. Furthermore, our ability to promptly sell one or more of our interests in our joint ventures in response to changing corporate strategy or economic, financial and investment conditions is limited. The market for such investments can be affected by various factors, such as general economic and market conditions, availability of financing, interest rates and investor demand, many of which are beyond our control. If we determine to sell any of our joint venture investments, we cannot predict if we will be successful or whether any price or other terms offered by a prospective purchaser would be acceptable to us.

Operationally, our joint venture partners have certain responsibilities and/or certain rights to exercise control or influence over operations and decision-making under the joint venture arrangements. Therefore, the success of our joint ventures depends on the efforts and abilities of our joint venture parties. For example, we appoint the general managers of Hutchison Sinopharm and Shanghai Hutchison Pharmaceuticals pursuant to the respective joint venture agreements governing these entities and therefore oversee the day-to-day management of these joint ventures. However, we still rely on our joint venture partners Sinopharm and Shanghai Pharmaceuticals to provide certain distribution and logistics services. See "—Risks Relating to Our Dependence on Third Parties—Joint ventures form an important part of our Other Ventures, and our ability to manage and develop the businesses conducted by these joint ventures depends in part on our relationship with our joint venture partners" for more information.

We may not be successful in building a commercial sales team to successfully manufacture, sell and market our approved drugs, and we may not be able to generate any revenue from such products.

We have leveraged our experience operating our prescription drugs business to commercialize certain of our approved, internally developed drug candidates in China. We must adapt our know-how to build a specific oncology and/or immunology focused sales and marketing team. As of December 31, 2021, we had an oncology commercial team with about 630 staff in China and about 30 staff in the United States to support the commercialization of Elunate, Sulanda, Orpathys and our other drug candidates, if approved. There are risks involved in establishing an in-house oncology commercial team. For example, recruiting and/or training a sales force to detail our approved drug candidates is time consuming and could delay any drug launch. Factors that may inhibit our efforts to commercialize our drug candidates include:

- our inability to recruit and retain adequate numbers of effective sales and marketing personnel;
- our inability to effectively manage the expansion of our operations and train additional qualified personnel in the relevant areas of oncology and/or immunology;
- the inability of our sales personnel to obtain access to physicians or educate adequate numbers of physicians who then prescribe any future drugs; and

- the lack of complementary drugs to be offered by our sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines.

In such case, our business, results of operations, financial condition and prospects will be materially and adversely affected.

We face substantial competition in selling our approved, internally developed drugs and the drugs of our Other Ventures.

The marketed drugs developed and sold by our Oncology/Immunology operations and the prescription drugs business which is part of our Other Ventures' operations face substantial competition in the pharmaceutical industry in China, which is characterized by a number of established, large pharmaceutical companies, as well as smaller emerging pharmaceutical companies, engaged in the development, production, marketing or sales of prescription drugs, in particular cardiovascular drugs. The identities of the key competitors with respect to drugs sold by our Oncology/Immunology and Other Ventures operations vary by product and, in certain cases, competitors have greater financial resources than us and may elect to focus these resources on developing, importing or in-licensing and marketing products in the PRC that are substitutes for our products and may have broader sales and marketing infrastructure with which to do so.

Such drugs may compete against products that have lower prices, superior performance, greater ease of administration or other advantages compared to our products. In some circumstances, price competition may drive our competitors to conduct illegal manufacturing processes to lower their manufacturing costs. Increased competition may result in price reductions, reduced margins and loss of market share, whether achieved by either legal or illegal means, any of which could materially and adversely affect our profit margins. We and our joint ventures may not be able to compete effectively against current and future competitors.

If we are not able to maintain and enhance brand recognition of our drugs to maintain a competitive advantage, our reputation, business and operating results may be harmed.

We believe that market awareness of our products sold through our Oncology/Immunology and Other Ventures operations, which include our joint ventures' branded products, such as Shang Yao, and the brands of third-party products which are distributed through our joint ventures, has contributed significantly to our success. We also believe that maintaining and enhancing such brands is critical to maintaining our competitive advantage. Although the sales and marketing staff of such businesses will continue to further promote such brands to remain competitive, they may not be successful. If we or our joint ventures are unable to further enhance brand recognition and increase awareness of such products, or are compelled to incur excessive marketing and promotion expenses in order to maintain brand awareness, our business and results of operations may be materially and adversely affected. Furthermore, our results of operations could be adversely affected if the Shang Yao brand, or the brands of any other products, or our reputation, are impaired by certain actions taken by our joint venture partners, distributors, competitors or relevant regulatory authorities.

Reimbursement may not be available for the products currently sold through our Oncology/Immunology and Other Ventures operations or our drug candidates in China, the United States or other countries, which could diminish our sales or affect our profitability.

The regulations that govern pricing and reimbursement for pharmaceuticals vary widely from country to country. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after regulatory approval is granted. In some foreign markets, pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. Furthermore, once marketed and sold, government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels. Adverse pricing reimbursement levels may hinder market acceptance of our drug candidates or other products sold by us.

In China, for example, the Ministry of Human Resources and Social Security of the PRC or provincial or local human resources and social security authorities, together with other government authorities, review the inclusion or removal of drugs from the Medicines Catalogue for the National Basic Medical Insurance, Labor Injury Insurance and Childbirth System in China, or the National Reimbursement Drug List, or NRDL, or provincial or local medical insurance catalogues for the National Medical Insurance Program, and the category under which a drug will be classified, both of which affect the amounts reimbursable to program participants for their purchases of those medicines. These determinations are made based on a number of factors, including price and efficacy. Depending on the category under which a drug is classified in the provincial medicine catalogue, a National Medical Insurance Program participant residing in that province can be reimbursed for the full cost of Category A medicine and for the majority of the cost of a Category B medicine. In some instances, if the price range designated by the local or provincial government decreases, it may adversely affect our business and could reduce our total revenue, and if our revenue falls below production costs, we may stop manufacturing certain products. In November 2019 and January 2022, Elunate and Sulanda were added to China's NRDL as a Category B medicine, respectively.

In addition, in order to access certain local or provincial-level markets, our joint ventures are periodically required to enter into competitive bidding processes for She Xiang Bao Xin (the best-selling product of our Shanghai Hutchison Pharmaceuticals joint venture) and other products with a pre-defined price range. The competitive bidding in effect sets price ceilings for those products, thereby limiting our profitability.

In the United States, there have been and continue to be a number of legislative initiatives to contain healthcare costs which may affect reimbursement rates of our drug candidates if approved. For example, in March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or the Affordable Care Act, was passed, which substantially changed the way health care is financed by both governmental and private insurers. The Affordable Care Act, among other things, established a new Medicare Part D coverage gap discount program, in which, effective 2019, manufacturers must agree to offer 70% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D. In addition, other legislative changes have been proposed and adopted in the United States since the Affordable Care Act was enacted.

Modifications to or repeal of all or certain provisions of the Affordable Care Act had been expected based on statements made by former President Trump and certain members of Congress. However, President Biden has indicated that his healthcare policy will build on the Affordable Care Act and that his administration will prioritize comprehensive drug pricing reform. We cannot predict the ultimate content, timing or effect of any changes to the Affordable Care Act or other federal and state reform efforts. Several U.S. states have also enacted laws to control drug pricing or require manufacturers to disclose information about drug pricing. There is no assurance that federal or state health care reform will not adversely affect our future business and financial results. We expect that additional U.S. state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our drug candidates or additional pricing pressures. We expect that the pharmaceutical industry will experience pricing pressures due to the increasing influence of managed care (and related implementation of managed care strategies to control utilization), consolidation in drug distribution industry, additional federal and state legislative and regulatory proposals to regulate pricing of drugs, limit coverage of drugs or reduce reimbursement for drugs, public scrutiny and recent regulatory initiatives to control the price of pharmaceuticals through government negotiations of drug prices in Medicare Part D and, eventually Medicare Part B, and importation of cheaper products from abroad.

Moreover, eligibility for reimbursement in the United States does not imply that any drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Interim U.S. reimbursement levels for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement rates may vary according to the use of the drug and the clinical setting in which it is used, may be based on reimbursement levels already set for lower cost drugs and may be incorporated into existing payments for other services. Net prices for drugs may be reduced by mandatory discounts or rebates required by U.S. government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. Third-party payors in the United States often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement policies. Our inability to promptly obtain coverage and profitable payment rates from both government-funded and private payors for any approved drugs that we develop could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize drugs and our overall financial condition.

Sales of our generic prescription drugs sold through our Other Ventures rely on the ability to win tender bids for the medicine purchases of hospitals in China.

Our prescription drugs business markets to hospitals in China that may make bulk purchases of a medicine only if that medicine is selected under a government-administered tender process that was initiated in 2018 and aimed at driving consolidation in the fragmented generic prescription drug market in China. Pursuant to this process, major cities bulk-buy certain generic drugs together, forcing companies to bid for contracts and driving down prices. The process was later expanded nationwide to cover more cities and drugs. This process, which only applies to generic prescription drugs, may reduce our Other Ventures' product portfolio as some of our third-party generic drug partners may fail to win bids.

Periodically, a bidding process is organized on a provincial or municipal basis. Whether a drug manufacturer is invited to participate in the tender depends on the level of interest that hospitals have in purchasing this drug. The interest of a hospital in a medicine is evidenced by:

- the inclusion of this medicine on the hospital's formulary, which establishes the scope of drug physicians at this hospital may prescribe to their patients, and
- the willingness of physicians at this hospital to prescribe a particular drug to their patients.

We believe that effective marketing efforts are critical in making and keeping hospitals interested in purchasing the prescription drugs sold through our Other Ventures so that we and our joint ventures are invited to submit the products to the tender. Even if we and our joint ventures are invited to do so, competitors may be able to substantially reduce the price of their products or services. If competitors are able to offer lower prices, our and our joint ventures' ability to win tender bids during the hospital tender process will be materially affected, and could reduce our total revenue or decrease our profit.

Counterfeit products could negatively impact our revenue, brand reputation, business and results of operations.

Our products are subject to competition from counterfeit products, especially counterfeit pharmaceuticals which are manufactured without proper licenses or approvals and are fraudulently mislabeled with respect to their content and/or manufacturer. Counterfeiters may illegally manufacture and market products under our or our joint venture's brand names, the brand names of the third-party products we or they sell, or those of our or their competitors. Counterfeit pharmaceuticals are generally sold at lower prices than the authentic products due to their low production costs, and in some cases are very similar in appearance to the authentic products. Counterfeit pharmaceuticals may or may not have the same chemical content as their authentic counterparts. If counterfeit pharmaceuticals illegally sold under our or our joint ventures' brand names or the brand names of third-party products we or they sell result in adverse side effects to consumers, we or our joint ventures may be associated with any negative publicity resulting from such incidents. In addition, consumers may buy counterfeit pharmaceuticals that are in direct competition with products sold through our Oncology/Immunology and Other Ventures operations, which could have an adverse impact on our revenue, business and results of operations. The proliferation of counterfeit pharmaceuticals in China and globally may grow in the future. Any such increase in the sales and production of counterfeit pharmaceuticals in China, or the technological capabilities of the counterfeiters, could negatively impact our revenue, brand reputation, business and results of operations.

Rapid changes in the pharmaceutical industry may render our Other Ventures' products or our internally developed drugs and drug candidates obsolete.

Future technological improvements by our competitors and continual product developments in the pharmaceutical market may render our and our joint ventures' existing products, our or their third-party licensed products or our drug candidates obsolete or affect our viability and competitiveness. Therefore, our future success will largely depend on our and our joint ventures' ability to:

- improve existing products;
- develop innovative drug candidates;
- diversify the product and drug candidate portfolio;

- license diverse third-party products; and
- develop new and competitively priced products which meet the requirements of the constantly changing market.

If we or our joint ventures fail to respond to this environment by improving our existing products, licensing new third-party products or developing new drug candidates in a timely fashion, or if such new or improved products do not achieve adequate market acceptance, our business and profitability may be materially and adversely affected.

Certain of our joint ventures' principal products involve the cultivation or sourcing of key raw materials including botanical products, and any quality control or supply failure or price fluctuations could adversely affect our ability to manufacture our products and/or could materially and adversely affect our operating results.

The key raw materials used in the manufacturing process of certain of our joint ventures' principal products are medicinal herbs whose properties are related to the regions and climatic conditions in which they are grown. Access to quality raw materials and products necessary for the manufacture of our products is not guaranteed. We rely on materials sourced from third-party growers and suppliers. The availability, quality and prices of these raw materials are dependent on and closely affected by weather conditions and other seasonal factors which have an impact on the yields of the harvests each year. The quality, in some instances, also depends on the operations of third-party growers or suppliers. There is a risk that such growers or suppliers sell or attempt to sell us or our joint ventures raw materials which are not authentic. If there is any supply interruption for an indeterminate period of time, our joint ventures may not be able to identify and obtain alternative supplies that comply with our quality standards in a timely manner. Any supply disruption could adversely affect our ability to satisfy demand for our products, and materially and adversely affect our product sales and operating results. Moreover, any use by us or our joint ventures of unauthentic materials illegally sold to us by third-party growers or suppliers in our or our joint ventures' products may result in adverse side effects to the consumers, negative publicity, or product liability claims against us or our joint ventures, any of which may materially and adversely affect our operating results.

The prices of necessary raw materials and products may be subject to price fluctuations according to market conditions, and any sudden increases in demand in the case of a widespread illness such as COVID-19, SARS, MERS or avian flu may impact the costs of production. Raw material price fluctuations could increase the cost to manufacture our products and adversely affect our operating results.

Adverse publicity associated with our company, our joint ventures or our or their products or third-party licensed products or similar products manufactured by our competitors could have a material adverse effect on our results of operations.

Sales of our and our joint ventures' products are highly dependent upon market perceptions of the safety and quality of such products, including proprietary products and third-party products we and they distribute. Concerns over the safety of biopharmaceutical products manufactured in China could have an adverse effect on the reputation of our industry and the sale of such products, including products manufactured or distributed by us and our joint ventures.

We and our joint ventures could be adversely affected if any of our or our joint ventures' products, third-party licensed products or any similar products manufactured by other companies prove to be, or are alleged to be, harmful to patients. Any negative publicity associated with severe adverse reactions or other adverse effects resulting from patients' use or misuse of our and our joint ventures' products or any similar products manufactured by other companies could also have a material adverse impact on our results of operations. We and our joint ventures have not, to date, experienced any significant quality control or safety problems. If in the future we or our joint ventures become involved in incidents of the type described above, such problems could severely and adversely impact our financial position and reputation.

We are dependent on our joint ventures' production facilities in Shanghai, China, our manufacturing facility in Suzhou, China and third-party manufacturing facilities for the manufacture of the principal products of our joint ventures and our own drug candidates and products.

The principal products sold by our Other Ventures are mainly produced or expected to be produced at our joint ventures' manufacturing facilities in Shanghai, China. Our commercial supplies of Elunate and Sulanda sold by our Oncology/Immunology operations are manufactured at our manufacturing facility in Suzhou, China. We outsourced the manufacturing of active pharmaceutical ingredients and finished product of Orpathys to a third-party manufacturer based in Shanghai, China. Until construction of our new manufacturing facility in Shanghai is completed and it receives the requisite government approvals, we have no back-up manufacturing facility for fruquintinib and surufatinib, and our ability to produce such drugs will be negatively impacted if we experience any significant production problems at our Suzhou facility. A significant disruption at our, our joint ventures' and/or our contract manufacturer's facilities, even on a short-term basis, could impair our and/or our joint ventures' ability to timely produce and ship products, which could have a material adverse effect on our business, financial position and results of operations.

Our, our joint ventures' and our contract manufacturer's manufacturing operations are vulnerable to interruption and damage from natural and other types of disasters, including earthquake, fire, floods, environmental accidents, power loss, communications failures and similar events. If any disaster were to occur, our ability to operate our, our joint ventures' or our contract manufacturer's business at these facilities would be materially impaired. In addition, the nature of our production and research activities could cause significant delays in our programs and make it difficult for us to recover from a disaster or switch to other contract manufacturers. We and our joint ventures maintain insurance for business interruptions to cover some of our potential losses; however, such disasters could still disrupt our operations and thereby result in substantial costs and diversion of resources.

In addition, our, our joint ventures' and our contract manufacturer's production process requires a continuous supply of electricity. We and they have encountered power shortages historically due to restricted power supply to industrial users during summers when the usage of electricity is high and supply is limited or as a result of damage to the electricity supply network. Because the duration of those power shortages was brief, they had no material impact on our or their operations. Interruptions of electricity supply could result in lengthy production shutdowns, increased costs associated with restarting production and the loss of production in progress. Any major suspension or termination of electricity or other unexpected business interruptions could have a material adverse impact on our business, financial condition and results of operations.

We may engage in strategic transactions, including acquisitions, investments, joint ventures or divestitures that may have an adverse effect on our business. If we engage in a strategic transaction, there is no assurance that the transaction will be consummated.

We may pursue transactions as part of our business strategy, including continuing to actively evaluate non-core assets divestment opportunities. For instance, on March 24, 2021, we entered into a sale and purchase agreement with GL Mountrose Investment Two Limited, a company controlled and managed by GL Capital Group, to sell our entire investment in Hutchison Baiyunshan. The sale was completed on September 28, 2021. We are also considering divesting other non-core businesses in our Other Ventures segment, including Shanghai Hutchison Pharmaceuticals. For more information, please refer to Item 4.A. "History and Development of the Company", "Disposal of Hutchison Baiyunshan."

Acquisitions and investments involve numerous risks such as difficulties in finding suitable partners or acquisition candidates, difficulties in obtaining financing on favorable terms, if at all, the assumption of certain known and unknown liabilities of acquired companies and difficulties in integrating operations, services, products and personnel. Divestitures also involve numerous risks. Any divestiture could result in a dilutive impact to our future earnings and significant write-offs, including those related to goodwill and other intangible assets, which could have a material adverse effect on our results of operations and financial condition. Divestitures could involve additional risks, including difficulties in the separation of operations, services, products and personnel, the diversion of management's attention from other business concerns, the disruption of our business and the potential loss of key employees.

We may not complete strategic transactions in a timely manner, on a cost-effective basis, or at all, and we may not realize the expected benefits of any transaction. We may not be successful in managing these or any other significant risks that we encounter if we engage in a strategic transaction. If we are not successful in managing the risks, uncertainties and potential disruptions, a strategic transaction could have a negative impact on our business, results of operations or financial position.

Risks Relating to Our Dependence on Third Parties

Disagreements or disputes with our current or future collaboration partners, the amendment of any collaboration agreement or the termination of any collaboration arrangement, could cause delays in our product development and materially and adversely affect our business.

Our collaborations, including those with our oncology drug partners AstraZeneca and Eli Lilly and our in-licensing arrangement with Epizyme, and any future collaborations that we enter into may not be successful. Disagreements or disputes between parties to a collaboration arrangement regarding issues such as clinical development and commercialization, intellectual property ownership and transfer, clinical supply of drug candidates or products, cost allocation and other matters can lead to delays in the development process or commercializing the applicable drug candidate and, in some cases, termination of the collaboration arrangement. In addition, we or our partners may seek to amend the terms of one or more our collaboration agreements to adjust, among other things, the respective roles of our company and our collaboration partners as circumstances change. Our interests may not always be aligned with those of our collaboration partners, for instance, we are much smaller than our collaboration partners and because they or their affiliates may sell competing products. This may result in potential conflicts between our collaborators and us on matters that we may not be able to resolve on favorable terms or at all.

Collaborations with pharmaceutical or biotechnology companies and other third parties, including our existing agreements with AstraZeneca and Eli Lilly, are often terminable by the other party for any reason with certain advance notice. Any such termination or expiration would adversely affect us financially and could harm our business reputation. For instance, in the event one of the strategic alliances with a current collaborator is terminated, we may require significant time and resources to secure a new collaboration partner, if we are able to secure such an arrangement at all. As noted in the following risk factor, establishing new collaboration arrangements can be challenging and time-consuming. The loss of existing or future collaboration arrangements would not only delay or potentially terminate the possible development or commercialization of products we may derive from our technologies, but it may also delay or terminate our ability to test specific target candidates.

We rely on our collaborations with third parties for certain of our drug development activities, and, if we are unable to establish new collaborations when desired on commercially attractive terms or at all, we may have to alter our development and commercialization plans.

Certain of our drug development programs and the potential commercialization of certain drug candidates rely on collaborations, such as savolitinib with AstraZeneca and fruquintinib with Eli Lilly. In addition, we recently entered into collaborations with BeiGene, Inmagene and Epizyme in 2020, 2021 and 2021, respectively. In the future, we may decide to collaborate with additional pharmaceutical and biotechnology companies for the development and potential commercialization of our other drug candidates.

We face significant competition in seeking appropriate collaborators. Whether we reach a definitive agreement for collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. Those factors may include the design or results of clinical trials, the likelihood of approval by the FDA, NMPA or similar regulatory authorities outside the United States and China, the potential market for the subject drug candidate, the costs and complexities of manufacturing and delivering such drug candidate to patients, the potential of competing drugs, the existence of uncertainty with respect to our ownership of technology, which can exist if there is a challenge to such ownership without regard to the merits of the challenge and industry and market conditions generally. The collaborator may also consider alternative drug candidates or technologies for similar indications that may be available to collaborate on and whether such collaboration could be more attractive than the one with us for our drug candidate. The terms of any additional collaboration or other arrangements that we may establish may not be favorable to us.

We may also be restricted under existing collaboration agreements from entering into future agreements on certain terms with potential collaborators. Collaborations are complex and time-consuming to negotiate and document. In addition, there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators.

We may not be able to negotiate additional collaborations on a timely basis, on acceptable terms, or at all. If we are unable to do so, we may have to curtail the development of the drug candidate for which we are seeking to collaborate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to increase our expenditures to fund development or commercialization activities on our own, we may need to obtain additional capital, which may not be available to us on acceptable terms or at all. If we do not have sufficient funds, we may not be able to further develop our drug candidates or bring them to market and generate drug revenue.

The third-party vendors upon whom we rely for the supply of the active pharmaceutical ingredients used in some of our drug candidates and drug products are our sole source of supply, and the loss of any of these suppliers could significantly harm our business.

The active pharmaceutical ingredients used in some of our drug candidates and products are supplied to us from third-party vendors. Our ability to successfully develop our drug candidates, and to supply our commercial drugs in quantities sufficient to meet the market demand, depends in part on our ability to obtain the active pharmaceutical ingredients for these drugs in accordance with regulatory requirements and in sufficient quantities for commercialization and clinical testing. We currently obtain active pharmaceutical ingredients for each of our drug candidates from a limited number of suppliers. For example, a single supplier based in Shanghai manufactures and provides us active pharmaceutical ingredient for savolitinib. In the event any of our current suppliers of such active pharmaceutical ingredient cease operations for any reason, it may lead to an interruption in our production and supply of the product.

For all of our drug candidates and products, we aim to identify and qualify a manufacturer to provide such active pharmaceutical ingredient prior to submission of an NDA to the FDA and/or NMPA. We are not certain, however, that our current supply arrangements will be able to meet our demand, either because of the nature of our agreements with third party suppliers, our limited experience with third party suppliers or our relative importance as a customer to those suppliers. It may be difficult for us to assess third party vendors' ability to timely meet our demand in the future based on past performance. While our suppliers have generally met our demand on a timely basis in the past, they may subordinate our needs in the future to their other customers.

Establishing additional or replacement suppliers for the active pharmaceutical ingredients used in our drug candidates and products, if required, may not be accomplished quickly. If we are able to find a replacement supplier, such alternative arrangements would need to be qualified and may require additional regulatory approval, which could result in further delay. While we seek to maintain adequate inventory of the active pharmaceutical ingredients used in our drug candidates and products, any interruption or delay in the supply of components or materials, or our inability to obtain such active pharmaceutical ingredient from alternate sources at acceptable prices in a timely manner could impede, delay, limit or prevent our development and commercialization efforts, which could harm our business, results of operations, financial condition and prospects.

We and our collaborators rely, and expect to continue to rely, on third parties to conduct certain of our clinical trials for our drug candidates. If these third parties do not successfully carry out their contractual duties, comply with regulatory requirements or meet expected deadlines, we may not be able to obtain regulatory approval for or commercialize our drug candidates and our business could be harmed.

We do not have the ability to independently conduct large-scale clinical trials. We and our collaboration partners rely, and expect to continue to rely, on medical institutions, clinical investigators, contract laboratories and other third parties, such as CROs, to conduct or otherwise support certain clinical trials for our drug candidates. Nevertheless, we and our collaboration partners (as applicable) will be responsible for ensuring that each clinical trial is conducted in accordance with the applicable protocol, legal and regulatory requirements and scientific standards, and reliance on CROs will not relieve us of our regulatory responsibilities. For any violations of laws and regulations during the conduct of clinical trials for our drug candidates, we could be subject to warning letters or enforcement action that may include civil penalties up to and including criminal prosecution.

Although we or our collaboration partners design the clinical trials for our drug candidates, CROs conduct most of the clinical trials. As a result, many important aspects of our development programs, including their conduct and timing, are outside of our direct control. Our reliance on third parties to conduct clinical trials results in less control over the management of data developed through clinical trials than would be the case if we were relying entirely upon our own staff. Communicating with outside parties can also be challenging, potentially leading to mistakes as well as difficulties in coordinating activities. Outside parties may:

- have staffing difficulties;

- fail to comply with contractual obligations;
- experience regulatory compliance issues;
- undergo changes in priorities or become financially distressed; or
- form relationships with other entities, some of which may be our competitors.

These factors may materially and adversely affect the willingness or ability of third parties to conduct our and our collaboration partners' clinical trials and may subject us or them to unexpected cost increases that are beyond our or their control.

If any of our and our collaboration partners' relationships with these third-party CROs terminate, we or they may not be able to enter into arrangements with alternative CROs on reasonable terms or at all. If CROs do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols, regulatory requirements or for other reasons, any clinical trials such CROs are associated with may be extended, delayed or terminated, and we may not be able to obtain regulatory approval for or successfully commercialize our drug candidates. As a result, we believe that our financial results and the commercial prospects for our drug candidates in the subject indication would be harmed, our costs could increase and our ability to generate revenue could be delayed.

We, our collaboration partners or our CROs may fail to comply with the regulatory requirements pertaining to clinical trials, which could result in fines, adverse publicity and civil or criminal sanctions.

We, our collaboration partners and our CROs are required to comply with regulations for conducting, monitoring, recording and reporting the results of clinical trials to ensure that the data and results are scientifically credible and accurate, and that the trial patients are adequately informed of the potential risks of participating in clinical trials and their rights are protected. These regulations are enforced by the FDA, the NMPA and comparable foreign regulatory authorities for any drugs in clinical development. In the United States, the FDA regulates GCP through periodic inspections of clinical trial sponsors, principal investigators and trial sites. If we, our collaboration partners or our CROs fail to comply with applicable GCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or comparable foreign regulatory authorities may require additional clinical trials before approving the marketing applications for the relevant drug candidate. We cannot assure you that, upon inspection, the FDA or other applicable regulatory authority will determine that any of the future clinical trials for our drug candidates will comply with GCPs. In addition, clinical trials must be conducted with drug candidates produced under applicable manufacturing regulations. Our failure or the failure of our collaboration partners or CROs to comply with these regulations may require us or them to repeat clinical trials, which would delay the regulatory approval process and could also subject us to enforcement action. We are also required to register applicable clinical trials and post certain results of completed clinical trials on a U.S. government-sponsored database, ClinicalTrials.gov, within certain timeframes. Failure to do so can result in fines, adverse publicity and civil sanctions.

Our collaboration partners, principal investigators, CROs and other third-party contractor and consultants may engage in misconduct or other improper activities.

We are exposed to the risk that collaboration partners, principal investigators, CROs and other third-party contractor and consultants may engage in fraudulent or other illegal activity with respect to our business. Their misconduct could include intentional, reckless and/or negligent conduct or unauthorized activity that violates NMPA, FDA or other regulations, including but not limited to those laws requiring the reporting of true, complete and accurate information. In addition, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of insurance, pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. We may not be able to identify and deter such misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, our collaboration partners, principal investigators, CROs and other third-party contractor and consultants, and we and/or such other parties are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of civil, criminal and administrative penalties, damages, monetary fines, contractual damages, reputational harm, diminished profits and future earnings and disruption of our operations.

Joint ventures form an important part of our Other Ventures, and our ability to manage and develop the businesses conducted by these joint ventures depends in part on our relationship with our joint venture partners.

We are party to joint venture agreements with each of Shanghai Pharmaceuticals, Sinopharm and Hain Celestial, which together form a major portion of our Other Ventures. Under these arrangements, our joint venture partners have certain operational responsibilities and/or certain rights to exercise control or influence over operations and decision-making.

Our equity interests in these operating companies do not provide us with the unilateral ability to control actions which require shareholder approval. In addition, under the joint venture contracts for these entities, the consent of the directors nominated by our joint venture partners is required for the passing of resolutions in relation to certain matters concerning the operations of these companies. As a result, although we participate in the management and nominate the management and run the day-to-day operations of our joint ventures, Hutchison Sinopharm, Hutchison Hain Organic and Shanghai Hutchison Pharmaceuticals, we may not be able to secure the consent of our joint venture partners to pursue activities or strategic objectives that are beneficial to or that facilitate our overall business strategies. Furthermore, disagreements or disputes which arise between us and our joint venture partners may potentially require legal action to resolve and hinder the smooth operation of our Other Ventures or adversely affect our financial condition, results of operations and prospects.

We are relying on third parties to construct our new manufacturing facility in Shanghai. Any delays in completing and receiving regulatory approvals for our new Shanghai facility, or any disruptions to the third parties' performance of their obligations, could reduce or restrict our production capacity for the drug candidates used in our clinical trials or our commercial supply for any drug candidates which are approved.

We are contracting with third parties to construct our new manufacturing facility in Shanghai. The new facility is expected to be a 55,000 square meter large-scale facility with a production capacity estimated to be five times that of our existing manufacturing plant in Suzhou. The first phase will be primarily for small molecule production, with production capacity expected to be able to produce 250 million tablets and capsules per year. The second phase is expected to include expansion into large molecule production. Third parties will be responsible for the construction of the buildings, including the production lines and other production facilities within such buildings.

We cannot assure you that we will not experience any disruptions to the third parties' performance of their obligations, and there could be delays in completing and receiving regulatory approvals for our new manufacturing facility. If the construction of our manufacturing facility or our production lines encounter unanticipated delays or incur additional expenses than expected, if regulatory evaluation and/or approval of our new manufacturing facility is delayed, or if our third party contracts are terminated or adversely affected, our manufacturing capacity of our drug candidates may be limited, which would delay or limit our development and commercialization activities and our opportunities for growth. Cost overruns associated with constructing or maintaining our Shanghai facility could also require us to raise additional funds from other sources. Any disruption that impedes our ability to manufacture our drug candidates in a timely manner could materially adversely affect our business, financial condition, results of operations and prospects.

We and our joint ventures rely on our distributors for logistics and distribution services.

We and our joint ventures rely on distributors to perform certain operational activities, including invoicing, logistics and delivery of the products we and they market to the end customers. Because we and our joint ventures rely on third-party distributors, we have less control than if we handled distribution logistics directly and can be adversely impacted by the actions of our distributors. Any disruption of our distribution network, including failure to renew existing distribution agreements with desired distributors, could negatively affect our ability to effectively sell our products and materially and adversely affect the business, financial condition and results of operations of us and our joint ventures.

There is no assurance that the benefits currently enjoyed by virtue of our association with CK Hutchison will continue to be available.

Historically, we have relied on the reputation and experience of, and support provided by, our founding shareholder, a wholly owned subsidiary of CK Hutchison, to advance our joint ventures and collaborations in China and elsewhere. CK Hutchison is interested in approximately 38.46% of our total outstanding share capital as of March 1, 2022. We believe that CK Hutchison group's reputation in China has given us an advantage in negotiating collaborations and obtaining opportunities.

We also benefit from sharing certain services with the CK Hutchison group including, among others, legal and regulatory services, company secretarial support services, tax and internal audit services, participation in the CK Hutchison group's pension, medical and insurance plans, participation in the CK Hutchison group's procurement projects with third-party vendors/suppliers, other staff benefits and staff training services, company functions and activities and operation advisory and support services. We pay a management fee to an affiliate of CK Hutchison for the provision of such services. In each of the years ended December 31, 2019, 2020 and 2021, we paid a management fee of approximately $0.9 million, $1.0 million and $1.0 million respectively. In addition, we benefit from the fact that two retail chains affiliated with the CK Hutchison group, PARKnSHOP and Watsons, sell certain of our Other Ventures' products in their stores throughout Hong Kong and in other Asian countries. For the years ended December 31, 2019, 2020 and 2021, sales of our products to members of the CK Hutchison group amounted to $7.6 million, $5.5 million and $4.3 million, respectively.

Our business also depends on certain intellectual property rights licensed to us by the CK Hutchison group. See "—Risks Relating to Intellectual Property—We and our joint ventures are dependent on trademark and other intellectual property rights licensed from others. If we lose our licenses for any of our products, we or our joint ventures may not be able to continue developing such products or may be required to change the way we market such products" for more information on risks associated with such intellectual property licensed to us.

There can be no assurance the CK Hutchison group will continue to provide the same benefits or support that they have provided to our business historically. Such benefit or support may no longer be available to us, in particular, if CK Hutchison's ownership interest in our company significantly decreases in the future.

Other Risks and Risks Relating to Doing Business in China

The COVID-19 pandemic and other adverse public health developments could materially and adversely affect our business.

In December 2019, an outbreak of a novel strain of coronavirus (COVID-19) was reported and has since spread around the world. In March 2020, the World Health Organization declared the COVID-19 outbreak a global pandemic. In response to the pandemic, many governments around the world have implemented a variety of measures to reduce the spread of COVID-19, including travel restrictions and bans, instructions to residents to practice social distancing, quarantine advisories, shelter-in-place orders and required closures of non-essential businesses. The COVID-19 pandemic has negatively impacted the global economy, disrupted global supply chains, and created significant volatility and disruption of financial markets.

The continued COVID-19 pandemic and other adverse public health developments could adversely impact our operations, given the impact they may have on the manufacturing and supply chain, our sales and marketing and clinical trial operations and those of our collaboration partners, and the ability to advance our research and development activities and pursue development of any of our drug candidates, each of which could have an adverse impact on our business and our financial results. For instance, our clinical studies have encountered some limitations to patient visits for screening, treatment and clinical assessment, and our prescription drug sales teams have seen some short-term limitations on conducting normal operations. Although COVID-19 did not impact our research, our clinical studies or commercial activities in any material manner in 2021, certain regulatory inspections of our manufacturing facilities in China by the U.S. FDA have, however, been postponed due to travel restrictions. We will continue to closely work with regulators and monitor the evolving situation. The ultimate impact of the current COVID-19 pandemic, or any other adverse public health development, is highly uncertain and will depend on future developments that cannot be predicted with confidence, such as the duration of the outbreak and the effectiveness of actions to contain and treat COVID-19. Although we do not expect any material impact on our long-term activity, we do not yet know the full extent of potential delays or impacts on our business, our clinical trials, our research programs, healthcare systems or the global economy as a whole, which could have a material adverse effect on our business, financial condition and results of operations and cash flows.

We are subject to stringent privacy laws, information security policies and contractual obligations related to data privacy and security, and we may be exposed to risks related to our management of the medical data of subjects enrolled in our clinical trials and other personal or sensitive information.

We routinely receive, collect, generate, store, process, transmit and maintain medical data, treatment records and other personal details of the subjects enrolled in our clinical trials, along with other personal or sensitive information. As such, we are subject to the relevant local, state, national and international data protection and privacy laws, directives regulations, and standards that apply to the collection, use, retention, protection, disclosure, transfer and other processing of personal data in the various jurisdictions in which we operate and conduct our clinical trials. We are also subject to contractual obligations regarding the processing of personal data. Legal requirements regarding data protection and privacy continue to evolve and may result in ever-increasing public scrutiny and escalating levels of enforcement and sanctions and increased costs of compliance. Failure to comply with any of these laws could result in enforcement action against us, including investigations, civil and criminal enforcement action, fines, imprisonment of company officers and public censure, claims for damages by customers and other affected individuals, damage to our reputation and loss of goodwill, any of which could have a material adverse effect on our business, financial condition, results of operations or prospects.

Data protection and privacy laws and regulations generally require clinical trial sponsors and operators and their personnel to protect the privacy of their enrolled subjects and prohibit unauthorized disclosure of personal information. We have established procedures to protect the confidentiality of medical records and personal data of subjects enrolled in our clinical trials. Access to clinical trial data has been strictly limited to authorized personnel only according to the relevant rules and regulations. External parties involved in clinical trials are also required to comply with all relevant data protection and confidentiality requirements. Data are to be used only for the intended use, as agreed by the patients and consistent with the patients' informed consent form. While we have adopted security policies and measures to protect our proprietary data and patients' privacy, personal patient information could be subject to leaks caused by hacking activities, human error, employee misconduct or negligence or system breakdown. We also cooperate with third parties including collaboration partners, principal investigators, hospitals, CROs and other third-party contractor and consultants for our clinical trials and operations. Any leakage or abuse of patient data by our third-party partners may be perceived by the patients as a result of our failure. Furthermore, any change in applicable laws and regulations could affect our ability to use medical data and subject us to liability for the use of such data for previously permitted purposes. Any failure or perceived failure by us to prevent information security breaches or to comply with privacy policies or privacy-related legal obligations, or any compromise of information security that results in the unauthorized release or transfer of personally identifiable information or other patient data, could cause our customers to lose trust in us and could expose us to legal claims.

There are numerous U.S. federal and state laws and regulations relating to the privacy and security of personal information. In particular, regulations promulgated pursuant to the Health Insurance Portability and Accountability Act of 1996, or HIPAA, as amended, establish privacy and security standards that limit the use and disclosure of individually identifiable health information (known as "protected health information"), require the implementation of administrative, physical and technological safeguards to protect the privacy of protected health information and ensure the confidentiality, integrity and availability of electronic protected health information, and create breach reporting obligations in cases of certain unauthorized uses or disclosures. Determining whether protected health information has been handled in compliance with applicable privacy standards and our contractual obligations can require complex factual and statistical analyses and may be subject to changing interpretations. Although we take measures to protect sensitive data from unauthorized access, use or disclosure, and whenever possible contractually require third-party partners to do the same, our information technology and infrastructure and those of our third-party partners may be vulnerable to attacks by hackers or viruses or breached due to employee error, malfeasance or other malicious or inadvertent disruptions. Any such breach or interruption could compromise those networks and the information stored there could be accessed by unauthorized parties, manipulated, publicly disclosed, lost or stolen. Any such access, breach, or other loss of information relating to our information technology and infrastructure or that of our third-party partners may subject us to liability including legal claims or proceedings and liability under federal or state laws that protect the privacy of personal information, such as HIPAA, the Health Information Technology for Economic and Clinical Health ("HITECH") Act, and regulatory penalties. If we or a third-party partner suffers a breach, we may need to send breach notifications to affected individuals and, if 500 or more individuals were affected, also notify the Secretary of the Department of Health and Human Services. Breach notifications may separately be required under applicable state breach notification laws, which may include notifications to affected individuals, and for extensive breaches, to the media, credit reporting agencies, and/or State Attorneys General. Such notices could harm our reputation and our ability to compete and could potentially attract enforcement scrutiny from governmental authorities.

Regulatory authorities in China have implemented and are considering a number of legislative and regulatory proposals concerning data protection. The PRC Cyber Security Law, which became effective in June 2017, created China's first national-level data protection for "network operators," which may include all organizations in China that provide services over the internet or another information network. The PRC Data Security Law, which took effect in September 2021, provides for a security review procedure for the data activities that may affect national security. The PRC Personal Information Protection Law, which took effect from November 2021, provides the circumstances under which a personal information processor could process personal information and the requirements for such circumstances. The PRC Personal Information Protection Law clarifies the scope of application, the definition of personal information and sensitive personal information, the legal basis of personal information processing and the basic requirements of notice and consent. The Measures for Cybersecurity Review, which took effect on February 15, 2022, provides that critical information infrastructure operators that purchase network products and services and online platform operators engaging in data processing activities that affect or may affect national security shall be subject to the cybersecurity review. The Measures for Cybersecurity Review further elaborates the factors to be considered when assessing the national security risks of the relevant activities, including, among others: (i) the risk of core data, important data, or a large amount of personal information being stolen, leaked, destroyed, and illegally used or transferred out of the country, and (ii) the risk of critical information infrastructure, core data, important data, or a large amount of personal information being affected, controlled, or maliciously used by foreign governments after listing. Drafts of some of these measures have now been published, including the Data Security Management Measures (Draft for Comments) published in May 2019, the Measures on Security Assessment for Individual Information Cross-border Transfer (Draft for Comments) in June 2019, and the Measures on Security Assessment of Cross-border Data Transfer (Draft for Comments) in October 2021, which may, upon enactment, require security review before transferring human health-related data out of China. In addition, certain industry-specific laws and regulations affect the collection and transfer of personal data in China. For example, the Regulations of the PRC on the Administration of Human Genetic Resources, or HGR Regulations, which became effective and implemented on July 1, 2019, stipulates that use of Chinese human genetic resources, or HGR, for the purposes of carrying out collaborative international scientific research shall be approved by the administrative department of science and technology under the State Council, with which the two parties shall file the type, quantity and usage of the human genetic resources, to be used before clinical trials. However, no approval is required for "international collaboration in clinical trials" that do not involve the export of HGR materials; the two parties to the international collaboration shall file the type, quantity and usage of the HGR to be used with the administrative department of science and technology under the State Council before clinical trials. The PRC Biosecurity Law, which took effect on April 15, 2021, stipulates that foreign organizations and individuals, as well as institutions they establish or are the actual controllers of, must not collect or preserve HGR within the territory of China and must not provide China's HGR to overseas. It is possible that these laws may be interpreted and applied in a manner that is inconsistent with our practices, potentially resulting in confiscation of HGR samples and associated data and administrative fines, penalties and negative publicity.

Our clinical trial programs may implicate European data privacy laws, including the General Data Protection Regulation, or the GDPR, and local laws further implementing or supplementing the GDPR. The GDPR implements more stringent operational requirements for processors and controllers of personal data including requirements for such companies to be able to ensure and be able to demonstrate compliance with the GDPR. If our or our third-party partners' privacy or data security measures fail to comply with the GDPR requirements, we may be subject to litigation, regulatory investigations, enforcement notices requiring us to change the way we use personal data and/or fines of up to 20 million Euros or up to 4% of the total worldwide annual turnover of the preceding financial year, whichever is higher. In addition to statutory enforcement, non-compliance can lead to compensation claims by affected individuals, negative publicity and a potential loss of business. We are also subject to European laws on personal data export, as we may transfer personal data from the E.U. (or U.K.) to other jurisdictions which are not considered by the European Commission to offer "adequate" protection of personal data (such as Hong Kong or the United States). Following the Schrems II decision of the European Court of Justice in 2020, there has been intensified focus on exports of personal data which do not meet the high standards of protection expected by the E.U. Certain supervisory authorities in the E.U. have now begun to take enforcement action in this area, ordering restrictions on certain transfers of personal data to third countries such as the United States. These changes could require us to make operational changes and could increase costs and may lead to governmental enforcement actions, litigation, fines and penalties or adverse publicity that could have an adverse effect on our business.

Complying with all applicable laws, regulations, standards and obligations relating to data privacy, security, and transfers may cause us to incur substantial operational costs or require us to modify our data processing practices and processes. Non-compliance could result in proceedings against us by data protection authorities, governmental entities or others, including class action privacy litigation in certain jurisdictions, which would subject us to significant fines, penalties, judgments and negative publicity. In addition, if our practices are not consistent or viewed as not consistent with legal and regulatory requirements, including changes in laws, regulations and standards or new interpretations or applications of existing laws, regulations and standards, we may become subject to audits, inquiries, whistleblower complaints, adverse media coverage, investigations, loss of export privileges, severe criminal or civil sanctions and reputational damage. Any of the foregoing could have a material adverse effect on our competitive position, business, financial conditions, results of operations and prospects.

Product liability claims or lawsuits could cause us, our collaborators or our joint ventures to incur substantial liabilities.

We, our collaborators and our joint ventures face an inherent risk of product liability exposure related to the use of our drug candidates in clinical trials, sales of our or our joint ventures' products or the products we or they license from third parties. If we, our collaborators and our joint ventures cannot successfully defend against claims that the use of such drug candidates in our clinical trials or any products sold by us or our joint ventures, including fruquintinib, surufatinib, savolitinib and/or any of our drug candidates which receive regulatory approval, caused injuries, we, our collaborators and our joint ventures could incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for our and our joint ventures' products;
- significant negative media attention and reputational damage;
- withdrawal of clinical trial participants;
- significant costs to defend the related litigation;
- substantial monetary awards to trial participants or patients;
- loss of revenue; and
- the inability to commercialize any drug candidates that we may develop.

Our principal insurance policies cover product liability for fruquintinib, surufatinib, savolitinib, certain prescription drugs and health supplements, property loss due to accidents or natural disasters and adverse events in clinical trials. Existing PRC laws and regulations do not require us, our collaborators or our joint ventures to have, nor do we or they, maintain liability insurance to cover product liability claims except with respect to fruquintinib, surufatinib, savolitinib, certain prescription drugs and health supplements, and liability with respect to our oncology and immunology clinical trials. Any litigation might, result in substantial costs and diversion of resources. While we maintain liability insurance for clinical trials and products, this insurance may not fully cover our potential liabilities. Inability to obtain sufficient insurance coverage at an acceptable cost or otherwise to protect against potential product liability claims could prevent or inhibit the commercialization of products that we or our collaborators develop.

We and our joint ventures may be exposed to liabilities under the U.S. Foreign Corrupt Practices Act, or FCPA, U.S. healthcare fraud and abuse laws, the Bribery Act 2010 of the United Kingdom, or U.K. Bribery Act, and Chinese anti-corruption laws, and any determination that we have violated these laws could have a material adverse effect on our business or our reputation.

In the day-to-day conduct of our business, we and our joint ventures are in frequent contact with persons who may be considered government officials under applicable anti-corruption, anti-bribery and anti-kickback laws, which include doctors at public hospitals in China and elsewhere. Therefore, we and our joint ventures are subject to risk of violations under the FCPA, the U.K. Bribery Act, and other laws in the countries where we do business. We and our joint ventures have operations in China, agreements with third parties in China, and we and our joint ventures make most of our sales in China. The PRC laws and regulations also strictly prohibit bribery of government officials. Our and our joint ventures' activities in China create the risk of unauthorized payments or offers of payments by the directors, employees, representatives, distributors, consultants or agents of our company or our joint ventures, even though they may not always be subject to our control. It is our policy to implement safeguards to discourage these practices by our and our joint ventures' employees and third parties. We have implemented and adopted policies designed by the R&D-based Pharmaceutical Association Committee, an industry association representing approximately 40 global biopharmaceutical companies, to ensure compliance by us and our joint ventures and our and their directors, officers, employees, representatives, distributors, consultants and agents with the anti-corruption laws and regulations. We cannot assure you, however, that our existing safeguards are sufficient or that our or our joint ventures' directors, officers, employees, representatives, distributors, consultants and agents have not engaged and will not engage in conduct for which we may be held responsible, nor can we assure you that our business partners have not engaged and will not engage in conduct that could materially affect their ability to perform their contractual obligations to us or even result in our being held liable for such conduct. Violations of the FCPA, the U.K. Bribery Act or Chinese anti-corruption laws may result in severe criminal or civil sanctions, and we may be subject to other liabilities, which could have a material adverse effect on our business, reputation, financial condition, cash flows and results of operations.

If we begin to commercialize products in the United States and secure governmental reimbursement of our products, we also will be subject to the risk of violating U.S. federal and state healthcare fraud and abuse laws, including the Anti-Kickback Statute and the False Claims Act. These laws broadly prohibit providing or receiving kickbacks in connection with government-reimbursed healthcare items or services, as well submitting or causing the submission of false or fraudulent claims to government healthcare programs. Violations of these laws may result in severe criminal or civil sanctions and other administrative sanctions, which could have a material adverse effect on our business, reputation, financial condition, cash flows and results of operations.

Ensuring that our and our joint ventures' future business arrangements with third parties comply with applicable laws could also involve substantial costs. It is possible that governmental authorities will conclude that our business practices do not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our or our joint ventures' operations were found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, disgorgement, individual imprisonment and exclusion from government funded healthcare programs, any of which could substantially disrupt our operations. If the physicians, hospitals or other providers or entities with whom we and our joint ventures do business are found not to be in compliance with applicable laws, they may also be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

If we or our joint ventures fail to comply with environmental, health and safety laws and regulations, we or they could become subject to fines or penalties or incur costs that could have a material adverse effect on the success of our business.

We and our joint ventures are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemical materials. Our operations also produce hazardous waste products. We and our joint ventures are therefore subject to PRC laws and regulations concerning the discharge of waste water, gaseous waste and solid waste during our manufacturing processes. We and our joint ventures are required to establish and maintain facilities to dispose of waste and report the volume of waste to the relevant government authorities, which conduct scheduled or unscheduled inspections of our facilities and treatment of such discharge. We and our joint ventures may not at all times comply fully with environmental regulations. Any violation of these regulations may result in substantial fines, criminal sanctions, revocations of operating permits, shutdown of our facilities and obligation to take corrective measures. We and our joint ventures generally contract with third parties for the disposal of these materials and waste. We and our joint ventures cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from the use of hazardous materials, we and/or our joint ventures could be held liable for any resulting damages, and any liability could exceed our resources. We and/or our joint ventures also could incur significant costs associated with civil or criminal fines and penalties.

Although we and our joint ventures maintain workers' compensation insurance to cover costs and expenses incurred due to on-the-job injuries to our employees and third-party liability insurance for injuries caused by unexpected seepage, pollution or contamination, this insurance may not provide adequate coverage against potential liabilities. Furthermore, the PRC government may take steps towards the adoption of more stringent environmental regulations. Due to the possibility of unanticipated regulatory or other developments, the amount and timing of future environmental expenditures may vary substantially from those currently anticipated. If there is any unanticipated change in the environmental regulations, we and our joint ventures may need to incur substantial capital expenditures to install, replace, upgrade or supplement our equipment or make operational changes to limit any adverse impact or potential adverse impact on the environment in order to comply with new environmental protection laws and regulations. If such costs become prohibitively expensive, we may be forced to cease certain aspects of our or our joint ventures' business operations.

We rely significantly on information technology and any failure, inadequacy, interruption or security lapse of that technology, including any cybersecurity incidents, could harm our ability to operate our business effectively.

We are heavily dependent on critical, complex and interdependent information technology systems, including internet-based systems, to support our business processes. Our information technology system security is continuously reviewed, maintained and upgraded in response to possible security breach incidents. Despite the implementation of these measures, our information technology systems and those of third parties with which we contract are vulnerable to damage from external or internal security incidents, breakdowns, malicious intrusions, cybercrimes, including State-sponsored cybercrimes, malware, misplaced or lost data, programming or human errors or other similar events. System failures, accidents or security breaches could cause interruptions in our operations and could result in inappropriately accessed, tampered with, modified or stolen scientific data or a material disruption of our clinical activities and business operations, in addition to possibly requiring substantial expenditures of resources to remedy. Such event could significantly harm our Oncology/Immunology operations, including resulting in the loss of clinical trial data which could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. Such events could also lead to the loss of important information such as trade secrets or other intellectual property and could accelerate the development or manufacturing of competing products by third parties. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and our research and development programs and the development of our drug candidates could be delayed.

We have granted, and may continue to grant, options, long-term incentive scheme ("LTIP") awards and other types of awards under our Option Schemes, our LTIP and the HUTCHMED Holdings Option Schemes, or collectively the Schemes, which may result in increased share-based compensation expenses and give rise to potential employment related disputes.

We and HUTCHMED Holdings have adopted the Schemes for the purpose of granting share-based compensation awards to certain management, Directors, employees and other eligible grantees as a means to retain, incentivize, reward, remunerate, compensate and/or provide benefits to eligible grantees. We recognized share-based compensation expenses of $11.6 million, $19.6 million and $42.0 million for the years ended December 31, 2019, 2020 and 2021, respectively, in our consolidated financial statements in accordance with U.S. GAAP.

We believe the granting of share-based compensation is of significant importance to our ability to attract and retain key personnel and employees, and we will continue to grant share-based compensation in the future. As a result, our expenses associated with share-based compensation may increase, which may have an adverse effect on our results of operations. We may re-evaluate the vesting schedules, exercise price or other key terms applicable to the grants under our currently effective Schemes from time to time, which may result in a substantial change in our share-based compensation expenses in the reporting periods. In addition, we could in the future become involved in disputes or legal proceedings with our employees or former employees on employment related matters (including disputes on the entitlement of options, awards and other share-based compensation or in connection with the employees' incentive or compensation arrangements). If such disputes or legal proceedings arise, there can be no assurance that we will prevail in them, and in any event defending against these disputes or legal proceedings could cause us to incur legal and other costs. Any adverse outcome of these disputes or legal proceedings could have a material adverse effect on our reputation, business and results of operations.

For more information on the Schemes, please refer to Item 6.B. "Directors, Senior Management and Employees," "Compensation," "Equity Compensation Schemes and Other Benefit Plans."

The PRC's economic, political and social conditions, as well as governmental policies, could affect the business environment and financial markets in China, our ability to operate our business, our liquidity and our access to capital.

Substantially all of our and our joint ventures' business operations are conducted in China. Accordingly, our results of operations, financial condition and prospects are subject to economic, political and legal developments in China to a significant degree. China's economy differs from the economies of developed countries in many respects, including with respect to the amount of government involvement, level of development, growth rate, control of foreign exchange and allocation of resources. While the PRC economy has experienced significant growth in the past 30 years, growth has been uneven across different regions and among various economic sectors of China. The PRC government has implemented various measures to encourage economic development and guide the allocation of resources. Some of these measures benefit the overall PRC economy, but may have a negative effect on us or our joint ventures. For example, our financial condition and results of operations may be adversely affected by government control over capital investments or changes in tax regulations that are applicable to us or our joint ventures. More generally, if the business environment in China deteriorates from the perspective of domestic or international investors, our or our joint ventures' business in China may also be adversely affected.

Uncertainties with respect to the PRC legal system and changes in laws, regulations and policies in China could materially and adversely affect us.

We conduct a substantial portion of our business through our subsidiaries and joint ventures in China. PRC laws and regulations govern our and their operations in China. Our subsidiaries and joint ventures are generally subject to laws and regulations applicable to foreign investments in China, which may not sufficiently cover all of the aspects of our or their economic activities in China. In particular, some laws, particularly with respect to drug price reimbursement, are relatively new, and because of the limited volume of published judicial decisions and their non-binding nature, the interpretation and enforcement of these laws and regulations are uncertain. Furthermore, recent regulatory reform in the China pharmaceutical industry will limit the number of distributors allowed between a manufacturer and each hospital to one, which may limit the rate of sales growth of Hutchison Sinopharm in future periods. In addition, the implementation of laws and regulations may be in part based on government policies and internal rules that are subject to the interpretation and discretion of different government agencies (some of which are not published on a timely basis or at all) that may have a retroactive effect. As a result, we may not be aware of our, our collaboration partners' or our joint ventures' violation of these policies and rules until sometime after the violation. In addition, any litigation in China, regardless of outcome, may be protracted and result in substantial costs and diversion of resources and management attention.

For further information regarding government regulation in China and other jurisdictions, see Item 4.B. "Business Overview—Regulation—Government Regulation of Pharmaceutical Product Development and Approval—PRC Regulation of Pharmaceutical Product Development and Approval," "Business Overview—Regulation—Coverage and Reimbursement—PRC Coverage and Reimbursement" and "Business Overview—Regulation—Other Healthcare Laws—Other PRC Healthcare Laws."

Restrictions on currency exchange may limit our ability to receive and use our revenue effectively.

Substantially all of our revenue is denominated in renminbi, which currently is not a freely convertible currency. A portion of our revenue may be converted into other currencies to meet our foreign currency obligations, including, among others, payments of dividends declared, if any, in respect of our ordinary shares or ADSs. Under China's existing foreign exchange regulations, our subsidiaries and joint ventures are able to pay dividends in foreign currencies or convert renminbi into other currencies for use in operations without prior approval from the PRC State Administration of Foreign Exchange, or the SAFE, by complying with certain procedural requirements. However, we cannot assure you that the PRC government will not take future measures to restrict access to foreign currencies for current account transactions.

Our PRC subsidiaries' and joint ventures' ability to obtain foreign exchange is subject to significant foreign exchange controls and, in the case of amounts under the capital account, requires the approval of and/or registration with PRC government authorities, including the SAFE. In particular, if we finance our PRC subsidiaries or joint ventures by means of foreign debt from us or other foreign lenders, the amount is not allowed to exceed either the cross-border financing risk weighted balance calculated based on a formula by the PBOC or the difference between the amount of total investment and the amount of the registered capital. Further, such loans must be filed with and registered with the SAFE or their local branches and the National Development and Reform Commission (if applicable). If we finance our PRC subsidiaries or joint ventures by means of additional capital contributions, the amount of these capital contributions must first be filed with the relevant government approval authority. These limitations could affect the ability of our PRC subsidiaries and joint ventures to obtain foreign exchange through debt or equity financing.

Our business benefits from certain PRC government tax incentives. Any changes to, or our PRC subsidiaries/joint ventures failing to continuously meet the criteria for these incentives could have a material adverse effect on our operating results by significantly increasing our tax expenses.

Certain of our PRC subsidiaries and a joint venture have been granted High and New Technology Enterprise, or HNTE, status by the relevant PRC authorities. This status allows the relevant enterprise to enjoy a reduced Enterprise Income Tax, or EIT, rate at 15% on its taxable profits. For the duration of its HNTE grant, the relevant PRC enterprise must continue to meet the relevant HNTE criteria or else the 25% standard EIT rate will be applied from the beginning of the calendar year when the enterprise fails to meet the relevant criteria. If the rules for such incentives are amended, it would be uncertain whether any criteria as amended can be met, in which case the higher EIT rate may apply resulting in increased tax burden which will impact our business, financial condition, results of operations and growth prospects.

We may be treated as a resident enterprise for PRC Tax purposes under China's Enterprise Income Tax Law and Implementation Rules, or the EIT Law, and our global income may therefore be subject to PRC income tax.

China's EIT Law defines the term "de facto management bodies" as "bodies that substantially carry out comprehensive management and control on the business operation, employees, accounts and assets of enterprises." Under the EIT Law, an enterprise incorporated outside of China whose "de facto management bodies" are located in China is considered a "resident enterprise" and will be subject to a uniform 25% EIT rate on its global income. On April 22, 2009, China's State Administration of Taxation, or the SAT, in the Notice Regarding the Determination of Chinese-Controlled Offshore-Incorporated Enterprises as PRC Tax Resident Enterprises on the Basis of De Facto Management Bodies, or Circular 82, further specified certain criteria for the determination of what constitutes "de facto management bodies." If all of these criteria are met, the relevant foreign enterprise may be regarded to have its "de facto management bodies" located in China and therefore be considered a resident enterprise in China. These criteria include: (i) the enterprise's day-to-day operational management is primarily exercised in China; decisions relating to the enterprise's financial and human resource matters are made or subject to approval by organizations or personnel in China; (ii) the enterprise's primary assets, accounting books and records, company seals, and board and shareholders' meeting minutes are located or maintained in China; and (iii) 50% or more of voting board members or senior executives of the enterprise habitually reside in China. Although Circular 82 only applies to foreign enterprises that are majority-owned and controlled by PRC enterprises, not those owned and controlled by foreign enterprises or individuals, the determining criteria set forth in Circular 82 may be adopted by the PRC tax authorities as the test for determining whether the enterprises are PRC tax residents, regardless of whether they are majority-owned and controlled by PRC enterprises.

Except for our PRC subsidiaries and joint ventures incorporated in China, we believe that none of our entities incorporated outside of China is a PRC resident enterprise for PRC tax purposes. However, the tax resident status of an enterprise is subject to determination by the PRC tax authorities, and uncertainties remain with respect to the interpretation of the term "de facto management body."

If we are treated as a PRC tax resident, dividends distributed by us to our non-PRC shareholders and ADS holders or any gains realized by non-PRC shareholders and ADS holders from the transfer of our shares or ADSs may be subject to PRC tax.

Under the EIT Law, dividends payable by a PRC enterprise to its foreign investor who is a non-PRC resident enterprise, as well as gains on transfers of shares of a PRC enterprise by such a foreign investor will generally be subject to a 10% withholding tax, unless such non-PRC resident enterprise's jurisdiction of tax residency has an applicable tax treaty with the PRC that provides for an exemption or a reduced rate of withholding tax.

If the PRC tax authorities determine that we should be considered a PRC resident enterprise for EIT purposes, any dividends payable by us to our non-PRC resident enterprise shareholders or ADS holders, as well as gains realized by such investors from the transfer of our shares or ADSs may be subject to a 10% withholding tax, unless an exemption or reduced rate is available under an applicable tax treaty. Furthermore, if we are considered a PRC resident enterprise for EIT purposes, it is unclear whether our non-PRC individual shareholders (including our ADS holders) would be subject to any PRC tax on dividends or gains obtained by such non-PRC individual shareholders. If any PRC tax were to apply to dividends or gains realized by non-PRC individuals, it would generally apply at a rate of up to 20% unless a reduced rate is available under an applicable tax treaty. If dividends payable to our non-PRC resident shareholders, or gains from the transfer of our shares or ADSs by such shareholders are subject to PRC tax, the value of your investment in our shares or ADSs may decline significantly.

There is uncertainty regarding the PRC withholding tax rate that will be applied to distributions from our PRC subsidiaries and joint ventures to their respective Hong Kong immediate holding companies, which could have a negative impact on our business.

The EIT Law provides that a withholding tax at the rate of 10% is applicable to dividends payable by a PRC resident enterprise to investors who are "non-resident enterprises" (i.e., that do not have an establishment or place of business in the PRC or that have such establishment or place of business but the relevant dividend is not effectively connected with the establishment or place of business). However, pursuant to Article 10.2(1), or the Article, of the Arrangement between the Mainland of China and the Hong Kong Special Administrative Region for the Avoidance of Double Taxation and the Prevention of Fiscal Evasion with respect to Taxes on Income, or the Arrangement, withholding tax at a reduced rate of 5% may be applicable to dividends payable by PRC resident enterprises to beneficial owners of the dividends that are Hong Kong tax residents if certain requirements are met. There is uncertainty regarding whether the PRC tax authorities will consider us to be eligible to the reduced tax rate. If the Article is deemed not to apply to dividends payable by our PRC subsidiaries and joint ventures to their respective Hong Kong immediate holding companies that are ultimately owned by us, the withholding tax rate applicable to us will be the statutory rate of 10% instead of 5% which may potentially impact our business, financial condition, results of operations and growth prospects.

We may be treated as a resident enterprise for U.K. corporate tax purposes, and our global income may therefore be subject to U.K. corporation tax.

U.K. resident companies are taxable in the United Kingdom on their worldwide profits. A company incorporated outside of the United Kingdom would be regarded as a resident if its central management and control resides in the United Kingdom. The place of central management and control generally means the place where the high-level strategic decisions of a company are made.

We are an investment holding company incorporated in the Cayman Islands and are admitted to trading on the AIM market of the London Stock Exchange or the AIM market. Our central management and control resides in Hong Kong, and therefore we believe that we are not a U.K. resident for corporate tax purposes. However, the tax resident status of a non-resident entity could be challenged by the U.K. tax authorities.

If the U.K. tax authorities determine that we are a U.K. tax resident, our profits will be subject to U.K. Corporation Tax rate at 19%, subject to the potential availability of certain exemptions related to dividend income and capital gains. This may have a material adverse effect on our financial condition and results of operations.

Any failure to comply with PRC regulations regarding our employee equity incentive plans may subject the PRC plan participants or us to fines and other legal or administrative sanctions, which could adversely affect our business, financial condition and results of operations.

In February 2012, the SAFE promulgated the Notices on Issues Concerning the Foreign Exchange Administration for Domestic Individuals Participating in Stock Incentive Plans of Overseas Publicly Listed Companies. Based on this regulation, PRC residents who are granted shares or share options by a company listed on an overseas stock market under its employee share option or share incentive plan are required to register with the SAFE or its local counterparts by following certain procedures. We and our employees who are PRC residents and individual beneficial owners who have been granted shares or share options have been subject to these rules due to our listing on the AIM market, Nasdaq and SEHK. We have registered the option schemes and the share incentive plan and will continue to assist our employees to register their share options or shares. However, any failure of our PRC individual beneficial owners and holders of share options or shares to comply with the SAFE registration requirements in the future may subject them to fines and legal sanctions and may, in rare instances, limit the ability of our PRC subsidiaries to distribute dividends to us.

In addition, the SAT has issued circulars concerning employee share options or restricted shares. Under these circulars, employees working in the PRC who exercise share options, or whose restricted shares vest, will be subject to PRC individual income tax. The PRC subsidiaries of an overseas listed company have obligations to file documents related to employee share options or restricted shares with relevant tax authorities and to withhold individual income tax of those employees related to their share options or restricted shares. Although the PRC subsidiaries currently withhold individual income tax from the PRC employees in connection with their exercise of share options, if they fail to report and pay the tax withheld according to relevant laws, rules and regulations, the PRC subsidiaries may face sanctions imposed by the tax authorities or other PRC government authorities.

We may be involved in litigation, legal disputes, claims or administrative proceedings which could be costly and time-consuming to resolve.

We may become subject, from time to time, to legal proceedings and claims that arise in the ordinary course of business or pursuant to governmental or regulatory enforcement activity. Any litigation or proceeding to which we become a party might result in substantial costs and divert management's attention and resources. Furthermore, any litigation, legal disputes, claims or administrative proceedings which are initially not of material importance may escalate and become important to us due to a variety of factors, such as changes in the facts and circumstances of the cases, the likelihood of loss, the monetary amount at stake and the parties involved. Our insurance might not cover claims brought against us, provide sufficient payments to financially cover all of the costs to resolve such claims or continue to be available on terms acceptable to us.

The political relationships between China and other countries may affect our business operations.

We conduct our business primarily through our subsidiaries and joint ventures in China, but we also have significant clinical operations in the United States and other foreign jurisdictions. As a result, China's political relationships with the United States and other jurisdictions may affect our business operations. There can be no assurance that our clinical trial participants or customers will not alter their perception of us or their preferences as a result of adverse changes to the state of political relationships between China and the relevant foreign jurisdictions. Any tensions and political concerns between China and the relevant foreign jurisdictions may adversely affect our business, financial condition, results of operations, cash flows and prospects.

Risks Relating to Intellectual Property

If we, our joint ventures or our collaboration partners are unable to protect our or their products and drug candidates through intellectual property rights, our competitors may compete directly against us or them.

Our success depends, in part, on our, our joint venture partners' and our collaboration partners' ability to protect our and our joint ventures' and our collaboration partners' products and drug candidates from competition by establishing, maintaining and enforcing our or their intellectual property rights. We, our joint ventures and our collaboration partners seek to protect the products and technology that we and they consider commercially important by filing PRC and international patent applications, relying on trade secrets or pharmaceutical regulatory protection or employing a combination of these methods. As of December 31, 2021, we had 270 issued patents, including 21 Chinese patents, 24 U.S. patents and 14 European patents, 184 patent applications pending in the above major market jurisdictions, and 13 pending Patent Cooperation Treaty, or PCT, patent applications relating to the drug candidates of our Oncology/Immunology operations. For more details, see Item 4.B. "Business Overview—Patents and Other Intellectual Property." Patents may become invalid and patent applications may not be granted for a number of reasons, including known or unknown prior art, deficiencies in the patent application or the lack of originality of the technology. In addition, the PRC and the United States have adopted the "first-to-file" system under which whoever first files an invention patent application will be awarded the patent. Under the first-to-file system, third parties may be granted a patent relating to a technology which we invented. Furthermore, the terms of patents are finite. The patents we hold and patents to be issued from our currently pending patent applications generally have a twenty-year protection period starting from the date of application.

We, our joint ventures and/or our collaboration partners may become involved in patent litigation against third parties to enforce our or their patent rights, to invalidate patents held by such third parties, or to defend against such claims. A court may refuse to stop the other party from using the technology at issue on the grounds that our or our joint ventures' patents do not cover the third-party technology in question. Further, such third parties could counterclaim that we or our joint ventures infringe their intellectual property or that a patent we, our joint ventures or our collaboration partners have asserted against them is invalid or unenforceable. In patent litigation, defendant counterclaims challenging the validity, enforceability or scope of asserted patents are commonplace. In addition, third parties may initiate legal proceedings against us or our intellectual property to assert such challenges to our intellectual property rights.

The outcome of any such proceeding is generally unpredictable. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness or non-enablement. Patents may be unenforceable if someone connected with prosecution of the patent withheld relevant information or made a misleading statement during prosecution. It is possible that prior art of which we, our joint ventures or our collaboration partners and the patent examiner were unaware during prosecution exists, which could render our or their patents invalid. Moreover, it is also possible that prior art may exist that we, our joint ventures or our collaboration partners are aware of but do not believe is relevant to our or their current or future patents, but that could nevertheless be determined to render our patents invalid. The cost to us or our joint ventures of any patent litigation or similar proceeding could be substantial, and it may consume significant management time. We and our joint ventures do not maintain insurance to cover intellectual property infringement.

An adverse result in any litigation proceeding could put one or more of our or our joint ventures' patents at risk of being invalidated or interpreted narrowly. If a defendant were to prevail on a legal assertion of invalidity or unenforceability of our patents covering one of our or our joint ventures' products or our drug candidates, we could lose at least part, and perhaps all, of the patent protection covering such product or drug candidate. Competing drugs may also be sold in other countries in which our or our joint ventures' patent coverage might not exist or be as strong. If we lose a foreign patent lawsuit, alleging our or our joint ventures' infringement of a competitor's patents, we could be prevented from marketing our drugs in one or more foreign countries. Any of these outcomes would have a materially adverse effect on our business.

Intellectual property and confidentiality legal regimes in China may not afford protection to the same extent as in the United States or other countries. Implementation and enforcement of PRC intellectual property laws may be deficient and ineffective. Policing unauthorized use of proprietary technology is difficult and expensive, and we or our joint ventures may need to resort to litigation to enforce or defend patents issued to us or them or to determine the enforceability, scope and validity of our proprietary rights or those of others. The experience and capabilities of PRC courts in handling intellectual property litigation varies, and outcomes are unpredictable. Further, such litigation may require a significant expenditure of cash and may divert management's attention from our or our joint ventures' operations, which could harm our business, financial condition and results of operations. An adverse determination in any such litigation could materially impair our or our joint ventures' intellectual property rights and may harm our business, prospects and reputation.

Developments in patent law could have a negative impact on our business.

From time to time, authorities in the United States, China and other government authorities may change the standards of patentability, and any such changes could have a negative impact on our business.

For example, in the United States, the Leahy-Smith America Invents Act, or the America Invents Act, which was signed into law in 2011, includes a number of significant changes to U.S. patent law. These changes include a transition from a "first-to-invent" system to a "first-to-file" system, changes to the way issued patents are challenged, and changes to the way patent applications are disputed during the examination process. As a result of these changes, patent law in the United States may favor larger and more established companies that have greater resources to devote to patent application filing and prosecution. The U.S. Patent and Trademark Office, or USPTO, has developed regulations and procedures to govern the full implementation of the America Invents Act, and many of the substantive changes to patent law associated with the America Invents Act, and, in particular, the first-to-file provisions became effective on March 16, 2013. Substantive changes to patent law associated with the America Invents Act, including continually developing case law, may affect our ability to obtain patents, and if obtained, to enforce or defend them. Accordingly, it is not clear what, if any, impact the America Invents Act will have on the cost of prosecuting our or our joint ventures' patent applications and our or their ability to obtain patents based on our or our joint ventures' discoveries and to enforce or defend any patents that may issue from our or their patent applications, all of which could have a material adverse effect on our business.

If we are unable to maintain the confidentiality of our and our joint ventures' trade secrets, the business and competitive position of ourselves and our joint ventures may be harmed.

In addition to the protection afforded by patents and the PRC's State Secret certification, we and our joint ventures rely upon unpatented trade secret protection, unpatented know-how and continuing technological innovation to develop and maintain our competitive position. We seek to protect our and our joint ventures' proprietary technology and processes, in part, by entering into confidentiality agreements with our and their collaborators, scientific advisors, employees and consultants, and invention assignment agreements with our and their consultants and employees. We and our joint ventures may not be able to prevent the unauthorized disclosure or use of our or their technical know-how or other trade secrets by the parties to these agreements, however, despite the existence generally of confidentiality agreements and other contractual restrictions. If any of the collaborators, scientific advisors, employees and consultants who are parties to these agreements breaches or violates the terms of any of these agreements, we and our joint ventures may not have adequate remedies for any such breach or violation, and we could lose our trade secrets as a result. Enforcing a claim that a third-party illegally obtained and is using our or our joint ventures' trade secrets, like patent litigation, is expensive and time consuming, and the outcome is unpredictable. In addition, courts in China and other jurisdictions outside the United States are sometimes less prepared or willing to protect trade secrets.

Our and our joint ventures' trade secrets could otherwise become known or be independently discovered by our or their competitors. For example, competitors could purchase our drugs and attempt to replicate some or all of the competitive advantages we derive from our development efforts, willfully infringe our intellectual property rights, design around our protected technology or develop their own competitive technologies that fall outside of our intellectual property rights. If any of our or our joint ventures' trade secrets were to be lawfully obtained or independently developed by a competitor, we and our joint ventures would have no right to prevent them, or others to whom they communicate it, from using that technology or information to compete against us or our joint ventures. If our or our joint ventures' trade secrets are unable to adequately protect our business against competitors' drugs, our competitive position could be adversely affected, as could our business.

We and our joint ventures are dependent on trademark and other intellectual property rights licensed from others. If we lose our licenses for any of our products, we or our joint ventures may not be able to continue developing such products or may be required to change the way we market such products.

We and our joint ventures are parties to licenses that give us or them rights to third-party intellectual property that are necessary or useful for our or our joint ventures' businesses. In particular, the "Hutchison," "Chi-Med", "Hutchison China MediTech" and "HUTCHMED" brands, among others, have been licensed to us by Hutchison Whampoa Enterprises Limited, an affiliate of our largest shareholder, Hutchison Healthcare Holdings Limited. Hutchison Whampoa Enterprises Limited grants us a royalty-free, worldwide license to such brands. For more details, please see "Item 7. Major Shareholders and Related Party Transactions—Related Party Transactions—Relationship with CK Hutchison—Intellectual property licensed by the CK Hutchison group." Under the terms of our brand license agreement, Hutchison Whampoa Enterprises Limited has the right to terminate the license if, among other things, we commit a material breach of the agreement, or within any twelve-month period the aggregate direct or indirect shareholding in our company held by CK Hutchison is reduced to less than 35%, 30% or 20%. Furthermore, the trademarks of Elunate and Orpathys are licensed to us in China by our collaboration partner Eli Lilly and AstraZeneca, respectively.

In some cases, our licensors have retained the right to prosecute and defend intellectual property rights licensed to us or our joint ventures. We depend in part on the ability of our licensors to obtain, maintain and enforce intellectual property protection for such licensed intellectual property. Such licensors may not successfully maintain their intellectual property, may determine not to pursue litigation against other companies that are infringing on such intellectual property, or may pursue litigation less aggressively than we or our joint ventures would. Without protection for the intellectual property we or our joint ventures license, other companies might be able to offer substantially identical products or branding, which could adversely affect our competitive business position and harm our business prospects.

If our or our joint ventures' products or drug candidates infringe the intellectual property rights of third parties, we and they may incur substantial liabilities, and we and they may be unable to sell these products.

Our commercial success depends significantly on our and our joint ventures' ability to operate without infringing the patents and other proprietary rights of third parties. In the PRC, invention patent applications are generally maintained in confidence until their publication 18 months from the filing date. The publication of discoveries in the scientific or patent literature frequently occurs substantially later than the date on which the underlying discoveries were made and invention patent applications are filed. Even after reasonable investigation, we may not know with certainty whether any third-party may have filed a patent application without our knowledge while we or our joint ventures are still developing or producing that product. While the success of pending patent applications and applicability of any of them to our or our joint ventures' programs are uncertain, if asserted against us or them, we could incur substantial costs and we or they may have to:

- obtain licenses, which may not be available on commercially reasonable terms, if at all;
- redesign products or processes to avoid infringement; and
- stop producing products using the patents held by others, which could cause us or them to lose the use of one or more of our or their products.

To date, we and our joint ventures have not received any material claims of infringement by any third parties. If a third-party claims that we or our joint ventures infringe its proprietary rights, any of the following may occur:

- we or our joint ventures may have to defend litigation or administrative proceedings that may be costly whether we or they win or lose, and which could result in a substantial diversion of management resources;
- we or our joint ventures may become liable for substantial damages for past infringement if a court decides that our technology infringes a third-party's intellectual property rights;
- a court may prohibit us or our joint ventures from producing and selling our or their product(s) without a license from the holder of the intellectual property rights, which may not be available on commercially acceptable terms, if at all; and

- we or our joint ventures may have to reformulate product(s) so that it does not infringe the intellectual property rights of others, which may not be possible or could be very expensive and time consuming.

Any costs incurred in connection with such events or the inability to sell our or our joint ventures' products may have a material adverse effect on our business and results of operations.

We, our joint ventures and our collaboration partners may not be able to effectively enforce our intellectual property rights throughout the world.

Filing, prosecuting and defending patents on our or our joint venture's products or drug candidates in all countries throughout the world would be prohibitively expensive. The requirements for patentability may differ in certain countries, particularly in developing countries. Moreover, our, our joint ventures' or our collaboration partners' ability to protect and enforce our or their intellectual property rights may be adversely affected by unforeseen changes in foreign intellectual property laws. Additionally, the patent laws of some foreign countries do not afford intellectual property protection to the same extent as the laws of the United States. Many companies have encountered significant problems in protecting and defending intellectual property rights in certain foreign jurisdictions. The legal systems of some countries, particularly developing countries, may not favor the enforcement of patents and other intellectual property rights. This could make it difficult for us or our joint ventures to stop the infringement of our or their patents or the misappropriation of our or their other intellectual property rights. For example, many foreign countries have compulsory licensing laws under which a patent owner must grant licenses to third parties. Consequently, we may not be able to prevent third parties from practicing our or our joint ventures' inventions throughout the world. Competitors may use our or our joint ventures' technologies in jurisdictions where we or they have not obtained patent protection to develop their own drugs and, further, may export otherwise infringing drugs to territories where we or our joint ventures have patent protection, if our, our joint ventures' or our collaboration partners' ability to enforce our or their patents to stop infringing activities is inadequate. These drugs may compete with our drug candidates, and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Proceedings to enforce our or our joint ventures' patent rights in foreign jurisdictions, whether or not successful, could result in substantial costs and divert our or their efforts and resources from other aspects of our and their businesses. While we intend to protect our intellectual property rights in the major markets for our drug candidates, we cannot ensure that we will be able to initiate or maintain similar efforts in all jurisdictions in which we may wish to market our drug candidates. Furthermore, as AstraZeneca is responsible for enforcing our intellectual property rights with respect to savolitinib on our behalf, we may be unable to ensure that such rights are enforced or maintained in all jurisdictions. Accordingly, our efforts to protect the intellectual property rights of our drug candidates in such countries may be inadequate.

We and our joint ventures may be subject to damages resulting from claims that we or they, or our or their employees, have wrongfully used or disclosed alleged trade secrets of competitors or are in breach of non-competition or non-solicitation agreements with competitors.

We and our joint ventures could in the future be subject to claims that we or they, or our or their employees, have inadvertently or otherwise used or disclosed alleged trade secrets or other proprietary information of former employers or competitors. Although we try to ensure that our and our joint ventures' employees and consultants do not improperly use the intellectual property, proprietary information, know-how or trade secrets of others in their work for us or our joint ventures, we or our joint ventures may in the future be subject to claims that we or they caused an employee to breach the terms of his or her non-competition or non-solicitation agreement, or that we, our joint ventures, or these individuals have, inadvertently or otherwise, used or disclosed the alleged trade secrets or other proprietary information of a former employer or competitor. Litigation may be necessary to defend against these claims. Even if we and our joint ventures are successful in defending against these claims, litigation could result in substantial costs and could be a distraction to management. If our or our joint ventures' defenses to these claims fail, in addition to requiring us and them to pay monetary damages, a court could prohibit us or our joint ventures from using technologies or features that are essential to our or their products or our drug candidates, if such technologies or features are found to incorporate or be derived from the trade secrets or other proprietary information of the former employers. An inability to incorporate such technologies or features would have a material adverse effect on our business, and may prevent us from successfully commercializing our drug candidates. In addition, we or our joint ventures may lose valuable intellectual property rights or personnel as a result of such claims. Moreover, any such litigation or the threat thereof may adversely affect our or our joint ventures' ability to hire employees or contract with independent sales representatives. A loss of key personnel or their work product could hamper or prevent our ability to commercialize our drug candidates, which would have an adverse effect on our business, results of operations and financial condition.

Patent terms may be inadequate to protect the competitive position of our drug candidates for an adequate amount of time, and the absence of patent linkage, patent term extension and data and market exclusivity for NMPA-approved pharmaceutical products could increase the risk of early generic competition for our drug candidates in China.

In the United States, the Drug Price Competition and Patent Term Restoration Act of 1984, generally referred to as the Hatch-Waxman Amendments, and similar legislation in the E.U. and certain other countries, provides the opportunity for limited patent term extension. The Hatch-Waxman Amendments permit a patent-term extension of up to five years to reflect patent term lost during certain portions of product development and the FDA regulatory review process. However, a patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of drug approval; only one patent may be extended and only those claims covering the approved drug, a method for using it, or a method for manufacturing it may be extended. The application for the extension must be submitted prior to the expiration of the patent for which extension is sought. A patent that covers multiple products for which approval is sought can only be extended in connection with one of the approvals. Depending upon the timing, duration and specifics of any FDA marketing approval process for any drug candidates we may develop, one or more of our U.S. patents may be eligible for limited patent term extension under the Hatch-Waxman Amendments. However, we may not be granted an extension because of, for example, failing to exercise due diligence during the testing phase or regulatory review process, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents, or otherwise failing to satisfy applicable requirements. Moreover, the applicable period or the scope of patent protection afforded could be less than we request. In addition, to the extent we wish to pursue patent term extension based on a patent that we in-license from a third party, we would need the cooperation of that third party. If we fail to obtain patent term extensions or if the term of any such extension is less than we request, our competitors may obtain approval of competing products following our patent expiration, and thus our revenue could be reduced. Further, if this occurs, our competitors may take advantage of our investment in development and trials by referencing our clinical and pre-clinical data and launch their product earlier than might otherwise be expected, and our competitive position, business, financial condition, results of operations and prospects could be materially adversely affected.

The Hatch-Waxman Amendments also include a process for patent linkage, pursuant to which the FDA will stay approval of certain follow-on applications during the pendency of litigation between the follow-on applicant and the patent holder or licensee, generally for a period of 30 months. Moreover, the Hatch-Waxman Amendments provide for statutory exclusivities that can prevent submission or approval of certain follow-on marketing applications. For example, federal law provides a five-year period of exclusivity within the United States to the first applicant to obtain approval of a new chemical entity and three years of exclusivity protecting certain innovations to previously approved active ingredients where the applicant was required to conduct new clinical investigations to obtain approval for the modification. Similarly, the U.S. Orphan Drug Act provides seven years of market exclusivity for certain drugs to treat rare diseases, where the FDA designates the drug candidate as an orphan drug and the drug is approved for the designated orphan indication. See “Risks Relating to Our Oncology/Immunology Operations and Development of Our Drug Candidates—Although we have obtained orphan drug designation for surufatinib for the treatment of pancreatic NETs in the United States, we may not be able to obtain or maintain the benefits associated with orphan drug status, including market exclusivity.”

Chinese regulators have set forth a framework for integrating patent linkage and data exclusivity into the China regulatory regime, as well as for establishing a pilot program for patent term extension. To be implemented, this framework will require adoption of regulations. On October 17, 2020, the Standing Committee of the National People’s Congress published the Patent Law of PRC (Amended in 2020), which came into effect on June 1, 2021, or the Amended Patent Law. The Amended Patent Law provides that, among other things, the owner of the patent for an innovative new drug that has been granted the marketing authorization in China is entitled to request the Patent Administration Department under the State Council to grant a patent term extension of up to five years, in order to compensate the time required for the regulatory approval for the commercialization of such innovative new drug, provided that the patent term of such innovative new drug shall not exceed a total of 14 years. Furthermore, the PRC government entered into the Economic and Trade Agreement Between the Government of the People’s Republic of China and the Government of the United States of America with the U.S. government in January 2020 which provides that the owner of the patent for an innovative new drug that has been granted the marketing authorization in China is entitled to request a patent term extension of up to five years, provided that the patent term of such innovative new drug shall not exceed a total of 14 years from the date of marketing approval in China. If we are unable to obtain patent term extension, or the term of any such extension is less than that we request, our competitors or other third parties may obtain approval of competing products following our patent expiration. Any of the foregoing could have a material adverse effect on our competitive position, business, financial condition, results of operations and prospects.

Risks Relating to Our ADSs

The Public Company Accounting Oversight Board, or the PCAOB, is currently unable to inspect our auditor in relation to their audit work performed for our financial statements and the inability of the PCAOB to conduct inspections over our auditor deprives our investors with the benefits of such inspections.

Our auditor, the independent registered public accounting firm that issues the audit report included elsewhere in this annual report, as an auditor of companies that are traded publicly in the United States and a firm registered with the Public Company Accounting Oversight Board, or the PCAOB, is subject to laws in the United States pursuant to which the PCAOB conducts regular inspections to assess its compliance with the applicable professional standards. Since our auditor is located in China, a jurisdiction where the PCAOB has been unable to conduct inspections without the approval of the Chinese authorities, our auditor is not currently inspected by the PCAOB.

This lack of the PCAOB inspections in China prevents the PCAOB from fully evaluating audits and quality control procedures of our independent registered public accounting firm. As a result, we and investors in our ordinary shares are deprived of the benefits of such PCAOB inspections. The inability of the PCAOB to conduct inspections of auditors in China makes it more difficult to evaluate the effectiveness of our independent registered public accounting firm's audit procedures or quality control procedures as compared to auditors outside of China that are subject to the PCAOB inspections, which could cause investors and potential investors in our stock to lose confidence in our audit procedures and reported financial information and the quality of our financial statements.

Our ADSs may be delisted and our ADSs and shares prohibited from trading in the over-the-counter market under the Holding Foreign Companies Accountable Act, or the HFCAA, if the PCAOB is unable to inspect or fully investigate auditors located in China. On December 16, 2021, PCAOB issued the HFCAA Determination Report, according to which our auditor is subject to the determinations that the PCAOB is unable to inspect or investigate completely. Under the current law, delisting and prohibition from over-the-counter trading in the U.S. could take place in 2024. If this happens there is no certainty that we will be able to list our ADS or shares on a non-U.S. exchange or that a market for our shares will develop outside of the U.S. The delisting of our ADSs, or the threat of their being delisted, may materially and adversely affect the value of your investment.

As part of a continued regulatory focus in the United States on access to audit and other information currently protected by national law, in particular China's, the Holding Foreign Companies Accountable Act, or the HFCAA has been signed into law on December 18, 2020. The HFCAA states if the SEC determines that we have filed audit reports issued by a registered public accounting firm that has not been subject to inspection for the PCAOB for three consecutive years beginning in 2021, the SEC shall prohibit our shares or ADS from being traded on a national securities exchange or in the over-the-counter trading market in the U.S. Accordingly, under the current law this could happen in 2024.

On December 2, 2021, the SEC adopted final amendments to its rules implementing the HFCAA (the "Final Amendments"). The Final Amendments include requirements to disclose information, including the auditor name and location, the percentage of shares of the issuer owned by governmental entities, whether governmental entities in the applicable foreign jurisdiction with respect to the auditor has a controlling financial interest with respect to the issuer, the name of each official of the Chinese Communist Party who is a member of the board of the issuer, and whether the articles of incorporation of the issuer contains any charter of the Chinese Communist Party. The Final Amendments also establish procedures the SEC will follow in identifying issuers and prohibiting trading by certain issuers under the HFCAA.

On December 16, 2021, PCAOB issued the HFCAA Determination Report, according to which our auditor is subject to the determinations that the PCAOB is unable to inspect or investigate completely.

The HFCAA or other efforts to increase U.S. regulatory access to audit information could cause investor uncertainty for affected issuers, including us, and the market price of the ADSs could be adversely affected. Additionally, whether the PCAOB will be able to conduct inspections of our auditor before the issuance of our financial statements on Form 20-F for the year ending December 31, 2023 which is due by April 30, 2024, or at all, is subject to substantial uncertainty and depends on a number of factors out of our control. If we are unable to meet the PCAOB inspection requirement in time, we could be delisted from the Nasdaq Stock Market and our ADSs will not be permitted for trading "over-the-counter" either. Such a delisting would substantially impair your ability to sell or purchase our ADSs when you wish to do so, and the risk and uncertainty associated with delisting would have a negative impact on the price of our ADSs. Also, such a delisting would significantly affect our ability to raise capital on terms acceptable to us, or at all, which would have a material adverse impact on our business, financial condition, and prospects.

The potential enactment of the Accelerating Holding Foreign Companies Accountable Act would decrease the number of non-inspection years from three years to two, thus reducing the time period before our ADSs may be prohibited from over-the-counter trading or delisted. If this bill were enacted, our ADS could be delisted from the exchange and prohibited from over-the-counter trading in the United States. in 2023.

On June 22, 2021, the U.S. Senate passed a bill known as the Accelerating Holding Foreign Companies Accountable Act, or the HFCAA, to amend Section 104(i) of the Sarbanes-Oxley Act of 2002 (15 U.S.C. 7214(i)) to prohibit securities of any registrant from being listed on any of the U.S. securities exchanges or traded over-the-counter if the auditor of the registrant's financial statements is not subject to PCAOB inspection for two consecutive years, instead of three consecutive years as currently enacted in the HFCAA.

On February 4, 2022, the U.S. House of Representatives passed the America Competes Act of 2022 which includes the exact same amendments as the bill passed by the Senate. The America Competes Act however includes a broader range of legislation not related to the HFCAA in response to the U.S. Innovation and Competition Act passed by the Senate in 2021. The U.S. House of Representatives and U.S. Senate will need to agree on amendments to these respective bills to align the legislation and pass their amended bills before the president of the United States can sign into law. It is unclear when the U.S. Senate and U.S. House of Representatives will resolve the differences in the U.S. Innovation and Competition Act and the America Competes Act of 2022 bills currently passed, or when the U.S. President will sign on the bill to make the amendment into law, or at all.

In the case that the bill becomes the law, it will reduce the time period before our ADSs could be delisted from the exchange and prohibited from over-the-counter trading in the U.S. from 2024 to 2023.

The listings of our shares in multiple venues may adversely affect the liquidity and value of them.

Our ADSs continue to be listed on Nasdaq, and our shares continue to be admitted to trading on the AIM. Our shares were listed on the SEHK in June 2021. The listing of the shares on the AIM and the SEHK, and the ADSs on Nasdaq, may reduce the liquidity of these securities in one or each of these markets and may adversely affect the development of an active trading market for the shares in each of these markets. The price of the shares could also be adversely affected by trading on Nasdaq. Similarly, the price of the ADSs could also be adversely affected by trading on the AIM and the SEHK. We may also seek further listings on other stock exchanges such as the Shanghai Stock Exchange, which could further affect the liquidity and value of the shares and the ADSs. Furthermore, the shares trade on the SEHK largely in electronic book-entry form. However, the ADSs are backed by physical ordinary share certificates, and the depositary for our ADS program is unable to accept book-entry interests into its custody in order to issue ADSs. As a result, if a holder of the shares wishes to deposit the shares into the ADS program and hold ADSs for trading on Nasdaq or vice versa, the issuance and cancellation process may be longer than if the depositary could accept such book-entry interests.

Our largest shareholder owns a significant percentage of our ordinary shares, which may limit the ability of other shareholders to influence corporate matters.

As of March 1, 2022, Hutchison Healthcare Holdings Limited owned approximately 38.46% of our ordinary shares. Accordingly, Hutchison Healthcare Holdings Limited can influence the outcome of any corporate transaction or other matter submitted to shareholders for approval and the interests of Hutchison Healthcare Holdings Limited may differ from the interests of our other shareholders. Under our Articles of Association, certain matters, such as amendments to our amended and restated Memorandum and Articles of Association, require the approval of not less than three-fourths of votes cast by such shareholders as, being entitled so to do, vote in person (or, in the case of such shareholders as are corporations, by their respective duly authorized representative) or by proxy. Therefore, Hutchison Healthcare Holdings Limited's approval will be required to achieve any such threshold. In addition, Hutchison Healthcare Holdings Limited has and will continue to have a significant influence over the management and the strategic direction of our company.

Substantial future sales or perceived potential sales of our ADSs, ordinary shares or other equity or equity-linked securities in the public market could cause the price of our ADSs to decline significantly.

Sales of our ADSs, ordinary shares or other equity or equity-linked securities in the public market, or the perception that these sales could occur, could cause the market price of our ADSs to decline significantly. All of our ordinary shares represented by ADSs are freely transferable by persons other than our affiliates without restriction or additional registration under the Securities Act of 1933, or the Securities Act. The ordinary shares held by our affiliates are also available for sale, subject to volume and other restrictions as applicable under Rules 144 and 701 under the Securities Act, under sales plans adopted pursuant to Rule 10b5-1 or otherwise.

We have filed with the SEC registration statements on Form F-3, commonly referred to as a "shelf registration," that permit us to sell any number of ADSs in a registered offering at our discretion. We have completed registered offerings raising aggregate gross proceeds of approximately $537.9 million under such shelf registration statements. Furthermore, our largest shareholder has completed registered secondary offerings raising aggregate gross proceeds of approximately $310.4 million for it as a selling shareholder under a shelf registration statement. In addition, we completed our initial public offering in Hong Kong and global offering of our ordinary shares in 2021, raising aggregate gross proceeds of approximately $614.9 million, including $80.2 million through the fulfillment of the over-allotment. We may decide to conduct future offerings from time to time, and such sales could cause the price of our ADSs to decline significantly.

In connection with the issuance of ordinary shares in private placements in 2020 and 2021, we agreed to provide three shareholders Form F-3 registration rights. Registration of the ordinary shares held by such shareholders may result in these shares becoming freely tradable without restriction under the Securities Act immediately upon the effectiveness of the registration. Sales of these shares, or the perception that such sales could occur, could cause the price of our ADSs to decline. In addition, any changes in the investment strategies or philosophies of our major shareholders may lead to the sale of our ADSs and other securities, which could cause the price of our ADSs to decline.

We may be at a risk of securities litigation.

Historically, securities litigation, particularly class action lawsuits brought in the United States, have often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because biotechnology and biopharmaceutical companies have experienced significant share price volatility in recent years. If we were to be sued, it could result in substantial costs and a diversion of management's attention and resources, which could harm our business.

If securities analysts do not publish research or reports about our business or if they publish negative evaluations of our business, the price of our ADSs could decline.

The trading market for our ADSs will rely in part on the research and reports that industry or financial analysts publish about us or our business. We may not be able to maintain continuous research coverage by industry or financial analysts. If one or more of the analysts covering our business downgrade their evaluations of our stock, the price of our stock could decline. If one or more of these analysts cease to cover our stock, we could lose visibility in the market for our stock, which in turn could cause our stock price to decline.

As a foreign private issuer, we are not subject to certain U.S. securities law disclosure requirements that apply to a domestic U.S. issuer, which may limit the information publicly available to our shareholders.

As a foreign private issuer we are not required to comply with all of the periodic disclosure and current reporting requirements of the Exchange Act and therefore there may be less publicly available information about us than if we were a U.S. domestic issuer. For example, we are not subject to the proxy rules in the United States, and disclosure with respect to our annual general meetings will be governed by the AIM Rules for Companies, or the AIM Rules, listing rules in Hong Kong and Cayman Islands requirements. In addition, our officers, directors and principal shareholders are exempt from the reporting and "short-swing" profit recovery provisions of Section 16 of the Exchange Act and the rules thereunder. Therefore, our shareholders may not know on a timely basis when our officers, directors and principal shareholders purchase or sell our ordinary shares or ADSs.

As a foreign private issuer, we are permitted to adopt certain home country practices in relation to corporate governance matters that differ significantly from Nasdaq corporate governance listing standards. These practices may afford less protection to shareholders than they would enjoy if we complied fully with corporate governance listing standards.

As a foreign private issuer, we are permitted to take advantage of certain provisions in the Nasdaq listing rules that allow us to follow Cayman Islands law for certain governance matters. Certain corporate governance practices in the Cayman Islands may differ significantly from corporate governance listing standards as, except for general fiduciary duties and duties of care, Cayman Islands law has no corporate governance regime which prescribes specific corporate governance standards. We intend to continue to follow Cayman Islands corporate governance practices in lieu of the corporate governance requirements of the Nasdaq Global Select Market in respect of the following: (i) the majority independent director requirement under Section 5605(b)(1) of the Nasdaq listing rules, (ii) the requirement under Section 5605(d) of the Nasdaq listing rules that a remuneration committee comprised solely of independent directors governed by a remuneration committee charter oversee executive compensation and (iii) the requirement under Section 5605(e) of the Nasdaq listing rules that director nominees be selected or recommended for selection by either a majority of the independent directors or a nominations committee comprised solely of independent directors. Cayman Islands law does not impose a requirement that our board of directors consist of a majority of independent directors, nor does Cayman Islands law impose specific requirements on the establishment of a remuneration committee or nominating committee or nominating process. Therefore, our shareholders may be afforded less protection than they otherwise would have under corporate governance listing standards applicable to U.S. domestic issuers. We have voluntarily complied with the Corporate Governance Code contained in Appendix 14 of the Rules Governing the Listing of Securities on SEHK. See Item 6.C. "Board Practice—Hong Kong Corporate Governance Code" for more details.

We may in the future lose our foreign private issuer status under U.S. securities laws, which could result in significant additional costs and expenses.

We are a foreign private issuer as defined in the Securities Act, and therefore, we are not required to comply with all of the periodic disclosure and current reporting requirements of the Exchange Act. The determination of foreign private issuer status is made annually on the last business day of an issuer's most recently completed second fiscal quarter, and, accordingly, the next determination will be made with respect to us on June 30, 2022. We would lose our foreign private issuer status if, for example, more than 50% of our ordinary shares are directly or indirectly held by residents of the United States on June 30, 2022 and we fail to meet additional requirements necessary to maintain our foreign private issuer status. If we lose our foreign private issuer status on this date, we will be required to file with the SEC periodic reports and registration statements on U.S. domestic issuer forms beginning on January 1, 2023, which are more detailed and extensive than the forms available to a foreign private issuer. We will also have to mandatorily comply with U.S. federal proxy requirements, and our officers, directors and principal shareholders will become subject to the short-swing profit disclosure and recovery provisions of Section 16 of the Exchange Act. In addition, we will lose our ability to rely upon exemptions from certain corporate governance requirements under the Nasdaq listing rules. As a U.S.-listed public company, should we lose our foreign private issuer status, we will incur significant additional legal, accounting and other expenses that we would not incur as a foreign private issuer.

Fluctuations in the value of the renminbi may have a material adverse effect on your investment.

The value of the renminbi against the U.S. dollar and other currencies fluctuates and is affected by, among other things, changes in China's and international political and economic conditions and the PRC government's fiscal and currency policies. Since 1994, the conversion of renminbi into foreign currencies, including U.S. dollars, has been based on rates set by the PBOC, which are set daily based on the previous business day's inter-bank foreign exchange market rates and current exchange rates on the world financial markets. It is expected that China may further reform its exchange rate system in the future.

Significant revaluation of the renminbi may have a material adverse effect on your investment. For example, to the extent that we need to convert U.S. dollars into renminbi for our operations, appreciation of the renminbi against the U.S. dollar would have an adverse effect on the renminbi amount we would receive from the conversion. Conversely, if we decide to convert our renminbi into U.S. dollars, appreciation of the U.S. dollar against the renminbi would have a negative effect on the U.S. dollar amount available to us. Appreciation or depreciation in the value of the renminbi relative to the U.S. dollar would affect our financial results reported in U.S. dollar terms regardless of any underlying change in our business or results of operations. In addition, our operating transactions and assets and liabilities in the PRC are mainly denominated in renminbi. Such amounts are translated into U.S. dollars for purpose of preparing our consolidated financial statements, with translation adjustments reflected in accumulated other comprehensive income/(loss) in shareholders' equity. We recorded a foreign currency translation loss of $4.3 million, a foreign currency translation gain of $9.5 million and a foreign currency translation gain of $3.0 million for the years ended December 31, 2019, 2020 and 2021, respectively.

Very limited hedging options are available in China to reduce our exposure to exchange rate fluctuations. To date, we have not entered into any hedging transactions in an effort to reduce our exposure to foreign currency exchange risk. While we may decide to enter into hedging transactions in the future, the availability and effectiveness of these hedges may be limited and we may not be able to adequately hedge our exposure or at all. In addition, our currency exchange losses may be magnified by PRC exchange control regulations that restrict our ability to convert renminbi into foreign currency.

We do not currently intend to pay dividends on our securities, and, consequently, your ability to achieve a return on your investment will depend on appreciation in the price of the ADSs.

We have never declared or paid any dividends on our ordinary shares. We currently intend to invest our future earnings, if any, to fund our growth. Therefore, you are not likely to receive any dividends on your ADSs at least in the near term, and the success of an investment in ADSs will depend upon any future appreciation in its value. Consequently, investors may need to sell all or part of their holdings of ADSs after price appreciation, which may never occur, to realize any future gains on their investment. There is no guarantee that the ADSs will appreciate in value or even maintain the price at which our shareholders have purchased the ADSs.

The trading prices for our ADSs may be volatile which could result in substantial losses to you.

The market price of our ADSs has been volatile. From March 17, 2016 to March 1, 2022, the closing sale price of our ADSs ranged from a high of $43.94 to a low of $11.26 per ADS.

The market price for our ADSs is likely to be highly volatile and subject to wide fluctuations in response to factors, including the following:

- announcements of competitive developments;
- regulatory developments affecting us, our customers or our competitors;
- announcements regarding litigation or administrative proceedings involving us;
- actual or anticipated fluctuations in our period-to-period operating results;
- changes in financial estimates by securities research analysts;
- additions or departures of our executive officers;
- release or expiry of lock-up or other transfer restrictions on our outstanding ordinary shares or ADSs; and
- sales or perceived sales of additional ordinary shares or ADSs.

In addition, the securities markets have from time to time experienced significant price and volume fluctuations that are not related to the operating performance of particular companies. Prolonged global capital markets volatility may affect overall investor sentiment towards our ADSs, which would also negatively affect the trading prices for our ADSs.

The triple listing of our ordinary shares and the ADSs may adversely affect the liquidity and value of the ADSs.

Our ordinary shares are listed on the AIM market and on the SEHK. The triple listing of our ordinary shares and the ADSs may dilute the liquidity of these securities in one or more of these markets and may adversely affect the development of an active trading market for the ADSs in the United States or shares in Hong Kong and the United Kingdom. The price of the ADSs could also be adversely affected by trading in our ordinary shares on the AIM market and the SEHK.

Fluctuations in the exchange rate between the U.S. dollar, Hong Kong dollar and the pound sterling may increase the risk of holding the ADSs.

Our share price is quoted on the SEHK and AIM market in Hong Kong dollar and pence sterling, respectively, while the ADSs trade on Nasdaq in U.S. dollars. Fluctuations in the exchange rate between the U.S. dollar, Hong Kong dollar and the pound sterling may result in temporary differences between the value of the ADSs and the value of our ordinary shares, which may result in heavy trading by investors seeking to exploit such differences. In addition, as a result of fluctuations in the exchange rate between the U.S. dollar, Hong Kong dollar and the pound sterling, the U.S. dollar equivalent of the proceeds that a holder of the ADSs would receive upon the sale in Hong Kong of any ordinary shares or in the United Kingdom of any ordinary shares withdrawn from the depositary and the dollar equivalent of any cash dividends paid in Hong Kong dollar or pound sterling on our shares represented by the ADSs could also decline.

Securities traded on the AIM market or on the SEHK may carry or be perceived to carry a higher risk than shares traded on other exchanges and may impact the value of your investment.

Our ordinary shares are currently traded on the AIM market and on the SEHK. Investment in equities traded on AIM and the SEHK may be perceived by some to carry a higher risk than an investment in equities quoted on exchanges, such as the New York Stock Exchange or the Nasdaq. You should be aware that the value of our ordinary shares may be influenced by many factors, some of which may be specific to us and some of which may affect AIM-listed or Hong Kong-listed companies generally, including the depth and liquidity of the market, our performance, a large or small volume of trading in our ordinary shares, legislative changes and general economic, political or regulatory conditions, and that the prices may be volatile and subject to extensive fluctuations. Therefore, the market price of our ordinary shares underlying the ADSs may not reflect the underlying value of our company.

The depositary for our ADSs gives us a discretionary proxy to vote our ordinary shares underlying your ADSs if you do not vote at shareholders' meetings, except in limited circumstances, which could adversely affect your interests.

Under the deposit agreement for the ADSs, the depositary gives us a discretionary proxy to vote our ordinary shares underlying your ADSs at shareholders' meetings if you do not vote, unless:

- we do not wish a discretionary proxy to be given;
- we are aware or should reasonably be aware that there is substantial opposition as to a matter to be voted on at the meeting; or
- a matter to be voted on at the meeting would materially and adversely affect the rights of shareholders.

The effect of this discretionary proxy is that you cannot prevent our ordinary shares underlying your ADSs from being voted, absent the situations described above, and it may make it more difficult for shareholders to influence the management of our company. Holders of our ordinary shares are not subject to this discretionary proxy.

Holders of ADSs have fewer rights than shareholders and must act through the depositary to exercise their rights.

Holders of our ADSs do not have the same rights as our shareholders and may only exercise the voting rights with respect to the underlying ordinary shares in accordance with the provisions of the deposit agreement. Under our amended and restated Memorandum and Articles of Association, an annual general meeting shall be called by notice with not less than 21 clear days, and all other general meetings (including an extraordinary general meeting) shall be called by notice with not less than 14 clear days. When a general meeting is convened, you may not receive sufficient notice of a shareholders' meeting to permit you to withdraw the ordinary shares underlying your ADSs to allow you to vote with respect to any specific matter. If we ask for your instructions, we will give the depositary notice of any such meeting and details concerning the matters to be voted upon at least 30 days in advance of the meeting date and the depositary will send a notice to you about the upcoming vote and will arrange to deliver our voting materials to you. The depositary and its agents, however, may not be able to send voting instructions to you or carry out your voting instructions in a timely manner. We will make all reasonable efforts to cause the depositary to extend voting rights to you in a timely manner, but we cannot assure you that you will receive the voting materials in time to ensure that you can instruct the depositary to vote the ordinary shares underlying your ADSs. Furthermore, the depositary will not be liable for any failure to carry out any instructions to vote, for the manner in which any vote is cast or for the effect of any such vote. As a result, you may not be able to exercise your right to vote and you may lack recourse if your ADSs are not voted as you request. In addition, in your capacity as an ADS holder, you will not be able to call a shareholders' meeting.

You may not receive distributions on our ADSs or any value for them if such distribution is illegal or if any required government approval cannot be obtained in order to make such distribution available to you.

Although we do not have any present plan to pay any dividends, the depositary of our ADSs has agreed to pay to you the cash dividends or other distributions it or the custodian receives on ordinary shares or other deposited securities underlying our ADSs, after deducting its fees and expenses and any applicable taxes and governmental charges. You will receive these distributions in proportion to the number of ordinary shares your ADSs represent. However, the depositary is not responsible if it decides that it is unlawful or impractical to make a distribution available to any holders of ADSs. For example, it would be unlawful to make a distribution to a holder of ADSs if it consists of securities whose offering would require registration under the Securities Act but is not so properly registered or distributed under an applicable exemption from registration. The depositary may also determine that it is not reasonably practicable to distribute certain property. In these cases, the depositary may determine not to distribute such property. We have no obligation to register under the U.S. securities laws any offering of ADSs, ordinary shares, rights or other securities received through such distributions. We also have no obligation to take any other action to permit the distribution of ADSs, ordinary shares, rights or anything else to holders of ADSs. This means that you may not receive distributions we make on our ordinary shares or any value for them if it is illegal or impractical for us to make them available to you. These restrictions may cause a material decline in the value of our ADSs.

Your right to participate in any future rights offerings may be limited, which may cause dilution to your holdings.

We may from time to time distribute rights to our shareholders, including rights to acquire our securities. However, we cannot make rights available to you in the United States unless we register the rights and the securities to which the rights relate under the Securities Act or an exemption from the registration requirements is available. Also, under the deposit agreement, the depositary bank will not make rights available to you unless either both the rights and any related securities are registered under the Securities Act, or the distribution of them to ADS holders is exempted from registration under the Securities Act. We are under no obligation to file a registration statement with respect to any such rights or securities or to endeavor to cause such a registration statement to be declared effective. Moreover, we may not be able to establish an exemption from registration under the Securities Act. If the depositary does not distribute the rights, it may, under the deposit agreement, either sell them, if possible, or allow them to lapse. Accordingly, you may be unable to participate in our rights offerings and may experience dilution in your holdings.

If we are classified as a passive foreign investment company, U.S. investors could be subject to adverse U.S. federal income tax consequences.

The rules governing passive foreign investment companies, or PFICs, can have adverse effects for U.S. investors for U.S. federal income tax purposes. The tests for determining PFIC status for a taxable year depend upon the relative values of certain categories of assets and the relative amounts of certain kinds of income. As discussed in "Taxation—Material U.S. Federal Income Tax Considerations," we do not believe that we are currently a PFIC. Notwithstanding the foregoing, the determination of whether we are a PFIC depends on particular facts and circumstances (such as the valuation of our assets, including goodwill and other intangible assets) and may also be affected by the application of the PFIC rules, which are subject to differing interpretations. The fair market value of our assets is expected to depend, in part, upon (1) the market price of our ordinary shares and ADSs and (2) the composition of our income and assets, which will be affected by how, and how quickly, we spend any cash that is raised in any financing transaction. In light of the foregoing, no assurance can be provided that we are not currently a PFIC or that we will not become a PFIC in any future taxable year. Furthermore, if we are treated as a PFIC, then one or more of our subsidiaries may also be treated as PFICs.

If we are or become a PFIC, and, if so, if one or more of our subsidiaries are treated as PFICs, U.S. holders of our ordinary shares and ADSs would be subject to adverse U.S. federal income tax consequences, such as ineligibility for any preferential tax rates on capital gains or on actual or deemed dividends, interest charges on certain taxes treated as deferred, and additional reporting requirements under U.S. federal income tax laws and regulations. Whether U.S. holders of our ordinary shares or ADSs make (or are eligible to make) a timely qualified electing fund, or QEF, election or a mark-to-market election may affect the U.S. federal income tax consequences to U.S. holders with respect to the acquisition, ownership and disposition of our ordinary shares and ADSs and any distributions such U.S. holders may receive. We do not, however, expect to provide the information regarding our income that would be necessary in order for a U.S. holder to make a QEF election if we are classified as a PFIC. Investors should consult their own tax advisors regarding all aspects of the application of the PFIC rules to our ordinary shares and ADSs.

You may have difficulty enforcing judgments obtained against us.

We are a company incorporated under the laws of the Cayman Islands, and substantially all of our assets are located outside the United States. Substantially all of our current operations are conducted in the PRC. In addition, most of our directors and officers are nationals and residents of countries other than the United States. A substantial portion of the assets of these persons are located outside the United States. As a result, it may be difficult for you to effect service of process within the United States upon these persons. It may also be difficult for you to enforce in U.S. courts judgments obtained in U.S. courts based on the civil liability provisions of the U.S. federal securities laws against us and our officers and directors, all of whom are not residents in the United States and whose assets are located outside the United States. In addition, there is uncertainty as to whether the courts of the Cayman Islands or the PRC would recognize or enforce judgments of U.S. courts against us or such persons predicated upon the civil liability provisions of the securities laws of the United States or any state.

You may be subject to limitations on transfers of your ADSs.

Your ADSs are transferable on the books of the depositary. However, the depositary may close its transfer books at any time or from time to time when it deems expedient in connection with the performance of its duties. In addition, the depositary may refuse to deliver, transfer or register transfers of ADSs generally when our books or the books of the depositary are closed, or at any time if we or the depositary deems it advisable to do so because of any requirement of law or of any government or governmental body, or under any provision of the deposit agreement, or for any other reason.

It may be difficult for overseas regulators to conduct investigations or collect evidence within China.

Shareholder claims or regulatory investigation that are common in the United States generally are difficult to pursue as a matter of law or practicality in China. For example, in China, there are significant legal and other obstacles to providing information needed for regulatory investigations or litigation initiated outside China. Although the authorities in China may establish a regulatory cooperation mechanism with the securities regulatory authorities of another country or region to implement cross-border supervision and administration, such cooperation with the securities regulatory authorities in the Unities States may not be efficient in the absence of mutual and practical cooperation mechanisms. Furthermore, according to Article 177 of the PRC Securities Law, or Article 177, which became effective in March 2020, no overseas securities regulator is allowed to directly conduct investigations or evidence collection activities within the territory of the PRC. While detailed interpretations of or implementation rules under Article 177 have yet to be promulgated, the inability for an overseas securities regulator to directly conduct investigations or evidence collection activities within China may further increase difficulties you may face in protecting your interests.

We are a Cayman Islands company. As judicial precedent regarding the rights of shareholders under Cayman Islands law is different from U.S. law, English law or Hong Kong law, shareholders may have different shareholder rights than they would have under U.S. law, English law or Hong Kong law and may face difficulties in protecting your interests.

We are an exempted company with limited liability incorporated in the Cayman Islands. Our corporate affairs are governed by our Articles of Association (as may be further amended from time to time), the Companies Act (as amended) of the Cayman Islands and the common law of the Cayman Islands. The rights of shareholders to take action against the directors, actions by minority shareholders and the fiduciary responsibilities of our directors are to a large extent governed by the common law of the Cayman Islands. This common law is derived in part from comparatively limited judicial precedent in the Cayman Islands as well as from English common law, which has persuasive, but not binding, authority on a court in the Cayman Islands. The laws of the Cayman Islands relating to the protection of the interests of minority shareholders differ in some aspects from those in the United States, the United Kingdom and Hong Kong. Such differences mean that the remedies available to our minority shareholders may be different from those they would have under the laws of United States, the United Kingdom, Hong Kong or other jurisdictions. In addition, some states in the United States, such as Delaware, have more fully developed and judicially interpreted bodies of corporate law than the Cayman Islands.

In addition, as a Cayman Islands exempted company, our shareholders have no general rights under Cayman Islands law to inspect corporate records and accounts or to obtain copies of lists of shareholders of these companies with the exception that the shareholders may request a copy of the Articles of Association. Our directors have discretion under our Articles of Association to determine whether or not, and under what conditions, our corporate records may be inspected by our shareholders, but are not obliged to make them available to our shareholders. This may make it more difficult for you to obtain the information needed to establish any facts necessary for a shareholder motion or to solicit proxies from other shareholders in connection with a proxy contest. As a Cayman Islands company, we may not have standing to initiate a derivative action in U.S. federal courts, English courts or Hong Kong courts. As a result, you may be limited in your ability to protect your interests if you are harmed in a manner that would otherwise enable you to sue in U.S. federal courts, English courts or Hong Kong courts. In addition, shareholders of Cayman Islands companies may not have standing to initiate a shareholder derivative action in U.S. federal courts, English courts or Hong Kong courts.

Most of our directors and executive officers reside outside of the United States and a substantial portion of their assets are located outside of the United States. As a result, it may be difficult or impossible for you to bring an action against us or against these individuals in the United States in the event that you believe that your rights have been infringed under the securities laws of the United States or otherwise. In addition, some of our operating subsidiaries are incorporated in China. To the extent our directors and executive officers reside in China or their assets are located in China, it may not be possible for investors to effect service of process upon us or our management inside China. Even if you are successful in bringing an action, the laws of the Cayman Islands and China may render you unable to enforce a judgment against our assets or the assets of our directors and officers. There is no statutory recognition in the Cayman Islands of judgments obtained in the United States, Hong Kong or China, although the courts of the Cayman Islands will generally recognize and enforce a non-penal judgment of a foreign court of competent jurisdiction without retrial on the merits subject to certain conditions.

As a result of all of the above, public shareholders may have more difficulty in protecting their interests in the face of actions taken by management, members of the board of directors or controlling shareholders than they would as public shareholders of an English company, a U.S. company or a Hong Kong company.

We cannot assure you that our ordinary shares will remain listed on the AIM or the SEHK or our ADSs will remain listed on Nasdaq.

Although it is currently intended that our ordinary shares and ADSs will remain listed on the AIM, the SEHK and Nasdaq, as applicable, there is no guarantee of the continued listing of our securities on any of these exchanges. We may decide at some point in the future to delist voluntarily (subject to the applicable regulatory requirements) from one or more of these exchanges, or we may be delisted involuntarily if, among other factors, we do not continue to satisfy the listing requirements of the applicable exchange or comply with applicable law. For example, we could be delisted from the Nasdaq if the PCAOB continues to be unable to inspect our independent registered public accounting firm for three consecutive years. The AIM Rules for companies provide that a voluntary cancellation of admission to AIM is conditional upon the consent of not less than 75% of votes cast by its shareholders at a general meeting unless the London Stock Exchange otherwise agrees. Circumstances where the London Stock Exchange might otherwise agree that shareholder consent at a general meeting is not required would include the situation where the AIM securities are already admitted to trading on an "AIM Designated Market" (which includes Nasdaq) to enable shareholders to trade their AIM securities in the future. The SEHK rules allow an issuer whose primary listing is on SEHK and which has an alternative listing on another stock exchange to withdraw its listing with the prior approval of shareholders by ordinary resolution obtained at a duly convened meeting of the shareholders and the satisfaction of other requirements. SEHK may also cancel the listing of any securities that have been suspended from trading for a continuous period of 18 months. We cannot predict the effect a delisting of our shares on the SEHK or AIM market or our ADSs on Nasdaq would have on the market price of our shares and/or ADSs. We may also seek further listings on other stock exchanges such as the Shanghai Stock Exchange. However, there is no assurance that we would proceed with a listing and if we do proceed, that a listing would materialize.

The characteristics of the Hong Kong, U.S. and U.K. capital markets are different.

The SEHK, Nasdaq and the AIM have different trading hours, trading characteristics (including trading volume and liquidity), trading and listing rules, market regulations, and investor bases (including different levels of retail and institutional participation). As a result of these differences, the trading prices of the shares and the ADSs might not be the same, even allowing for currency differences. Circumstances peculiar to the U.S. capital markets could materially and adversely affect the price of the shares. Because of the different characteristics of the Hong Kong, U.S. and U.K. equity markets, the historical market prices of our securities may not be indicative of the performance of the shares.

We are subject to Hong Kong, Nasdaq and AIM listing and regulatory requirements concurrently.

As we are listed on the SEHK, the Nasdaq and the AIM, we are required to comply with the listing rules (where applicable) and other regulatory regimes of each stock exchange, unless otherwise agreed by the relevant regulators. We may also seek further listings on other stock exchanges such as the Shanghai Stock Exchange. Accordingly, we may incur additional costs and resources in complying with the requirements of each stock exchange.

ITEM 4. INFORMATION ON THE COMPANY

A. History and Development of the Company.

HUTCHMED (China) Limited (formerly Hutchison China MediTech Limited) was incorporated in the Cayman Islands on December 18, 2000 as an exempted company with limited liability under the Companies Act, Cap 22 (Act 3 of 1961, as consolidated and revised) of the Cayman Islands. Our company was founded by a wholly owned subsidiary of CK Hutchison, a multinational conglomerate with operations in over 50 countries. CK Hutchison is the ultimate parent company of our largest shareholder Hutchison Healthcare Holdings Limited.

We launched our novel drug research and development operations in 2002 with the establishment of our subsidiary HUTCHMED Limited, which is focused on discovering, developing and marketing drugs for the treatment of cancer and immunological diseases. Twelve of our in-house discovered drug candidates have entered clinical trials around the world and three have so far been approved for sale. Since 2001, we have also developed drug marketing and distribution platforms in China, which primarily focus on prescription drug and consumer health products through several joint ventures and subsidiary companies and are included in our Other Ventures.

We listed our ordinary shares on the AIM market in 2006, ADSs on the Nasdaq Global Select Market in 2016 and our ordinary shares on the SEHK in 2021.

On March 4, 2021 we announced the consolidation of the two corporate identities that we have used since our inception. Hutchison China MediTech, or Chi-Med, has been used as our group identity, while Hutchison MediPharma has been the identity of our novel drug research and development operations under which our oncology products have been developed and are now being marketed. The brand HUTCHMED immediately replaced Chi-Med as our abbreviated name, and we changed our group company name at our Annual General Meeting in April 2021 from Hutchison China MediTech Limited to HUTCHMED (China) Limited.

On April 14, 2021, we completed the sale of $100 million of ordinary shares at a price of $6.10 per share via a private placement to Pachytene Limited, an investment holding company wholly owned by Baring Asia Private Equity Fund VII.

In June 2021, we sold a total of 104,000,000 ordinary shares in our initial public offering on the SEHK, raising gross proceeds of approximately $534.7 million. In July 2021, the over-allotment option of our initial public offering on the SEHK was fully exercised, and we sold a total of 15,600,000 ordinary shares, raising gross proceeds of approximately $80.2 million.

On September 28, 2021, we disposed of our entire investment in Hutchison Baiyunshan, our non-core and non-consolidated over-the-counter drug joint venture business, to GL Mountrose Investment Two Limited, a company controlled and managed by GL Capital Group. GL Capital Group is an investment firm that focuses on buyout and growth opportunities in China's healthcare industry. As our focus is the discovery and development of novel therapies in oncology and immunology, the sale of our interest in Hutchison Baiyunshan allows us to focus resources on our primary aim of accelerating investment in our Oncology/Immunology assets. We are also considering divesting other non-core businesses in our Other Ventures segment, including Shanghai Hutchison Pharmaceuticals.

Our principal executive offices are located at 48th Floor, Cheung Kong Center, 2 Queen's Road Central, Hong Kong. Our telephone number at that address is +852 2121 8200. The address of our registered office in the Cayman Islands is P.O. Box 309, Ugland House, Grand Cayman, KY1-1104, Cayman Islands.

See Item 5.B. "Liquidity and Capital Resources" for details on our capital expenditures for the years ended December 31, 2019, 2020 and 2021.

We are subject to the informational requirements of the Exchange Act and are required to file reports and other information with the SEC. The SEC maintains a website at *www.sec.gov* that contains reports, proxy and information statements, and other information regarding registrants that make electronic filings with the SEC using its EDGAR system. We also make available on our website's investor relations page, free of charge, our annual report and the text of our reports on Form 6-K, including any amendments to these reports, as well as certain other SEC filings, as soon as reasonably practicable after they are electronically filed with or furnished to the SEC. The address for our investor relations page is *www.hutch-med.com/shareholder-information.* The information contained on our website is not incorporated by reference in this annual report.

B. Business Overview.

Overview

We are a global commercial-stage biopharmaceutical company focused on the discovery, development and commercialization of targeted therapies and immunotherapies for the treatment of patients with cancer and immunological diseases. Our company started in China in 2000 and has since developed fully integrated capabilities and expanded oncology and immunology drug development operations globally. Our operational achievements and capabilities to date include:

Broad pipeline of differentiated targeted therapies and immunotherapies built for the global market. We have a pipeline of differentiated drug candidates covering both novel and validated targets, including MET, VEGFR, FGFR, CSF-1R, PI3Kδ, Syk, EZH2, IDH, ERK, BTK, and EGFR. The aim of our research is to develop drugs with high selectivity and superior safety profiles, a key benefit of which is that our drug candidates have the potential to be effectively paired with other oncology and immunology therapies at effective dosages with fewer side effects.

Commercially launching products while continuing to discover new assets. In China, we have launched three of our internally developed drugs, Elunate (fruquintinib), Sulanda (surufatinib) and Orpathys (savolitinib), to patients. All three drugs are in late-stage development outside of China, with the most advanced being surufatinib for which an NDA submission to the United States FDA is under review. Our marketing authorization application for surufatinib for the treatment of NETs to the European Medicines Agency, or EMA, is also under review. In addition, we have ten additional drug candidates that have entered earlier stages of clinical development (Phase I/Ib and Phase Ib/II proof of concept studies) and one advanced pre-clinical drug candidate.

Comprehensive global in-house discovery and development capabilities. We have a comprehensive drug discovery and development operation covering chemistry, biology, pharmacology, toxicology, chemistry and manufacturing controls for clinical and commercial supply, clinical and regulatory and other functions. It is led by a team of approximately 820 scientists, who have created one of the broadest global clinical pipelines among our peer oncology and immunology focused biotechnology companies. Currently, we are conducting and planning over 40 different clinical studies in oncology patients globally, including over a dozen Phase III registration and Phase II registration-intent studies underway.

Fast expanding and productive international organization. Our U.S. and European teams of approximately 130 mainly consisting of clinical, regulatory and commercial staff significantly broadened our international operations, particularly in the United States, Europe, Japan and Australia. This team has established a productive track record since it was established in 2018, including the submission and acceptance of a rolling U.S. NDA filing for surufatinib, initiation and full enrollment of a large global randomized controlled study for fruquintinib, and ongoing U.S. and European Phase I and II trials for our drug candidates sovleplenib, amdizalisib, HMPL-306 and HMPL-760. The FDA granted surufatinib two fast track designations as well as an orphan drug designation for NETs. Fruquintinib has also received FDA fast track designation, for late stage colorectal cancer (CRC). Furthermore, we are now building a commercial team in the United States, having recruited a team of over 30 personnel, to support the potential upcoming launch of surufatinib in the United States.

Long-standing drug marketing and distribution experience to support the realization of in-house oncology innovations in China. We have built large-scale and profitable drug marketing and distribution capabilities through our Other Ventures operations, which primarily manufacture, market and distribute prescription drugs in China. Our 20-year track record and deep institutional knowledge of the drug marketing and distribution process are being leveraged to bring our in-house oncology innovations to patients. We have built and continue to expand our in-house oncology drug sales team of about 630 persons to support the commercialization of Elunate, Sulanda and our other innovative drugs, if approved, throughout China. Our oncology drug sales team covers over 2,500 oncology hospitals and over 29,000 oncology physicians in China, a network that we estimate represents over 90% of oncology drug sales in China.

Our Strategies

Our vision is to be a global leader in the discovery, development and commercialization of targeted therapies and immunotherapies for the treatment of patients with cancer and immunological diseases. Key elements of our strategy are to:

Realize the global potential of our oncology drug candidates

Our first wave of innovation, surufatinib (unpartnered), fruquintinib (partnered in China with Eli Lilly) and savolitinib (partnered globally with AstraZeneca), are either commercialized, under review for marketing authorization or in registrational studies in multiple jurisdictions. In tandem with our ongoing progression of such drugs, we will continue to invest in the future with our deep pipeline of unpartnered next wave of oncology assets for which we own all rights globally and have significant flexibility in driving their development. We intend to accelerate our global drug development by leveraging our advanced clinical trial data from China and selectively conduct clinical trials concurrently in China and other jurisdictions so that the programs progress in parallel globally. To broaden and scale our international operations and support the increasing clinical activities in the United States and Europe, we plan to continue significantly expanding our clinical teams in those geographies.

Continue designing and creating molecules to develop into medicines with specific and differentiated characteristics for the benefit of patients

We believe our world-class drug discovery engine is our key competitive advantage. We strive to create differentiated novel oncology and immunology treatments with global potential. Our drug discovery team has utilized our expertise in advanced medicinal chemistry to develop next-generation TKI that have both high selectivity and superior pharmacokinetic properties. Equally importantly, we will continue to design chemical and biologic drug candidates with profiles that allow them to be used in innovative combinations with other selective inhibitors, chemotherapy agents and immunotherapies. Such combination therapies enable treatment of cancer via multiple pathways and modalities simultaneously, which has the potential to significantly improve treatment outcomes.

We plan to continue to build out our global pipeline of self-discovered drug candidates by advancing a rich pipeline of early-stage drug candidates, which include small molecule drugs targeting new pathways such as MAPK and biologics addressing novel targets designed for use in combination with our small molecules, as well as potentially a broad range of third-party therapies.

Build and scale our marketing and commercialization capabilities globally

We plan to leverage our long-standing drug marketing and distribution know-how and infrastructure to support our innovative oncology product launches, focusing in particular on the Chinese and U.S. markets. We have a 20-year track record of marketing and selling products in China. We aim to grow our in-house oncology drug sales team in China of about 630 persons to about 700 persons by the end of 2023. Outside of China, we intend to commercialize our products, if approved, in the United States where we have already begun to build our own sales team. In Europe, Japan and other major markets, we will look to form collaborations with leading biopharmaceutical companies and/or contract sales organizations to fully realize the value of our assets. We will also continue to scale our manufacturing capacity to support the sales of our approved drugs, including through the expansion of our existing Suzhou facility production team and the ongoing construction of our new plant in Shanghai, which will provide a five-fold increase in our existing production capacity.

Identify global business development and strategic acquisition opportunities to complement our internal research and development activities

We plan to explore opportunities to access complementary drug candidates and/or acquire interests in other biopharmaceutical companies to supplement our in-house research and development capabilities and to enhance our current drug candidate pipeline. We will also continue to seek in-licensing opportunities in China, with a focus on drug candidates with the potential to both complement our existing drug pipeline and have synergistic effects with each other, such as Tazverik from Epizyme. In addition, we expect to progress some of our drug candidates by pursuing business development opportunities with other biopharmaceutical companies both in China and globally such as our collaboration with BeiGene to evaluate combining surufatinib and fruquintinib with its anti-PD-1 antibody tislelizumab for the treatment of various solid tumor cancers. We will also continue to work with our partners, AstraZeneca and Eli Lilly, to optimize the potential of our drug candidates savolitinib (globally with AstraZeneca) and fruquintinib (in China with Eli Lilly).

Capitalize on regulatory reforms currently underway in China aimed at addressing existing unmet medical needs and improving the health of its people

We believe the Chinese oncology market, which comprises approximately a quarter of the global oncology patient population, represents a substantial and fast-growing market opportunity. Over the past decade, the PRC government has endeavored to foster an innovative biopharmaceutical ecosystem, and in the last few years, the pace of reforms has accelerated with a clear focus on providing Chinese patients access to world-class oncology therapies through expanded insurance reimbursement and reduced time for clinical trials and drug approvals. As a result, the oncology drug market in China is growing rapidly. Having invested in drug innovation in China for about 20 years, beginning at a time when almost no other domestic companies were involved in innovative oncology research, we believe we are well positioned to capture this market opportunity.

Oncology Commercial Operations

Surufatinib – Sulanda in China

We received approval from the NMPA for Sulanda as a treatment for patients with advanced non-pancreatic NETs in December 2020 and advanced pancreatic NETs in June 2021. During 2021, we introduced Sulanda through a campaign of local, regional and national launch events involving approximately 12,000 healthcare professionals. We have also confirmed a total of approximately 50 investigator-initiated studies in a broad range of exploratory solid tumor indications all of which are expected to gradually expand awareness of Sulanda in China. In 2021, we used means-test early access and patient access programs to help patients afford Sulanda, and we estimate approximately 4,800 new patients were treated. By the end of 2021, Sulanda prescriptions had been written in more than 30 provinces in China. Total in-market sales of Sulanda were $11.6 million in 2021, and in January 2022, Sulanda was included on China's NRDL, making it available in all public hospitals in China. There are an estimated approximately 34,000 new patients of advanced NETs per year in China and were potentially over 300,000 patients living with NET in China in 2021.

Fruquintinib – Elunate in China

We received approval from the NMPA for Elunate as a treatment for metastatic colorectal cancer, or mCRC, in September 2018. At the end of 2018, our collaboration partner Eli Lilly commenced commercial sales of Elunate, targeting the more than 80,000 mCRC third-line patients in China each year. In January 2020, Elunate was included on China's NRDL, and is therefore now available in public hospitals throughout China, paving the way to significantly broaden access for advanced CRC patients and rapidly build penetration in China over the coming years. In October 2020, we took over the development and execution of all on-the-ground medical detailing, promotion and local and regional marketing responsibilities in China through an amendment to our collaboration terms with Eli Lilly. Since taking on these commercial responsibilities, we have deployed our oncology drug sales force to market Elunate. We are quickly expanding hospital pharmacy listings, one of the most important factors affecting broad-scale adoption of Elunate in China, which now total over 400.

Driven in part by the inclusion of Elunate on the 2020 NRDL and our assumption of responsibility for detailing, promoting and marketing the drug in China in October 2020, total in-market sales of Elunate by Eli Lilly, as provided to us by Eli Lilly, increased by 111% to $71.0 million for the year ended December 31, 2021 compared to $33.7 million for the year ended December 31, 2020. We recognize revenue for royalties and manufacturing costs and, since October 1, 2020, additional service payments in association with our expanded role in the commercialization of Elunate paid to us by Eli Lilly. Subject to meeting pre-agreed sales targets, Eli Lilly will pay us an estimated total of 70% to 80% of Elunate in-market sales in the form of royalties, manufacturing costs and service payments. In 2021, we recorded $53.5 million in revenue for Elunate, equal to 75.4% of in-market sales. Following negotiations with the China National Healthcare Security Administration, Elunate continues to be included in the NRDL for a new two-year term starting in January 2022. For this renewal, we agreed to a discount of 5% relative to the 2021 NRDL price.

During 2021, our medical marketing and affairs teams conducted about 4,800 educational/scientific events for Elunate in China.

Savolitinib – Orpathys in China

On June 22, 2021, Orpathys became the first-in-class selective MET inhibitor to be approved in China. Our partner, AstraZeneca, then launched Orpathys in mid-July 2021, less than three weeks after its conditional approval by the NMPA for patients with MET exon 14 skipping alteration NSCLC. We are responsible for manufacturing and all other marketing authorization holder, or MAH, responsibilities, and our commercial collaboration partner AstraZeneca is responsible for the commercialization of Orpathys. In return for these commercial rights, AstraZeneca pays us a 30% royalty on all sales, various development and commercial milestones and manufacturing fees.

More than a third of the world's lung cancer patients are in China and, among those with NSCLC, approximately 2-3% have tumors with MET exon 14 skipping alterations, representing an approximate incidence of 13,000 new patients per year in China. Importantly also, MET plays a role in multiple other solid tumors, with an estimated total incidence of 120,000 new patients per year in China. In-market sales of Orpathys since its launch in July 2021, as provided to us by AstraZeneca, were $15.9 million showing rapid initial self-pay uptake for being the first-in-class selective MET inhibitor in China. These in-market sales also resulted in a $25.0 million first sale milestone payment from AstraZeneca to us and $11.3 million in revenues recognized by us from manufacturing fees and royalties in 2021. Since mid-2021, the progress made in the research, development and commercialization of savolitinib has triggered a total of $40 million in milestone payments from AstraZeneca to us. We estimate that approximately 1,900 new patients were treated with Orpathys in 2021.

AstraZeneca introduced a patient access program in late 2021 which subsidizes the use of Orpathys through progressive disease. Following negotiations with the China National Healthcare Security Administration, we and AstraZeneca declined inclusion in the 2022 NRDL, a position that will be reassessed for potential 2023 inclusion.

International Clinical Drug Development (Outside China)

Seven of our oncology drug candidates are in development outside China. Our fast expanding international organization, led mainly from the United States, is developing these candidates. We completed the rolling submission of our first U.S. NDA in April 2021, for surufatinib, and this NDA was accepted by the FDA in June 2021 subject to certain clinical site inspections by the FDA. The EMA also validated and accepted our marketing authorization application for surufatinib for advanced NETs in July 2021, and we completed the 120 day assessment and are now entering the later stages of MAA review. For savolitinib in combination with Tagrisso in EGFR TKI refractory NSCLC, we conducted an end of phase 2 meeting with the FDA. We also completed clinical trial applications in the United States, Europe and Japan for the SAFFRON study, a global pivotal Phase III of savolitinib and Tagrisso in patients with NSCLC who have progressed following Tagrisso treatment due to MET amplification or overexpression. In addition to the SAFFRON study, which we are preparing to initiate in mid-2022, we continue to evaluate the possibility of using the ongoing SAVANNAH study as the basis for U.S. accelerated approval. Among other progress we have made, enrollment was completed for fruquintinib in a fourteen-country global Phase III study, the FRESCO-2 study, in CRC which is expected to read-out later in 2022, and positive and differentiated proof-of-concept data was presented for amdizalisib.

The following table summarizes the status of our international clinical drug portfolio's development as of the date of the filing of this annual report:

Program	Investigational treatment	Disease	Target patient	Study name	Sites	Dose finding / safety run-in	Proof-of-concept	Registration
Savolitinib MET	**Savolitinib** + Tagrisso	NSCLC	2L/3L EGFRm; Tagrisso ref.; MET+	SAVANNAH	Global	*		
	Savolitinib + Tagrisso	NSCLC	2L/3L EGFRm; Tagrisso ref.; MET+	SAFFRON	Global	**		
	Savolitinib + Imfinzi (PD-L1)	Papillary RCC	MET+	SAMETA	Global			
	Savolitinib + Imfinzi (PD-L1)	Papillary RCC	All	CALYPSO	UK/Spain	***		
	Savolitinib + Imfinzi (PD-L1)	Clear cell RCC	VEGFR TKI refractory	CALYPSO	UK/Spain	***		
	Savolitinib	Gastric cancer	MET+	VIKTORY	S Korea	***		
Surufatinib VEGFR 1/2/3; FGFR 1; CSF-1R	**Surufatinib**	NET	Refractory		US			NDA under review
	Surufatinib	NET			EU			MMA under review
	Surufatinib	NET			JP	(Bridging)		
	Surufatinib + tislelizumab (PD-1)	Solid tumors			US/EU			
Fruquintinib VEGFR 1/2/3	**Fruquintinib**	Colorectal cancer	Refractory	FRESCO-2	US/EU/JP			
	Fruquintinib	Breast cancer			US			
	Fruquintinib + tislelizumab (PD-1)	TN breast cancer, EMC			US			
	Fruquintinib + tislelizumab (PD-1)	Solid tumors			S Korea			
Amdizalisib (HMPL-689) PI3Kδ	**Amdizalisib**	Indolent NHL, PTCL			US/EU			
	Amdizalisib	Healthy volunteers			Australia			
Sovleplenib (HMPL-523) Syk	**Sovleplenib**	Indolent NHL			Australia			
	Sovleplenib	Indolent NHL			US/EU			
HMPL-306 IDH 1/2	**HMPL-306**	Solid tumors			US/EU			
	HMPL-306	Heme. malignancies			US/EU			
HMPL-760 BTK, 3G	**HMPL-760**	B-Cell NHL			US/EU	**		

* Phase II registration-intent study subject to regulatory discussion; ** In planning; *** Investigator-initiated trials (IIT)

Note: NDA = New Drug Application; MAA = Marketing Authorization Application; MET = mesenchymal epithelial transition receptor; NSCLC = non-small cell lung cancer; EGFRm = epidermal growth factor receptor mutation; RCC = renal cell carcinoma; VEGFR = vascular endothelial growth factor receptor; TKI = tyrosine kinase inhibitor; FGFR 1 = fibroblast growth factor receptor 1; CSF-1R = colony stimulating factor-1 receptor; NET = neuroendocrine tumors; TN = triple negative; EMC = endometrial cancer; PI3Kδ = Phosphatidylinositol-3-Kinase delta; NHL = Non-Hodgkin's Lymphoma; PTCL = peripheral T-cell lymphoma; Syk = spleen tyrosine kinase; IDH 1/2 = isocitrate dehydrogenase 1/2; BTK = Bruton's tyrosine kinase.

Savolitinib – selective MET inhibitor in late-stage clinical development as a monotherapy and in combination therapies in global partnership with AstraZeneca

Savolitinib, which has been approved in China for the treatment of patients with locally advanced or metastatic NSCLC, is a potent and selective small molecule inhibitor of the MET receptor tyrosine kinase, an enzyme which has been shown to function abnormally in many types of solid tumors. We designed savolitinib through chemical structure modification to specifically address kidney toxicity, the primary issue that halted development of several other selective MET inhibitors. In clinical trials to date in over 1,500 patients globally, savolitinib has shown promising signs of clinical efficacy in patients with multiple types of MET gene alterations in lung cancer, kidney cancer and gastric cancer with an acceptable safety profile.

We are currently testing savolitinib in global partnership with AstraZeneca, both as a monotherapy and in combination with immunotherapy and targeted therapy. Most notably, MET-amplification is a major mechanism for acquired resistance to both first-generation EGFR TKIs as well as third-generation EGFR TKIs like Tagrisso. Savolitinib has been studied extensively in these patients in the TATTON and SAVANNAH studies. Final results from the TATTON study were presented at World Conference on Lung Cancers, or WCLC, in January 2021, and initial results from SAVANNAH are in preparation for submission to a scientific conference in 2022. The successful results led to the initiation and planning of three Phase III studies: SACHI and SANOVO were initiated in China in 2021, and the global, pivotal Phase III study, the SAFFRON study, is planned to commence enrollment in mid-2022. In addition to a planned Phase III study, we continue to evaluate the possibility of using data from the TATTON and SAVANNAH studies to seek accelerated approval in the United States.

Proof-of-concept studies of savolitinib in kidney cancer (as a monotherapy as well as in combination with a PD-L1 inhibitor) and gastric cancer (as a monotherapy as well as in combinations with chemotherapy) have demonstrated positive results, with subsequent clinical development ongoing or in planning. For example, we initiated a global Phase III pivotal trial (SAMETA) in October 2021 for savolitinib in combination with Imfinzi, AstraZeneca's anti-PD-L1 antibody durvalumab, in MET positive patients with papillary renal cell carcinoma or PRCC, a form of kidney cancer. Savolitinib opportunities are also continuing to be explored in multiple other MET-driven tumor settings via investigator-initiated studies including CRC.

Surufatinib—unique angio-immuno kinase inhibitor with NDA submission completed in the United States and MAA in Europe; potential first VEGFR/FGFR/CSF-1R inhibitor for all advanced NETs

Surufatinib, which has been approved in China for the treatment of advanced NETs, is a novel, oral angio-immuno kinase, small molecule inhibitor that selectively inhibits the tyrosine kinase activity associated with VEGFR and FGFR, which both inhibit angiogenesis, and colony stimulating factor-1 receptor, or CSF-1R, which regulates tumor-associated macrophages, promoting the body's immune response against tumor cells. Its unique dual mechanism of action may be very suitable for possible combinations with other immunotherapies. We believe surufatinib is potentially the first VEGFR/FGFR/CSF-1R inhibitor for all advanced NETs.

In the United States, the FDA granted orphan drug designation to surufatinib for the treatment of pancreatic NETs in November 2019 and granted fast track designations for the treatment of both pancreatic NETs and non-pancreatic NETs in April 2020. In May 2020, we reached an agreement with the FDA that the completed SANET-ep (non-pancreatic NET) and SANET-p (pancreatic NET) studies in China, along with existing data from surufatinib in U.S. non-pancreatic and pancreatic NET patients, could form the basis to support an NDA submission. Pharmacokinetic and safety data from U.S. Phase Ib neuroendocrine tumor cohorts demonstrated similar profiles of surufatinib between Chinese and U.S. patients.

We completed a U.S. NDA submission in April 2021 for surufatinib for the treatment of pancreatic and non-pancreatic NETs. This is our first NDA in the United States, and it was accepted by the FDA in June 2021. The related clinical site inspections and pre-approval inspections of our manufacturing facilities are ongoing. The data package has also been used to file a marketing authorization application, to the EMA, based on scientific advice from the EMA Committee for Medicinal Products for Human Use, or CHMP. The EMA has validated and accepted our marketing authorization application in July 2021.

We have various additional clinical trials of surufatinib ongoing as a single agent, as well as in combination with checkpoint inhibitors. In March 2021, we dosed the first patient in a combination study of surufatinib with tislelizumab, an anti-PD-1 antibody being developed by BeiGene, in the United States and Europe, and we expect to submit the data from this study for presentation in late 2022. In September 2021, we dosed our first patient in a registration-enabling bridging study in Japan to support the registration of surufatinib in the treatment of patients with advanced NETs. In addition, we believe surufatinib has potential in a number of other tumor types such as CRC, small cell lung cancer, gastric cancer and soft tissue sarcoma.

Surufatinib is the first oncology medicine that we have launched in China and expanded development globally without the support of a development partner. We own all rights to surufatinib globally.

Fruquintinib—selective VEGFR 1, 2 and 3 inhibitor with the best selectivity for its targets in global Phase III development

Fruquintinib, which has been approved in China for the treatment of advanced mCRC, is a highly selective and potent oral inhibitor of vascular endothelial growth factor or VEGF receptors, known as VEGFR 1, 2 and 3. We believe that fruquintinib has the potential to become a selective small molecule VEGFR 1, 2 and 3 inhibitor for many types of solid tumors that has the highest selectivity, and we are currently studying fruquintinib in CRC, gastric cancer, breast cancer and other solid tumor types. Fruquintinib was designed to improve kinase selectivity to minimize off-target toxicities, improve tolerability and provide more consistent target coverage. The tolerability in patients to date, along with fruquintinib's low potential for drug-drug interaction based on pre-clinical assessment, suggests that it may be highly suitable for combinations with other anti-cancer therapies.

Building on the data collected from our successful Phase III trial in China, known as the FRESCO study, which supported fruquintinib's approval in China, we initiated FRESCO-2, a large randomized controlled study of fruquintinib in the United States, Europe, Japan and Australia. The first patient was dosed in September 2020, and the study enrolled over 690 patients in over 150 sites in 14 countries. The FDA granted fast track designation for the development of fruquintinib for the treatment of patients with mCRC in June 2020. The FDA has acknowledged the totality of the fruquintinib clinical data, including the FRESCO-2 study, if positive, the prior positive Phase III FRESCO study demonstrating improvement in overall survival, or OS, that led to fruquintinib approval for metastatic CRC in China in 2018 and additional completed and ongoing supporting studies in metastatic CRC, could support a future NDA for the treatment of patients with third-line and above mCRC. The EMA and Japanese Pharmaceuticals and Medical Devices Agency or PMDA have reviewed and endorsed the FRESCO-2 study design. Preliminary data of U.S. Phase I/Ib CRC cohorts demonstrated encouraging efficacy in patients refractory or intolerant to Stivarga and Lonsurf.

We are conducting and planning global combination studies of fruquintinib with BeiGene's anti-PD-1 antibody tislelizumab for the treatment of various solid tumor cancers, including an ongoing Phase Ib/II study in advanced, refractory triple negative breast cancer or advanced endometrial cancer.

Fruquintinib is being commercialized and developed in partnership with Eli Lilly in China, where we are responsible for development, manufacturing, on-the-ground medical detailing, promotion and local and regional marketing activities. We own all rights to fruquintinib outside of China.

Amdizalisib (HMPL-689)—novel, highly selective PI3Kδ inhibitor with potential in hematological cancer

Amdizalisib is a novel, highly selective and potent small molecule inhibitor targeting the isoform PI3Kδ. In pre-clinical pharmacokinetic studies, amdizalisib's pharmacokinetic properties have been found to be favorable with good oral absorption, moderate tissue distribution and low clearance. Amdizalisib is also expected to have low risk of drug accumulation and drug-drug interaction and is highly potent, particularly at the whole blood level. Amdizalisib received Breakthrough Therapy Designation from the CDE of the NMPA in China for the treatment of refractory follicular lymphoma in September 2021. The NMPA grants Breakthrough Therapy Designation to new drugs that treat life-threatening diseases or serious conditions for which there are no effective treatment options, and where clinical evidence demonstrates significant advantages over existing therapies. Drug candidates with Breakthrough Therapy Designation may be considered for conditional approval and priority review when submitting an NDA.

We have early-stage clinical trials of amdizalisib ongoing and preliminary evidence suggests that amdizalisib may perform in the clinic as designed. Based on extensive Phase I/Ib proof-of-concept clinical data in China and Australia on amdizalisib, we have opened 18 U.S. and European sites for a Phase I/Ib study with patient enrollment underway, focusing on advanced relapsed or refractory lymphoma. We have initiated the dose expansion portion of the Phase I study in the United States and Europe in the second half of 2021 in multiple types of non-Hodgkin's lymphoma.

We own all rights to amdizalisib globally.

Sovleplenib (HMPL-523)—potentially the first selective Syk inhibitor for hematological cancer

Sovleplenib is a novel, highly selective, oral, small molecule inhibitor targeting the spleen tyrosine kinase, or Syk, for the treatment of hematological cancers and certain chronic immune diseases. Syk is a major component in B-cell receptor signaling and is an established therapeutic target in multiple subtypes of B-cell lymphomas. Because B-cell malignancies are heterogeneous and patients commonly experience relapse despite current therapies, there is a need for new therapies.

We have various clinical trials of sovleplenib ongoing. We have multiple sites in the United States and Europe for a Phase I/Ib study with patient enrollment underway, focusing on advanced relapsed or refractory lymphoma and are close to establishing our Phase II dose.

We own all rights to sovleplenib globally.

HMPL-306—potentially the first dual inhibitor of IDH1 and IDH2 with applications in hematological malignancies and solid tumors

HMPL-306 is a novel small molecule dual-inhibitor of isocitrate dehydrogenase 1 and 2, or IDH 1 and 2, enzymes. IDH1 and IDH2 mutations have been implicated as drivers of certain hematological malignancies and solid tumors, particularly among acute myeloid leukemia patients. We initiated two international Phase I studies, one for AML and the other for solid tumors, with the first patient dosed in the United States in March 2021.

We own all rights to HMPL-306 globally.

HMPL-760—an investigational, highly selective, third-generation oral inhibitor of BTK with improved potency versus first generation BTK inhibitors against both wild type & C481S mutant enzymes

We initiated a Phase I study in patients with advanced hematological malignancies in China in January 2022. We are also initiating an international Phase I study in patients with advanced hematological malignancies in the United States. We own all rights to HMPL-760 globally.

China Clinical Drug Development

We are the MAH of three internally discovered and developed innovative oncology medicines, Orpathys, Sulanda and Elunate. We have additional drug candidates in earlier stage clinical development (Phase I/Ib and Phase Ib/II proof-of-concept studies) and several advanced pre-clinical drug candidates. Our four submitted China NDAs were classified by the NMPA as Category 1. If submitted for approval, all of our drug candidates are expected to be classified as Category 1, as they are innovative drugs that have not been marketed inside or outside of China.

The following table summarizes the status of our China clinical programs as of the date of the filing of this annual report.

Program	Investigational treatment	Disease	Target patient	Study name	Sites	Dose finding / safety run-in	Proof-of-concept	Registration
Savolitinib MET	**Savolitinib**	NSCLC	MET Exon 14 skipping		China			Marketed
	Savolitinib + Tagrisso	NSCLC	Naïve MET+ & EGFRm NSCLC	SANOVO	China			
	Savolitinib + Tagrisso	NSCLC	2L EGFR TKI ref. NSCLC; MET+	SACHI	China			
	Savolitinib	Gastric cancer	2L; MET+		China			
Surufatinib VEGFR 1/2/3; FGFR 1; CSF-1R	**Surufatinib**	Pancreatic NET	All	SANET-p	China			Marketed
	Surufatinib	Non-Pancreatic NET	All	SANET-ep	China			Marketed
	Surufatinib + Tuoyi (PD-1)	NEC		SURTORI- 01	China			
	Surufatinib + Tuoyi (PD-1)	ESCC			China			
	Surufatinib + Tuoyi (PD-1)	GC, SCLC			China			
	Surufatinib + Tuoyi (PD-1)	BTC, Sarcoma			China			
	Surufatinib + Tuoyi (PD-1)	TC, EMC, NSCLC			China			
Fruquintinib VEGFR 1/2/3	**Fruquintinib**	Colorectal cancer	≥3L; chemotherapy refractory	FRESCO	China			Marketed
	Fruquintinib + Taxol	Gastric cancer	2L	FRUTIGA	China			
	Fruquintinib + Tyvyt (PD-1)	EMC			China			
	Fruquintinib + Tyvyt (PD-1)	CRC			China			
	Fruquintinib + Tyvyt (PD-1)	RCC, HCC			China			
	Fruquintinib + Tyvyt (PD-1)	GI tumors			China			
	Fruquintinib + tislelizumab (PD-1)	Solid tumors			China			
Amdizalisib (HMPL-689) PI3Kδ	**Amdizalisib**	FL			China			
	Amdizalisib	MZL			China			
	Amdizalisib	MCL, DLBCL			China			
	Amdizalisib	CLL/SLL, HL			China			
Sovleplenib (HMPL-523) Syk	**Sovleplenib**	ITP	All	ESLIM-01	China			
	Sovleplenib	B-cell malignancies	All		China			
	Sovleplenib	wAIHA	All		China	*		
Tazemetostat EZH2	**Tazemetostat** **	FL	Relapsed/Refractory	SYMPHONY-1	China	*		
	Tazemetostat **	FL	3L		China	* (Bridging)		
	Note: Tazemetostat developed by Epizyme. Approved in the U.S. for ES and FL as a monotherapy. HUTCHMED rights are for Greater China – bridging study being planned.							
HMPL-306 IDH 1/2	**HMPL-306**	Heme. malignancies			China			
HMPL-760 BTK, 3G	**HMPL-760**	B-Cell NHL			China			
HMPL-453 FGFR 1/2/3	**HMPL-453**	IHCC			China			
	HMPL-453	Solid tumors	Multiple combos		China			
HMPL-295 ERK, MAPK pathway	**HMPL-295**	Solid tumors			China			
HMPL-653 CSF-1R	**HMPL-653**	Solid tumors, TGCT			China			

* In planning; ** development in collaboration with Epizyme

Note: MET = mesenchymal epithelial transition receptor; NSCLC = non-small cell lung cancer; EGFRm = epidermal growth factor receptor mutation; TKI = tyrosine kinase inhibitor; VEGFR = vascular endothelial growth factor receptor; FGFR 1 = fibroblast growth factor receptor 1; CSF-1R = colony stimulating factor-1 receptor; NET = neuroendocrine tumors; NEC = neuroendocrine carcinoma; ESCC = esophageal cancer; GC = gastric cancer; SCLC = small cell lung cancer; BTC = biliary tract cancer; TC = thyroid cancer; EMC = endometrial cancer; CRC = colorectal cancer; RCC = renal cell carcinoma; HCC = hepatocellular carcinoma; GI = gastrointestinal; PI3Kδ = Phosphatidylinositol-3-Kinase delta; FL = follicular lymphoma; MZL = marginal zone lymphoma; MCL = mantle cell lymphoma; DLBCL = diffuse large B cell lymphoma; CLL/SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma; HL = Hodgkin's lymphoma; Syk = spleen tyrosine kinase; ITP = immune thrombocytopenic purpura; wAIHA = warm autoimmune hemolytic anemia; EZH2 = enhancer of zeste homolog 2; IHCC = intrahepatic cholangiocarcinoma; IDH 1/2 = isocitrate dehydrogenase 1/2; ERK = extracellular-signal-regulated kinase; MAPK pathway = RAS-RAF-MEK-ERK signaling cascade; BTK = Bruton's tyrosine kinase; TGCT = Tenosynovial Giant Cell Tumors.

Savolitinib – commercially launched as Orpathys and first selective MET inhibitor in China

In June 2021, the NMPA approved savolitinib for marketing for the treatment of NSCLC with MET exon 14 skipping alterations, making savolitinib the first-in-class selective MET inhibitor in China. This approval follows a priority review designation by the NMPA and is the first regulatory approval globally for this oral, potent and selective MET TKI. The approval by the NMPA was based on positive results from a Phase II trial conducted in China in patients with NSCLC with this mutation, including patients with the more aggressive pulmonary sarcomatoid carcinoma subtype. Savolitinib demonstrated effective anti-tumor activity based on an independent review of objective response rate or ORR and disease control rate or DCR. The approval is conditional upon successful completion of a confirmatory study in this patient population. The results reviewed by the NMPA when it approved savolitinib were also published in *The Lancet Respiratory Medicine*.

In 2021, we initiated several new trials in a variety of indications, including for example, SAMETA, a global Phase III pivotal study of savolitinib with Imfinzi in MET-driven, unresearchable and locally advanced or metastatic PRCC, and a confirmatory China Phase IIIb post-approval study of savolitinib monotherapy in MET exon 14 skipping alteration patients. In the same year, we also presented CALYPSO Phase II study data in MET-drive patients for savolitinib in combination with Imfinzi at the 2021 American Society of Clinical Oncology, or ASCO, annual meeting and the final Phase II data for the TATTON study at 2020 WCLC annual meeting.

In 2022, we plan to submit for presentation the SAVANNAH Phase II study for the savolitinib plus Tagrisso combination in NSCLC patients harboring EGFR mutation and MET amplification or overexpression. SAVANNAH has informed the regulatory, biomarker and dose regimen strategy for the China Phase III studies SANOVO and SACHI, and the global Phase III study in planning. We also plan to initiate a global, pivotal Phase III study for the savolitinib plus Tagrisso combination in mid-2022, in patients with NSCLC who have progressed following Tagrisso treatment due to MET amplification.

Surufatinib—commercially launched as Sulanda in China in advanced NETs; first VEGFR/FGFR/CSF-1R inhibitor for all advanced NETs

Surufatinib was approved by the NMPA in December 2020 for the treatment of non-pancreatic NETs and is now being marketed by us in China under the brand name Sulanda. This NMPA approval of surufatinib was based on results from the SANET-ep study, a Phase III trial in patients with advanced non-pancreatic NETs conducted in China. The positive results of this trial were highlighted in an oral presentation at the 2019 ESMO Congress and published in *The Lancet Oncology* in September 2020. In June 2021, surufatinib was approved by the NMPA for the treatment of advanced pancreatic NETs. This NMPA approval of surufatinib was based on results from the SANET-p study, a Phase III trial in patients with advanced pancreatic NETs conducted in China. The positive results of this trial were highlighted in an oral presentation at the 2020 ESMO Congress and published in *The Lancet Oncology* in September 2020. Sulanda was included in the NRDL starting January 2022, thereby broadening access to patients with advanced NETs in China. Our in-house oncology drug sales team is now responsible for the marketing and commercialization of surufatinib throughout China for such indications. In 2021, we initiated, among others, the SURTORI-01 Phase III trial in NEC patients in China, the first pivotal study combining surufatinib and toripalimab.

In 2021, we presented NEC cohort and gastric and gastroesophageal junction cancers cohort data from the China Phase II study of surufatinib plus Tuoyi at the 2021 ASCO and updated data at ESMO Immuno-Oncology Congress 2021 annual meetings. We also presented encouraging data from the subgroup analysis by Ki-67 and baseline CgA of the Phase III monotherapy study in pancreatic NET (SANET-p) and Phase II study for surufatinib monotherapy in BTC patients at the 2021 ASCO annual meeting.

Fruquintinib – commercially launched as Elunate in China in CRC in November 2018; potential VEGFR 1, 2 and 3 inhibitor with the best selectivity for many solid tumors

Fruquintinib was first commercially launched in China, marketed by our partner Eli Lilly, in November 2018 for the treatment of advanced CRC. In January 2020 (and subsequently extended for another two-year term starting in January 2022), fruquintinib was included on the NRDL thereby broadening access by advanced CRC patients in China. Since launch, Eli Lilly has deployed a dedicated team of over 140 oncology commercial personnel to market fruquintinib in China. Since October 1, 2020, we have taken over development and execution of all on-the-ground medical detailing, promotion and local and regional marketing activities for fruquintinib in China, using our in-house oncology drug sales team supported by our long-standing drug marketing and distribution platforms. Subject to meeting pre-agreed sales targets, Eli Lilly will pay us an estimated total of 70% to 80% of Elunate in-market sales in the form of royalties, manufacturing costs and service payments.

We believe that fruquintinib is a VEGFR 1, 2 and 3 inhibitor with the best selectivity and could be considered for development in China in many solid tumor indications in which VEGFR inhibitors have been approved globally. To this end, since 2018, we have assumed all planning, execution and decision-making responsibilities for life cycle indication development of fruquintinib in China.

In addition to its commercial launch in CRC in China, we have made progress with fruquintinib in various other cancer indications, including the FRUTIGA study in China, a pivotal Phase III study in approximately 700 patients to evaluate the efficacy and safety of fruquintinib in combination with Taxol, a chemotherapy medication, compared with Taxol monotherapy for second-line treatment of advanced gastric cancer in patients who had failed first-line chemotherapy. We expect to complete enrollment of the study in 2022.

We are conducting Phase Ib/II dose expansion studies in China of fruquintinib with Tyvyt, a PD-1 monoclonal antibody being developed by Innovent, in different tumor types, including HCC, endometrial cancer, RCC and CRC. Furthermore, we intend to conduct studies of fruquintinib in combination with BeiGene's tislelizumab for the treatment of various solid tumor cancers in China. At the 2021 ASCO annual meeting, encouraging preliminary Phase I/Ib results were presented for fruquintinib in combination with two different PD-1 inhibitors: Tyvyt and geptanolimab.

Amdizalisib—novel, highly selective PI3Kδ inhibitor with potential in hematological cancer

Our Phase I dose escalation study on amdizalisib in China has been completed, and a recommended Phase II dose was selected. Amdizalisib was well tolerated, exhibiting dose-proportional pharmacokinetics, a manageable toxicity profile, and single-agent clinical activity in relapsed/refractory B-cell lymphoma patients. Our Phase Ib expansion study in China is ongoing in multiple sub-categories of indolent non-Hodgkin's lymphoma. In April 2021, we commenced a registration-intent Phase II trial of amdizalisib a highly selective and potent PI3Kδ inhibitor in China in patients with relapsed or refractory follicular lymphoma and marginal zone lymphoma, two subtypes of non-Hodgkin's lymphoma.

Sovleplenib—potentially the first selective Syk inhibitor for hematological diseases

Data from an extensive Phase I/Ib dose escalation and expansion study (covering more than 200 patients) on sovleplenib has encouraged us to initiate exploratory studies in China on multiple indolent non-Hodgkin's lymphoma sub-categories, including chronic lymphocytic leukemia/small lymphocytic lymphoma, follicular lymphoma, marginal zone lymphoma, Waldenstrom's macroglobulinemia and mantle cell lymphoma.

Furthermore, in August 2019 we commenced a Phase I study of sovleplenib in China for the treatment of immune thrombocytopenia, an autoimmune disorder characterized by low platelet count and an increased bleeding risk. Based on the encouraging data from Phase Ib study of sovleplenib in adult patients with immune thrombocytopenia, we commenced a Phase III study in the same indication and dosed the first patient in October 2021. In January 2022, sovleplenib received the Breakthrough Therapy Designation in China for treatment of primary immune thrombocytopenia.

Tazemetostat

In August 2021, we entered into a strategic collaboration with Epizyme, Inc. to research, develop, manufacture and commercialize tazemetostat (Tazverik) in Greater China, including mainland China, Hong Kong, Macau and Taiwan. Tazemetostat is an inhibitor of EZH2 developed by Epizyme that is approved by the FDA for the treatment of certain epithelioid sarcoma and follicular lymphoma patients. It received accelerated approval from the FDA based on ORR and DOR in January and June 2020 for epithelioid sarcoma and follicular lymphoma, respectively. We plan to develop and seek approval for tazemetostat in various hematological and solid tumors, including epithelial sarcoma, follicular lymphoma and diffuse large b-cell lymphoma in Greater China. We are participating in Epizyme's SYMPHONY-1 (EZH-302) study, leading it in Greater China. We and Epizyme also intend to conduct additional global studies jointly.

HMPL-306—potentially the first dual inhibitor of IDH1 and IDH2 with applications in hematological malignancies and solid tumors

A Phase I trial in China was initiated in July 2020, in patients of relapsed or refractory hematological malignancies with an IDH1 and/or IDH2 mutation. Multiple sites have been initiated and we aim to establish the Phase II dose in mid-2022.

HMPL-760—highly potent, selective, and reversible inhibitor with long target engagement against BTK

In January 2022, we initiated a Phase I trial in China in patients with previously treated chronic lymphocytic leukemia/small lymphocytic lymphoma or other types of non-Hodgkin lymphoma, including patients treated with a prior regimen containing a BTK inhibitor, whose disease carries either wild-type BTK or acquired resistance to first generation BTK inhibitors due to additional mutations to BTK. An initial dose escalation stage to determine the maximum tolerated dose and/or the RP2D is planned, to be followed by a dose expansion phase where patients will receive HMPL-760 to further evaluate the safety, tolerability, and clinical activity at the RP2D. Approximately 100 patients are expected to be enrolled.

HMPL-453—highly selective FGFR 1/2/3 inhibitor with potential in solid tumors

Aberrant FGFR signaling is associated with tumor growth, promotion of angiogenesis, as well as resistance to anti-tumor therapies. A Phase II study is ongoing in patients with advanced intrahepatic cholangiocarcinoma, or IHCC, with FGFR2 fusion that had failed at least one line of systemic therapy. IHCC is a cancer that develops within the bile ducts, the second most common primary hepatic malignancy after hepatocellular carcinoma. Approximately 10-15% of IHCC patients have tumors that harbor FGFR2 fusion. We also initiated a Phase Ib/II study of HMPL-453 in combination with chemotherapies or toripalimab for advanced solid tumors in China in January 2022.

HMPL-295 – an investigative and highly selective small molecule inhibitor of ERK in the MAPK pathway with the potential to address intrinsic or acquired resistance from upstream mechanisms such as RAS-RAF-MEK

HMPL-295, a novel ERK inhibitor, is our tenth in-house discovered small molecule oncology drug candidate. ERK is a downstream component of the RAS-RAF-MEK-ERK signaling cascade (MAPK pathway). This is our first of multiple candidates in discovery targeting the MAPK pathway. A China Phase I study of HMPL-295 as a monotherapy has been initiated in July 2021.

HMPL-653—CSF-1R inhibitor

HMPL-653 is a novel, highly selective, and potent CSF-1R inhibitor designed to target CSF-1R driven tumors as a monotherapy or in combination with other drugs. A China Phase I initiated in January 2022.

Discovery Research & Pre-clinical Development

We have built a drug discovery engine based in China, which has already produced a pipeline of 17 differentiated clinical and late pre-clinical stage drug candidates covering both novel and validated targets of which two are now marketed and one is under review for approval. We strive to create differentiated novel oncology and immunology treatments with global potential. These include furthering both small molecule and biologic therapies which address aberrant genetic drivers and cancer cell metabolism; modulate tumor immune microenvironment; and target immune cell checkpoints. We design drug candidates with profiles that enable them to be used in innovative combinations with other therapies, such as chemotherapy, immunotherapy and other targeted therapies in order to attack disease simultaneously through multiple modalities and pathways. We believe that this approach can significantly improve treatment outcomes for patients. In addition to our clinical-stage assets, we have another novel oncology drug candidate in late pre-clinical stage, namely HMPL-A83, targeting solid tumors and hematological malignancies.

Beyond these clinical and pre-clinical stage candidates, we continue to conduct research into discovering new types of drug candidates, including among others, small molecules addressing cancer-related apoptosis, cell signaling, epigenetics and protein translation; biologic drug candidates including bispecific antibodies; and novel technologies including antibody-drug conjugates and heterobifunctional small molecules.

Manufacturing

Our manufacturing facility in Suzhou complies with applicable GMP standards, providing supplies of our drug candidates for clinical trials and Elunate and Sulanda for commercial sale. We plan to continue to invest resources in the Suzhou facility, expanding the production team in phases. At the end of 2020, we commenced construction of a large-scale manufacturing plant for innovative drugs in Shanghai. The Shanghai factory will be our largest manufacturing facility, with a production capacity estimated to be five times that of our manufacturing plant in Suzhou.

The first phase will be primarily for small molecule production, while the second phase is expected to include expansion into large molecule production. The Shanghai factory is designed to increase our novel drug product manufacturing capacity by over five-fold, and we plan to complete the small molecule equipment installation in late 2022, with GMP compliance targeted for late 2023.

Currently, our commercial supplies of Elunate and Sulanda sold by our Oncology/Immunology operations are manufactured at our manufacturing facility in Suzhou, China. Our commercial supplies of Orpathys are outsourced and manufactured by a third-party manufacturer based in Shanghai, China. We have completed the manufacturing process studies for amdizalisib and sovleplenib in preparation for potential NDA submissions.

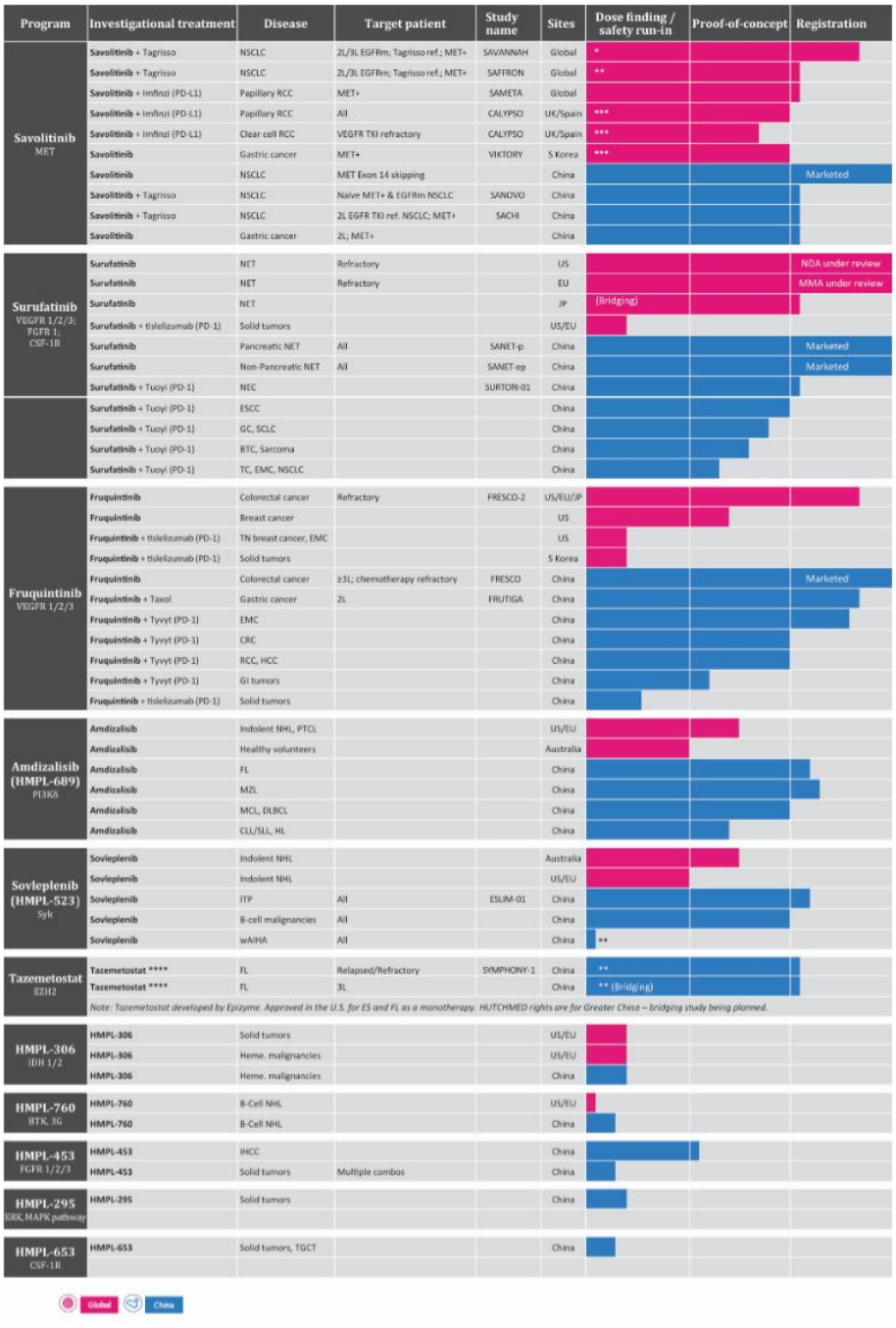
Other Ventures

In addition to our Oncology/Immunology operations, our Other Ventures include large-scale drug marketing and distribution platforms covering about 290 cities and towns in China with approximately 2,900 manufacturing and commercial personnel as of December 31, 2021. Built over the past 20 years, it primarily focuses on prescription drug and consumer health products mainly through: (i) Shanghai Hutchison Pharmaceuticals, a non-consolidated joint venture with a commercial team of over 2,200 staff managing the medical detailing and marketing of a range of own-brand prescription drug products and (ii) Hutchison Sinopharm, a consolidated joint venture focused on providing commercial services for our own marketed drugs, as well as marketing third-party prescription drug products and our science-based infant nutrition products. Hutchison Baiyunshan, a former non-consolidated joint venture focused on the manufacturing, marketing and distribution of primarily own-brand OTC drugs, was also a part of our Other Ventures' operations before its disposal in September 2021.

Net income attributable to our company from our Other Ventures totaled $41.5 million, $72.8 million and $142.9 million for the years ended December 31, 2019, 2020 and 2021, respectively, and are remitted to our group through dividend payments primarily from our non-consolidated joint ventures mentioned above. In 2021, dividends of an aggregate amount of $103.0 million were declared from these joint ventures to our group, with aggregate dividends declared to our group since inception of over $400 million.

Our Clinical Pipeline

The following table summarizes the status of our clinical programs as of the date of the filing of this annual report:



* Phase II registration-intent study subject to regulatory discussion; ** In planning;

*** Investigator-initiated trials (IIT); **** development in collaboration with Epizyme

Note: NDA = New Drug Application; MAA = Marketing Authorization Application; MET = mesenchymal epithelial transition receptor; NSCLC = non-small cell lung cancer; EGFRm = epidermal growth factor receptor mutation; RCC = renal cell carcinoma; VEGFR = vascular endothelial growth factor receptor; TKI = tyrosine kinase inhibitor; FGFR 1 = fibroblast growth factor receptor 1; CSF-1R = colony stimulating factor-1 receptor; NET = neuroendocrine tumors; NEC = neuroendocrine carcinoma; ESCC = esophageal cancer; GC = gastric cancer; SCLC = small cell lung cancer; BTC = biliary tract cancer; TC = thyroid cancer; EMC = endometrial cancer; TN = triple negative; CRC = colorectal cancer; HCC = hepatocellular carcinoma; GI = gastrointestinal; PI3Kδ = Phosphatidylinositol-3-Kinase delta; NHL = Non-Hodgkin's Lymphoma; PTCL = peripheral T-cell lymphoma; FL = follicular lymphoma; MZL = marginal zone lymphoma; MCL = mantle cell lymphoma; DLBCL = diffuse large B cell lymphoma; CLL/SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma; HL = Hodgkin's lymphoma; Syk = spleen tyrosine kinase; ITP = immune thrombocytopenic purpura; wAIHA = warm autoimmune hemolytic anemia; EZH2 = enhancer of zeste homolog 2; IHCC = intrahepatic cholangiocarcinoma; IDH ½ = isocitrate dehydrogenase 1/2; ERK = extracellular-signal-regulated kinase; MAPK pathway = RAS-RAF-MEK-ERK signaling cascade; BTK = Bruton's tyrosine kinase; TGCT = Tenosynovial Giant Cell Tumors.

The following is a summary of the clinical pipeline for our drug candidates, many of which are being investigated against multiple indications.

1. Savolitinib (HMPL-504), MET Inhibitor

Savolitinib is a potent and selective inhibitor of MET, an enzyme which has been shown to function abnormally in many types of solid tumors. We designed savolitinib to address human metabolite-related renal toxicity, the primary issue that halted development of several other selective MET inhibitors. In clinical studies to date, savolitinib has shown promising signs of clinical efficacy in patients with MET gene alterations in NSCLC, PRCC, CRC, gastric cancer and prostate cancer with an acceptable safety profile. In global partnership with AstraZeneca, savolitinib has been studied in over 1,500 patients to date, both as a monotherapy and in combinations. For more information regarding our partnership with AstraZeneca, see "—Overview of Our Collaborations—AstraZeneca."

Mechanism of Action

MET is a signaling pathway that has specific roles in normal mammalian growth and development. However, the MET pathway has also been shown to function abnormally in a range of different cancers, primarily through MET gene amplification, overexpression and gene mutations. The aberrant activation of MET has been demonstrated to be highly correlated in many cancer indications, including kidney, lung, gastric, colorectal, esophageal and brain cancer. It plays a major role in cancer pathogenesis (i.e., the development of the cancer), including tumor growth, survival, invasion, metastasis, the suppression of cell death as well as tumor angiogenesis.

MET also plays a role in drug resistance in many tumor types. For instance, MET gene amplification has been found in NSCLC and CRC following anti-EGFR treatment, leading to drug resistance. Furthermore, MET dysregulation is considered to play a role in the immunosuppression and pathogenesis of kidney cancer.

Savolitinib Research Background

First generation selective MET inhibitors previously discovered by multinational pharmaceutical companies had positive pre-clinical data that supported their high MET selectivity and pharmacokinetic and toxicity profiles, but did not progress very far due to kidney toxicity. The issue appeared to be that certain metabolites of earlier compounds had dramatically reduced solubility and appeared to crystalize in the kidney, resulting in obstructive toxicity. With this understanding, we designed our compound, savolitinib (also known as AZD6094 and HMPL-504, formerly known as volitinib), differently while preserving high MET inhibition properties across multiple types of MET aberrations. Savolitinib has not shown any renal toxicity to date and does not appear to carry the same metabolite problems as the earlier selective MET compounds based on studies in over 1,500 patients conducted by AstraZeneca in global partnership with the company.

Savolitinib Pre-clinical Evidence

In pre-clinical trials, savolitinib demonstrated strong in vitro activity against MET, affecting its downstream signaling targets and thus blocking the related cellular functions effectively, including proliferation, migration, invasion, scattering and the secretion of VEGF that plays a pivotal role in tumor angiogenesis.

One of our key areas of focus in our pre-clinical trials is to achieve superior selectivity on a number of kinases. A commonly used quantitative measure of selectivity is through comparing enzyme IC_{50}, which represents the concentration of a drug that is required for 50% inhibition of the target kinase in vitro and the plasma concentration required for obtaining 50% of a maximum effect in vivo. High selectivity is achieved with a very low IC_{50} for the target cells, and a very high IC_{50} for the healthy cells (approximately 100 times higher than for the target cells). IC_{50} is measured in nM (nano-mole, a microscopic unit of measurement for the number of small molecules required to deliver the desired inhibitory effect).

In the MET enzymatic assay, savolitinib showed potent activity with IC_{50} of 5 nM. In a kinase selectivity screening with 274 kinases, savolitinib had potent activity against the MET Y1268T mutant (comparable to the wild-type), weaker activity against other MET mutants and almost no activity against all other kinases. Savolitinib was found to be approximately 1,000 times more potent to MET than the next non-MET kinase. Similarly, in cell-based assays measuring activity against MET phosphorylation, savolitinib demonstrated potent activity in both ligand-independent (gene amplified) and ligand-dependent (overexpressed) cells with IC_{50} at low nanomolar levels. In target related tumor cell function assays, savolitinib showed high potency with IC_{50} of less than 10 nM. Furthermore, savolitinib demonstrated cytotoxicity only on tumor cells that were MET gene amplified or MET overexpressed. In other cells, inhibition measurements demonstrated that IC_{50} amounts were over 30,000 nM, which is thousands of times higher than the IC_{50} on MET tumor cells.

The data above suggest that (i) savolitinib has potent activity against tumor cell lines with MET gene amplification in the absence of hepatocyte growth factor, or HGF, indicating that there is HGF-independent MET activation in these cells; (ii) savolitinib has potent activity in tumor cell lines with MET overexpressed, but only in the presence of HGF, indicating HGF-dependent MET activation; and (iii) savolitinib has no activity in tumor cell lines with low MET overexpression/gene amplification, suggesting that savolitinib has strong kinase selectivity.

Savolitinib Clinical Development

As discussed below, we have tested, and are currently testing, savolitinib in partnership with AstraZeneca in multiple indications, both as a monotherapy and in combination with other targeted therapies.

Non-small Cell Lung Cancer

We have two ongoing studies, which subject to positive clinical outcome, are designed to support NDA submission in NSCLC. The table below shows a summary of the clinical trials that we have recently completed and underway for savolitinib in NSCLC patients.

Current and Recent Clinical Trials of Savolitinib in NSCLC

Treatment	Sponsors/Partners	Name, Line, Patient Focus	Sites	Phase	Status/Plan	NCT #
Savolitinib monotherapy	HUTCHMED	MET exon 14 skipping alterations	China	II Registration	Approved and launched	NCT02897479
Savolitinib monotherapy	HUTCHMED	MET exon 14 skipping alterations	China	III Confirmatory	Ongoing	NCT04923945
Savolitinib + Tagrisso	AstraZeneca and HUTCHMED	SAVANNAH: 2L/3L EGFRm+; Tagrisso refractory; MET+	Global	II Registration-intent	Ongoing. Data has supported progression into Phase IIIs	NCT03778229
Savolitinib + Tagrisso	AstraZeneca and HUTCHMED	SAFFRON:2L/3L EGFRm+; Tagrisso refractory; MET+	Global	III	In planning, Intend to initiate in mid-2022	NCT05261399
Savolitinib + Tagrisso	AstraZeneca and HUTCHMED	SACHI: 2L EGFR TKI refractory NSCLC; MET+	China	III	Ongoing	NCT05015608
Savolitinib + Tagrisso	AstraZeneca and HUTCHMED	SANOVO: Naïve patients with EGFRm & MET+	China	III	Ongoing	NCT05009836

Notes: Global = more than two countries; 2L = second line; 3L = third line; and refractory = resistant to prior treatment.

Savolitinib Monotherapy

More than one third of the world's lung cancer patients are in China and, among those with NSCLC, approximately 2-3% have tumors with MET exon 14 skipping alterations, representing an approximate incidence of 13,000 new patients per year in China. Importantly also, MET plays a role in multiple other solid tumors, with an estimated total incidence of 120,000 new patients per year in China.

Phase II study of savolitinib monotherapy in NSCLC patients with MET exon 14 alteration (Status: Approved and launched; NCT02897479).

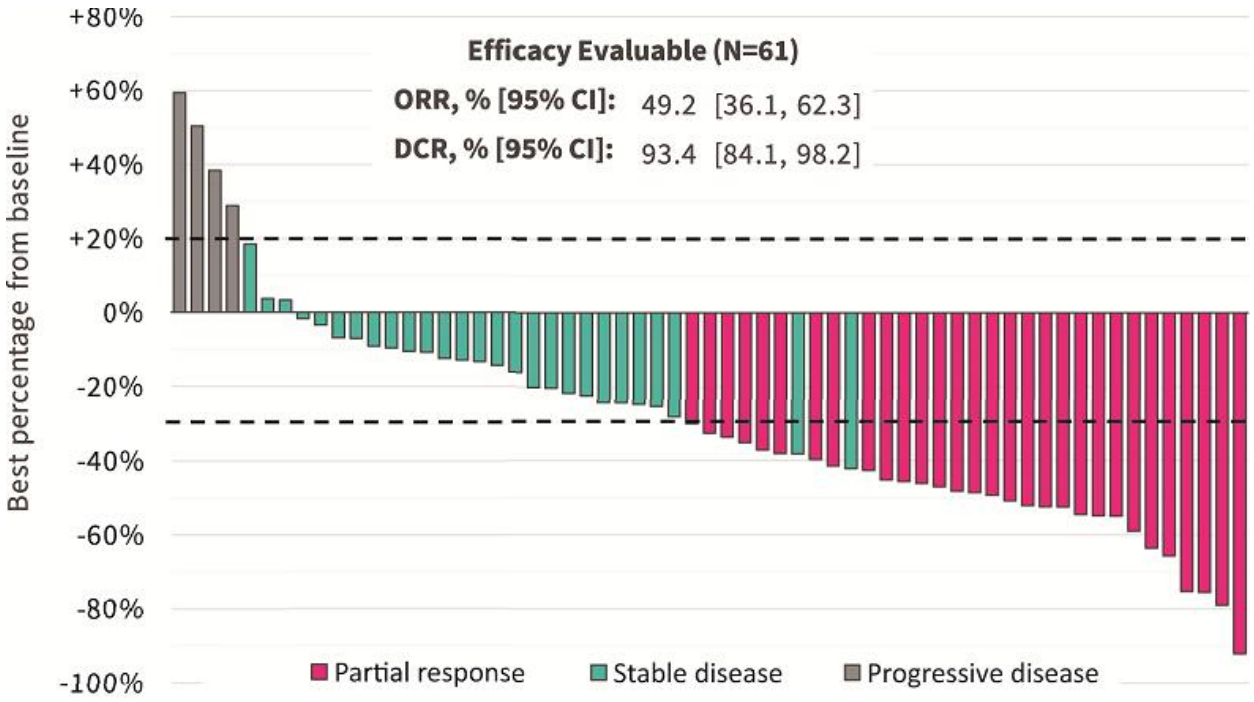
We have completed a 70-patient Phase II registration-intent study in China of savolitinib as a monotherapy for MET exon 14 skipping NSCLC patients who have progressed following prior systemic therapy, or unable to receive chemotherapy.

At the ASCO annual meeting in June 2020, we presented interim data on 70 treated patients, of which 61 patients were efficacy evaluable at the data cut-off date of March 31, 2020. The overall data were encouraging, with efficacy in line with other selective MET inhibitors, despite the inclusion of patients with a more aggressive subtype (36% with pulmonary sarcomatoid carcinoma) and with tolerable safety. Efficacy measurements included the objective response rate, or ORR, (the percentage of patients in the study who show either partial response (tumor measurement reduction of greater than 30%) or complete response), disease control rate, median progression-free survival or PFS and median OS.

At subsequent data cut-off date of August 3, 2020, in the 61 evaluable patients, ORR was 49.2% and disease control rate was 93.4%. Median duration of response was 8.3 months (95% confidence interval: 5.3-16.6). In the full analysis set of 70 patients, median PFS was 6.8 months (95% confidence interval: 4.2-9.6). Median OS was 12.5 months (95% confidence interval: 10.5-23.6). A 95% confidence interval means that there is a 95% chance that the results will be within the stated range. CTC grade 3 or above TEAEs, with greater than 5% incidence related to savolitinib treatment were peripheral edema (9%), increased aspartate aminotransferase (13%) and increased alanine aminotransferase (10%). Clinical data demonstrated an acceptable safety profile with an adverse events-related discontinuations rate of 14.3%.

Results from this study were published in *The Lancet Respiratory Medicine* and formed the basis for an NDA filing, which was approved by the NMPA in June 2021. The approval is conditional upon successful completion of a Phase III confirmatory study in the same patient population, which is expected to enroll approximately 160 patients from about 40 sites.

Phase II Study of Savolitinib Monotherapy Showing Effect in MET Exon 14 Alteration NSCLC Patients



Notes: N = number of patients; ORR = objective response rate; DCR = disease control rate; and CI = confidence interval.

Source: Lu S, Fang J et al. Phase II study of savolitinib in patients (pts) with pulmonary sarcomatoid carcinoma (PSC) and other types of non-small cell lung cancer (NSCLC) harboring MET exon 14 skipping mutations (METex14+). Journal of Clinical Oncology 2020 38:15_suppl, 9519-9519.

Savolitinib and Tagrisso Combination

In 2015, AstraZeneca received FDA approval for Tagrisso, its drug for the treatment of T790M+ EGFRm+, TKI-resistant NSCLC. A drug with this type of activity is known as a third-generation EGFR inhibitor. In 2018, Tagrisso's label was expanded to include previously untreated patients with EGFRm+ NSCLC. In December 2020, Tagrisso's label was further expanded to include adjuvant therapy after tumor resection in EGFRm+ NSCLC patients. Tagrisso has been established as a new standard of care in the treatment of EGFRm+ NSCLC and has now been approved in over 80 countries. Understanding the mechanism of acquired resistance following Tagrisso treatment is a key clinical question to inform the next treatment choice. A portion of EGFRm+ TKI-resistant patients and a portion of T790M+ EGFRm+ TKI-resistant patients progress because of MET gene amplification.

At the ESMO Congress in 2018, AstraZeneca presented the first results on the acquired resistance spectrum detected in patient plasma samples after progression in the first-line (FLAURA) and second-line T790M (AURA3) Phase III studies. MET amplification was among the most frequent mechanisms of acquired resistance to Tagrisso, with 15% of patients in the FLAURA study and 19% of patients in the AURA3 study exhibiting MET amplification after treatment with Tagrisso. Ongoing research with tissue (biopsy) samples will further elucidate the incidence of MET and other mechanisms in the development of resistance to EGFR inhibitors.

Data presented in June 2017 at the ASCO by the Harvard Medical School and Massachusetts General Hospital Cancer Center showed that about 30% (7/23 patients) of Tagrisso-resistant third-line NSCLC patients harbored MET gene amplification based on analysis of tissue samples. This third-line patient population was generally heavily pre-treated and highly complex from a molecular analysis standpoint, with the study showing that more than half of the MET gene amplification patients also harbored additional genetic alterations, including EGFR gene amplification and K-Ras mutations.

As discussed in more detail below, we and AstraZeneca are studying savolitinib in combination with Tagrisso as a treatment choice for patients who have developed a resistance to TKI (primarily Tagrisso). The acceptance and uptake of Tagrisso indicates that the market potential for savolitinib in Tagrisso-resistant, NSCLC could be material.

TATTON study: Phase Ib/II expansion studies of savolitinib in combination with Tagrisso in NSCLC EGFRm+ inhibitor refractory patients (Status: complete; NCT02143466).

The TATTON study is a global exploratory Phase I/Ib study in NSCLC aiming to recruit patients with MET gene amplification who had progressed after prior treatment with EGFR inhibitors to support a decision on global Phase II/III registration strategy. This followed the completion of TATTON Part A, a Phase I study that established that a savolitinib and Tagrisso combination could be safe and well tolerated and also demonstrated preliminary signs of efficacy. In 11 evaluable patients who were MET positive, the ORR was 55% with a disease control rate of 100%.

As of data cut-off on March 4, 2020, a total of over 220 patients had received the savolitinib plus the Tagrisso combination treatment across six TATTON treatment arms, Parts A, B1, B2, B3, C and D. Final analysis for the B and D parts of the study were most recently presented at the 2020 WCLC Worldwide Virtual Event held in January 2021, and interim data (data cut-off on March 29, 2019) were previously published in *The Lancet Oncology* in February 2020. As summarized below, the combination demonstrated an encouraging anti-tumor activity and an acceptable risk-benefit profile, regardless of dose.

First and second-generation EGFRm+ inhibitor refractory patients with acquired resistance driven by MET amplification

TATTON Part B2 tested patients who were T790M negative with no prior third-generation EGFR TKI treatment. Of the 51 patients who received treatment (48 efficacy evaluable), 33 patients had confirmed responses (65% of treated patients; 69% of evaluable patients) with 45 patients experiencing disease control (88% of treated patients; 94% of evaluable patients). The median PFS was 9.1 months (95% confidence interval: 5.5-12.8 months). Pooled CTC grade 3 or above TEAEs in Part B of the study with greater than 5% incidence independent of causality were decreased neutrophil count (7%), increased aspartate aminotransferase (6%), increased alanine aminotransferase (5%), and pneumonia (5%).

TATTON Part B3 tested patients who were T790M positive with no prior third-generation EGFR TKI treatment. Of the 18 patients who received treatment, 12 patients had confirmed responses (67%) with 18 patients experiencing disease control (100%). The median PFS was 11.1 months (95% confidence interval: 4.1 months – 22.1 months).

In late 2017, the TATTON Part D study was initiated to study Tagrisso combined with a lower savolitinib dose (300 mg once daily) in the context of maximizing long-term tolerability of the combination for patients who could be in poor condition and/or on the combination for long periods of time. Of the 42 patients who received treatment (40 efficacy evaluable), 26 patients had confirmed responses (62% of all patients; 65% of evaluable patients) with 39 patients experiencing disease control (93% of all patients; 98% of evaluable patients). The median PFS was 9.0 months (95% confidence interval: 5.6-12.7 months). CTC grade 3 or above TEAEs in Part D of the study with greater than 5% incidence independent of causality were pneumonia (10%), drug hypersensitivity (7%), pulmonary embolism (5%), diarrhea (5%), myalgia (5%) and generalized edema (5%). Overall the combination regimen of savolitinib 300 mg and Tagrisso was tolerable. In Part D of the study, there was lower incidence of grade ≥ 3 AEs and SAEs as compared to Part B. The TATTON Part D study demonstrated that a lower dose did not impair clinical efficacy, while maintaining a better tolerability profile. The results led to the selection of the 300 mg savolitinib plus 80 mg Tagrisso combination dose for the SAVANNAH study, and two additional cohorts of savolitinib 300 mg twice daily dose (BID) and 600 mg once daily dose (QD) plus 80 mg Tagrisso combination doses are recruiting, as discussed below.

Tagrisso or another experimental third-generation EGFRm TKI refractory patients with acquired resistance driven by MET amplification

The TATTON Part B1 study also enrolled NSCLC patients that had progressed after treatment with a third-generation EGFR inhibitor as a result of MET gene amplification acquired resistance. These patients were recruited prior to the April 2018 FDA approval of Tagrisso as a first-line treatment and the January 2019 update to the National Comprehensive Cancer Network guidelines that state that Tagrisso is the preferred first-line treatment for patients with EGFR mutation regardless of pre-treatment T790M mutation status.

Savolitinib in combination with Tagrisso from the TATTON Part B1 study showed promising data. Of the 69 patients that had progressed on Tagrisso monotherapy and harbored MET amplification (60 patients were efficacy evaluable), there were 23 patients with confirmed responses (33% of all patients; 38% of evaluable patients) with 52 patients experiencing disease control (75% of all patients; 87% of evaluable patients). The median PFS was 5.5 months (95% confidence interval: 4.1-7.7 months).

The savolitinib and Tagrisso combination is being studied in second line setting as one of several treatment arms in the ORCHARD study. ORCHARD is a global, phase II, open-label, multi-centre, biomarker-directed platform study in adult patients with locally advanced/metastatic EGFRm NSCLC whose disease has progressed on first-line Tagrisso monotherapy. Initial results from interim analysis demonstrated preliminary activities of this combination in Tagrisso refractory patients. Of the 20 patients enrolled, 17 were evaluable for confirmed response analysis at data cut-off, with an ORR of 41% (7/17). Safety profile was consistent with the known profiles of Tagrisso and savolitinib, and no new safety signals were identified.

Savolitinib plus Tagrisso combination showing effect in EGFR refractory patients who are either Tagrisso refractory (ORCHARD, TATTON Part B1) or Tagrisso naïve (TATTON Parts B2, B3, D)

	ORCHARD [1] **Savo 300/600mg** + TAGRISSO®	**TATTON B** [2] **Savo 600mg** [3] + TAGRISSO®			**TATTON D** [2] **Savo 300mg** + TAGRISSO®
	(n=17) 2L, Prior third–generation EGFR-TKI	**Part B1 (n=69)** 2L+, Prior third–generation EGFR-TKI	**Part B2 (n=51)** 2L+, No prior third–generation EGFR-TKI (T790M neg.)	**Part B3 (n=18)** 2L+, No prior third-generation EGFR-TKI (T790M pos.)	**Part D (n=42)** 2L+, No prior third–generation EGFR-TKI (T790M neg.)
ORR, % [95% CI] Complete Response, % Partial response, %	**41%** [25-59] * 0 41%	**33%** [22–46] 0 33%	**65%** [50–78] 0 65%	**67%** [41–87] 0 67%	**62%** [46–76] 0 62%
DCR#, % [95% CI]	82%	**75%** [64–85]	**88%** [76–96]	**100%** [81–100]	**93%** [81–99]
Median DoR, mo. [95% CI]	NR	**9.5** [4.2–14.7]	**10.7** [6.1–14.8]	**11.0** [2.8–NR]	**9.7** [4.5–14.3]
Median PFS, mo. [95% CI]	NR	**5.5** [4.1–7.7]	**9.1** [5.5–12.8]	**11.1** [4.1–22.1]	**9.0** [5.6–12.7]

Notes: [1] Data cut-off as of January 21, 2021; [2] Data cut-off as of March 4, 2020; [3] Most patients were enrolled to Part B1, B2, B3 on 600 mg savolitinib, prior to weight-based dosing implementation, but following a protocol amendment in response to a safety signal of hypersensitivity, the final 21 patients enrolled in Part B were dosed with savolitinib by body weight as follows: patients who weighed ≤55 kg (n=8) received 300 mg daily and those weighing >55 kg (n=13) received 600 mg daily; Best response data are for patients who had an opportunity to have two follow-up scans;

* 80% CI; CI = confidence interval; n = number of patients; 2L = second line; 2L+ = second line above; NR = not reached; ORR = objective response rate; DoR = duration of response; PFS = progression free survival; and EGFR-TKI = epidermal growth factor receptor tyrosine kinase; neg. = negative; pos. = positive

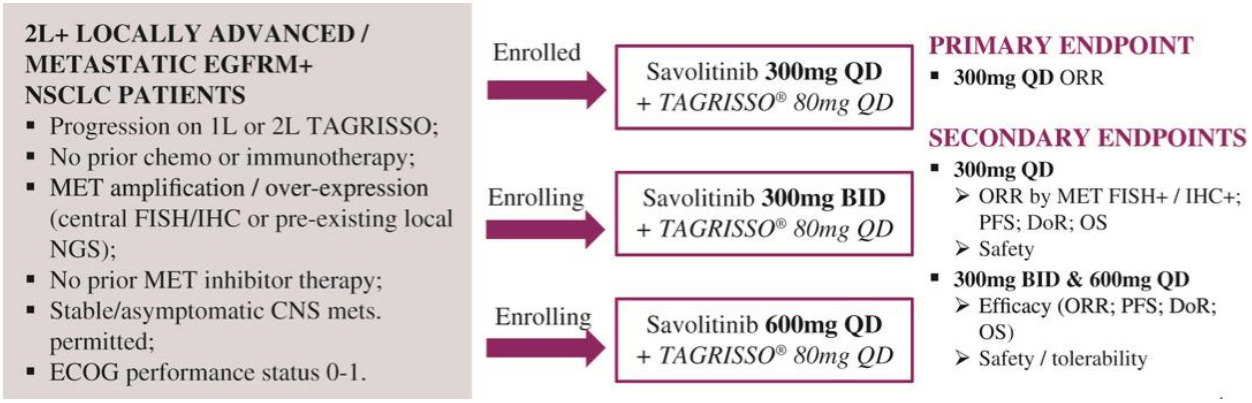
Source: [1] Yu H.A. et al. "ORCHARD osimertinib + savolitinib interim analysis: A biomarker-directed phase II platform study in patients (pts) with advanced non-small cell lung cancer (NSCLC) whose disease has progressed on first-line (1L) osimertinib" Presented at the 2021 European Society for Medical Oncology (ESMO) Virtual Congress on September 13, 2021. Presentation #1239P.

[2] Han JY, Sequist LV, Ahn MJ, et al. Osimertinib + savolitinib in patients with EGFRm MET-amplified/overexpressed NSCLC: Phase Ib TATTON Parts B and D final analysis. Poster presented at: 2021 World Conference on Lung Cancer Singapore; January 28-21, 2021; Virtual. https://bit.ly/3cl7QRE

SAVANNAH study: Phase II study of savolitinib in combination with Tagrisso in NSCLC Tagrisso-refractory EGFRm+ patients (Status: ongoing; NCT03778229).

Based on the encouraging results of the multiple TATTON studies, we and AstraZeneca have initiated a global Phase II study of savolitinib in combination with Tagrisso in EGFRm+ NSCLC patients with MET gene amplification who have progressed following first or second-line Tagrisso therapy. The SAVANNAH study is a single-arm study in North and South America, Europe and Asia. We plan to submit results for presentation at a scientific conference in 2022. In addition to the global Phase III currently under preparation to commence enrollment in mid-2022, we continue to evaluate the possibility of using the SAVANNAH study as the basis for U.S. accelerated approval.

The SAVANNAH Study Design: Addressing Tagrisso Resistance Through Combination Therapies



Notes: 1L = first line; 2L = second line; 2L+ = second line and above; EGFRM+ = epidermal growth factor receptor mutation positive; ECOG = Eastern Cooperative Oncology Group; BID = twice daily; QD = once daily; FISH (+) = fluorescence in situ hybridization (positive); IHC (+) = immunohistochemistry (positive); ORR = objective response rate; PFS = progression free survival; DoR = duration of response; OS = overall survival; and MET = mesenchymal epithelial transition receptor.

Source: HUTCHMED.

SANOVO study: China Phase III study of combination with Targrisso in naïve NSCLC patients with EGFR mutant and MET positive (Status: ongoing; NCT05009836).

We have initiated SANOVO, a China Phase III study of savolitinib in combination with AstraZeneca's third-generation, irreversible epidermal growth factor receptor TKI, Targrisso as a first-line treatment in certain NSCLC patients whose tumors harbor EGFR mutations and overexpress MET. The Phase III trial is a blinded, randomized, controlled study in previously untreated patients with locally advanced or metastatic NSCLC with activating EGFR mutations and MET overexpression. The study will evaluate Targrisso in combination with savolitinib comparing to Targrisso alone, a standard of care treatment option for these patients. The primary endpoint of the study is median progression free survival as assessed by investigators. Other endpoints include median progression-free survival assessed by an independent review committee, median overall survival, ORR, duration of response, disease control rate, time to response and safety. The first patient was dosed in September 2021.

SACHI study: China Phase III study of combination with Targrisso in 2L EGFR TKI refractory, MET amplified NSCLC patients (Status: ongoing; NCT05015608).

We have initiated SACHI, a China Phase III study of savolitinib in combination with Tagrisso. The Phase III trial is a multi-center, open-label, randomized, controlled study in patients with locally advanced or metastatic EGFR mutation-positive NSCLC with MET amplification after disease progression on EGFR inhibitor therapy. The study will evaluate the efficacy and safety of savolitinib in combination with Tagrisso, compared to platinum-based doublet-chemotherapy (pemetrexed plus cisplatin or carboplatin), the standard of care treatment option in this setting. The primary endpoint of the study is median PFS as assessed by investigators. Other endpoints include median PFS assessed by an independent review committee, median overall survival, ORR, duration of response, disease control rate, time to response, and safety. The first patient was dosed in November 2021.

Kidney Cancer

The table below shows a summary of the clinical trials that we have recently completed or are underway for savolitinib in kidney cancer patients.

Current and Recent Clinical Trials of Savolitinib in Kidney Cancer

Treatment	Sponsors/Partners	Name, Line, Patient Focus	Sites	Phase	Status/Plan	NCT #
Savolitinib + Imfinzi	AstraZeneca and HUTCHMED	SAMETA: MET-driven, unresectable and locally advanced or metastatic PRCC	Global	III	Ongoing	NCT05043090
Savolitinib + Imfinzi	Queen Mary University of London, Vall d'Hebron Institute of Oncology, AstraZeneca	CALYPSO: PRCC	U.K./Spain	II	Data updated at ASCO 2021	NCT02819596
Savolitinib + Imfinzi	Queen Mary University of London, Vall d'Hebron Institute of Oncology, AstraZeneca	CALYPSO: Clear cell RCC; VEGFR TKI refractory	U.K./Spain	II	Ongoing	NCT02819596

Notes: PRCC = papillary renal cell carcinoma; RCC = renal cell carcinoma; VEGFR TKI refractory = resistant to prior VEGFR tyrosine kinase inhibitor treatment; Global = more than two countries; PFS = progression-free survival; and MET = mesenchymal epithelial transition receptor.

MET is a key genetic driver in RCC, and emerging evidence suggests that combining immunotherapies with a MET inhibitor could enhance anti-tumor activity. PRCC is a subtype of kidney cancer, representing about 15% of patients, with no treatments approved for patients with tumors that harbor MET-driven alterations.

During an Australian Phase I study, our investigators noted positive outcomes among PRCC patients with a strong correlation to MET gene amplification status. Out of a total of eight PRCC patients in our Australia Phase I study who were treated with various doses of savolitinib, three achieved confirmed partial responses. A further three of these eight PRCC patients achieved stable disease, which means patients without partial response but with a tumor measurement increase of less than 20%. This aggregate ORR of 38% was very encouraging for PRCC, which has no effective approved treatments. These responses were also durable as demonstrated by a patient who has been on the therapy for over 30 months and had tumor measurement reduction of greater than 85%. Importantly, the level of tumor response among these PRCC patients correlated closely with the level of MET gene amplification. The patients with consistent MET gene amplification across the whole tumor responded most to savolitinib, and with those patients with the highest level of MET gene amplification responding most to the treatment.

Savolitinib and Immunotherapy Combinations

Immunotherapy combinations are rapidly changing the treatment landscape in kidney cancer. Immune checkpoints such as PD-L1 are sometimes used by cancer cells to avoid being attacked by the immune system. As such, drugs that target these checkpoints are being developed or marketed as cancer treatments. Imfinzi is an anti-PD-L1 antibody owned by AstraZeneca. Anti-PD-L1 antibodies have been associated with clinical benefits in metastatic RCC, and MET dysregulation has been considered to play an important role in PRCC pathogenesis (including in our savolitinib Phase I and Phase II monotherapy studies) and is a mechanism of resistance against kinase inhibitors in clear cell RCC. Moreover, it is believed that the MET signaling pathway has a complex interplay with the immune system, including correlation with PD-L1 expression, immune suppression through angiogenesis and many other facets of the immune system. Our CALYPSO study discussed below aims to explore and potentially confirm this interplay.

CALYPSO study: Phase II study of savolitinib in combination with Imfinzi in both PRCC and clear cell RCC patients (Status: dose expansion ongoing; NCT02819596).

The CALYPSO study is an investigator-initiated open-label Phase II study of savolitinib in combination with Imfinzi. The study is evaluating the safety and efficacy of the savolitinib and Imfinzi combination in both PRCC and clear cell RCC patients at sites in the U.K. and Spain.

Interim results of the PRCC cohort of the CALYPSO study were most recently presented at the 2021 ASCO annual meeting and showed encouraging efficacy across all patients, both MET+ and MET-. In the 41 patients who were selected regardless of PD-L1 or MET status, ORR was 29% (12/41), while median PFS was 4.9 months (95% confidence interval: 2.5-10.0 months). Median OS was 14.1 months (95% confidence interval: 7.3-30.7 months). For the 14 patients whose tumors are MET-driven, ORR was 57% (8/14), median PFS was 10.5 months (95% confidence interval: 2.9-15.7), and median OS was 27.4 months (95% confidence interval: 7.3-NR). Tolerability was consistent with established single agent safety profiles. In the analysis previously presented at ASCO's Genitourinary Cancers Symposium in 2020, there were 13 treatment related CTC grade 3 or above TEAEs that occurred in more than three patients, with edema (10%), nausea (5%) and transaminitis (5%) being most frequent. We and AstraZeneca continue to explore development of the savolitinib-Imfinzi combination in PRCC patients.

SAMETA study: Phase III in combination with Imfinzi PD-L1 inhibitor in MET-driven, unresectable and locally advanced or metastatic PRCC (Status: ongoing; NCT05043090)

The Phase III trial is an open-label, randomized, controlled study in treatment-naïve patients with MET-driven, unresectable and locally advanced or metastatic PRCC, to evaluate the efficacy and safety of savolitinib in combination with Imfinzi compared to single agent Imfinzi or single agent Sutent, an oral multi-kinase inhibitor considered as the standard of care treatment option in PRCC. The primary endpoint of the study is median PFS. Other endpoints include median OS, ORR, duration of response, 6-months and 12-months DCR, time to second progression, safety, pharmacokinetics and quality of life. The first patient was dosed in October 2021.

Gastric Cancer

The table below shows a summary of our clinical trial for savolitinib in gastric cancer patients.

Clinical Trials of Savolitinib in Gastric Cancer

Treatment	Sponsors/Partners	Name, Line, Patient Focus	Sites	Phase	Status/Plan	NCT #
Savolitinib monotherapy	HUTCHMED and Samsung Medical Center	VIKTORY: Gastric cancer (MET amplification)	China / South Korea	Ib/II	Completed. Support decision to progress into Phase II registration intent study	NCT01985555/ NCT02449551
Savolitinib monotherapy	HUTCHMED	2L+ gastric cancer with MET amplification	China	II registration intent	Ongoing	NCT04923932

Phase Ib/II study of savolitinib monotherapy in MET amplified gastric cancer in China (Status: completed; NCT01985555)

Preliminary results of the China study were presented at the 2017 Chinese Society of Clinical Oncology, or CSCO, for the efficacy evaluable MET gene amplified patients. Based on confirmed and unconfirmed partial responses, the ORR was 43% (3/7) and disease control rate was 86% (6/7), with ORR of 14% (3/22) and disease control rate of 41% (9/22) among the overall efficacy evaluable aberrant MET set of patients with MET amplification (n=7) and MET overexpression (n=15). As of the data cut-off, the longest duration of treatment was in excess of two years. Savolitinib monotherapy was determined to be safe and well tolerated in patients with advanced gastric cancer. CTC grade 3 or above TEAEs with greater than 5% incidence included abnormal hepatic function in 13% (4/31), gastrointestinal bleeding or decreased appetite in 10% (3/31 each), and diarrhea or gastrointestinal perforation in 6% (2/31 each). This China study concluded that savolitinib monotherapy demonstrated promising anti-tumor efficacy in gastric cancer patients with MET gene amplification and that the potential benefit to these patients warranted further exploration, with enrollment continuing.

VIKTORY Phase II study of savolitinib in MET amplified gastric cancer in South Korea (Status: completed; NCT02449551)

The VIKTORY study is a biomarker-based, Phase II umbrella trial in gastric cancer conducted by the Samsung Medical Center in South Korea. Patients were allocated to one of 12 biomarker-driven arms, based on a master screening protocol with tissue-based molecular analyses. Patients that tested positive for MET amplification or overexpression were treated with either savolitinib monotherapy or a combination of savolitinib and Taxotere. A total of 715 gastric cancer patients were successfully sequenced and MET amplification was observed in 3.5% of these patients (25/715). Of the 10 associated clinical trials under the VIKTORY umbrella, the highest ORR was observed in the MET amplification arm in patients treated with savolitinib monotherapy, which reported an ORR of 50% (10/20, 95% confidence interval: 28.0-71.9) and met pre-specified 6-week PFS rates. While the savolitinib and Taxotere combination was well tolerated, the VIKTORY study investigators decided to stop enrollment in the two combination cohorts in order to direct patients to the savolitinib monotherapy arm of the VIKTORY study as discussed above.

The VIKTORY study investigators have concluded that encouraging clinical efficacy of savolitinib in MET-amplified gastric cancer warrants further study.

Phase II study of savolitinib with potential for registration intent in 2L+ gastric cancer with MET amplification (Status: ongoing; NCT04923932)

This Phase II registration-intent study is a two-stage and single-arm study to evaluate the efficacy, safety and pharmacokinetics of savolitinib in locally advanced or metastatic GC or GEJ patients whose disease progressed after at least one line of standard therapy. The primary endpoint is ORR as assessed by an independent review committee. Other endpoints include 12-week and 6-month progression-free survival rates, median progression-free survival, duration of response, disease control rate, median overall survival, safety, pharmacokinetics and quality of life. The first patient was dosed in July 2021. Subject to the results of the first stage of this study, we will discuss with the CDE of NMPA the appropriate approach and necessary criteria for registration.

Partnership with AstraZeneca

In December 2011, we entered into a global licensing, co-development, and commercialization agreement for savolitinib with AstraZeneca. As noted above, given the complexity of many of the signal transduction pathways and resistance mechanisms in oncology, the industry is increasingly studying combinations of targeted therapies (TKI, monoclonal antibodies and immunotherapies) and chemotherapy as potentially the best approach to treating this complex and constantly mutating disease. Based on savolitinib's clinical progress as a highly selective MET inhibitor in a number of cancers, in August 2016, December 2020 and November 2021, we and AstraZeneca amended our global licensing, co-development, and commercialization agreement for savolitinib. We believe that AstraZeneca's portfolio of proprietary targeted therapies is well suited to be used in combinations with savolitinib, and we are studying combinations with Tagrisso (EGFRm+, T790M+) and Imfinzi (PD-L1). These combinations of multiple global first-in-class compounds are difficult to replicate, and we believe represent a significant opportunity for us and AstraZeneca. For more information regarding our partnership with AstraZeneca, see "—Overview of Our Collaborations—AstraZeneca."

2. Surufatinib (HMPL-012), VEGFR 1, 2 and 3, FGFR1 and CSF-1R Inhibitor

Surufatinib is a novel, oral angio-immuno kinase inhibitor that selectively inhibits the tyrosine kinase activity associated with VEGFR and FGFR, both of which have been shown to be involved in tumor angiogenesis, and CSF-1R, which plays a key role in regulating tumor-associated macrophages, promoting the body's immune response against tumor cells. Surufatinib has been studied in clinical trials with around 1,200 patients to date, both as a monotherapy and in combinations, and is approved in China. We currently retain all rights to surufatinib worldwide.

Initial approvals for surufatinib in China are for the treatment of advanced NET patients. NETs present in the body's organ system with fragmented epidemiology. Surufatinib's ability to inhibit angiogenesis, block the accumulation of tumor associated macrophages and promote infiltration of effector T cells into tumors could help improve the anti-tumor activity of PD-1 antibodies. Several combination studies with PD-1 antibodies have shown promising data.

Mechanism of Action

Both VEGFR and FGFR signaling pathways can mediate tumor angiogenesis. CSF-1R plays an important role in the functions of macrophages. Recently, the roles in increasing tumor immune evasion of VEGFR, FGFR in regulation of T cells, tumor-associated macrophages and myeloid-derived suppressor cells have been demonstrated. Therefore, blockade of tumor angiogenesis and tumor immune evasion by simultaneously targeting VEGFR 1, 2 and 3, FGFR1 and CSF-1R kinases may represent a promising approach for oncology therapy.

Surufatinib Pre-clinical Evidence

Surufatinib inhibited VEGFR 1, 2, and 3, FGFR1 and CSF-1R kinases with IC_{50} in a range of 1 nM to 24 nM. It also strongly blocked VEGF-induced VEGFR2 phosphorylation in HEK293 cells and CSF-1R phosphorylation in RAW264.7 cells with an IC_{50} of 2 nM and 79 nM, respectively. Surufatinib also reduced VEGF- or FGF-stimulated human umbilical vein endothelial cell proliferation with an $IC_{50} < 50$ nM. In animal studies, a single oral dose of surufatinib inhibited VEGF-stimulated VEGFR2 phosphorylation in lung tissues of nude mice in an exposure-dependent manner. Furthermore, elevation of FGF23 levels in plasma 24 hours post dosing suggested suppression of FGFR signaling.

Surufatinib demonstrated potent tumor growth inhibition in multiple human xenograft models and decreased cluster of differentiation 31 expression remarkably, suggesting strong inhibition on angiogenesis through VEGFR and FGFR signaling. In a syngeneic murine colon cancer model, surufatinib demonstrated moderate tumor growth inhibition after single-agent treatment. Flow cytometry and immunohistochemistry analysis revealed an increase of certain T cells and a significant reduction in certain tumor-associated macrophages, including CSF-1R mutation positive tumor-associated macrophages in tumor tissue, indicating surufatinib has a strong effect on CSF-1R. Interestingly, a combination of surufatinib with a PD-L1 antibody resulted in enhanced anti-tumor effect. These results suggested that surufatinib has a strong effect in modulating angiogenesis and cancer immunity.

Surufatinib Clinical Trials

We currently have various clinical trials of surufatinib as a monotherapy and in combination with checkpoint inhibitors ongoing or expected to begin in the near term.

Neuroendocrine Tumors

Neuroendocrine tumors begin in the specialized cells of the body's neuroendocrine system. Cells have traits of both hormone-producing endocrine cells and nerve cells. Neuroendocrine tumors are found throughout the body's organ system and have complex and fragmented epidemiology with about 65-75% of NETs originating in the gastrointestinal tract and pancreas, 25-35% in the lung or bronchus, and a further 20-30% in other organs or unknown origins.

In China, there are an estimated approximately 34,000 new patients of advanced NETs per year and were potentially over 300,000 patients living with NET in China in 2021.

NETs can be functional, releasing hormones and peptides that cause symptoms like diarrhea and flushing, or non-functional with no symptoms. Early-stage NETs, which are often functional, can be treated with somatostatin analogue subcutaneous injections, which are approved and reimbursed in China and alleviate symptoms and slow NET growth, but have limited tumor reduction efficacy.

Advanced NETs grow more quickly. In China, Sutent is approved in pancreatic NET while Afinitor, an mTOR inhibitor, is approved in non-functional NETs in the pancreas, lung and gastrointestinal tract. These approvals, however, cover only about half of advanced neuroendocrine tumor patients.

The table below shows a summary of the clinical trials that we have completed or are in planning for surufatinib in neuroendocrine cancer patients. Our Phase Ib study in planning for the U.S. and Europe will also include expansion cohorts to explore surufatinib in patients with BTC and sarcoma.

Clinical Trials of Surufatinib in NETs

Treatment	Sponsors/Partners	Name, Line, Patient Focus	Sites	Phase	Status/Plan	NCT #
Surufatinib monotherapy	HUTCHMED	SANET-ep: Non-pancreatic NET	China	III	Approved and launched	NCT02588170
Surufatinib monotherapy	HUTCHMED	SANET-p: Pancreatic NET	China	III	Approved and launched; subgroup analysis presented at ASCO 2021	NCT02589821
Surufatinib monotherapy(1)	HUTCHMED	NETs	U.S.	Ib	FDA accepted NDA (June 2021); updated Ib data presented at ASCO 2021	NCT02549937
Surufatinib monotherapy	HUTCHMED	NETs	Europe	II	EMA accepted MAA (July 2021)	NCT04579679
Surufatinib monotherapy	HUTCHMED	NETs	Japan	Bridging	Ongoing. Reg-enabling study	NCT05077384

Notes: (1) FDA granted surufatinib orphan drug designation for the treatment of pancreatic NETs in November 2019 and fast track designation for our pancreatic and non-pancreatic NET development programs in April 2020.

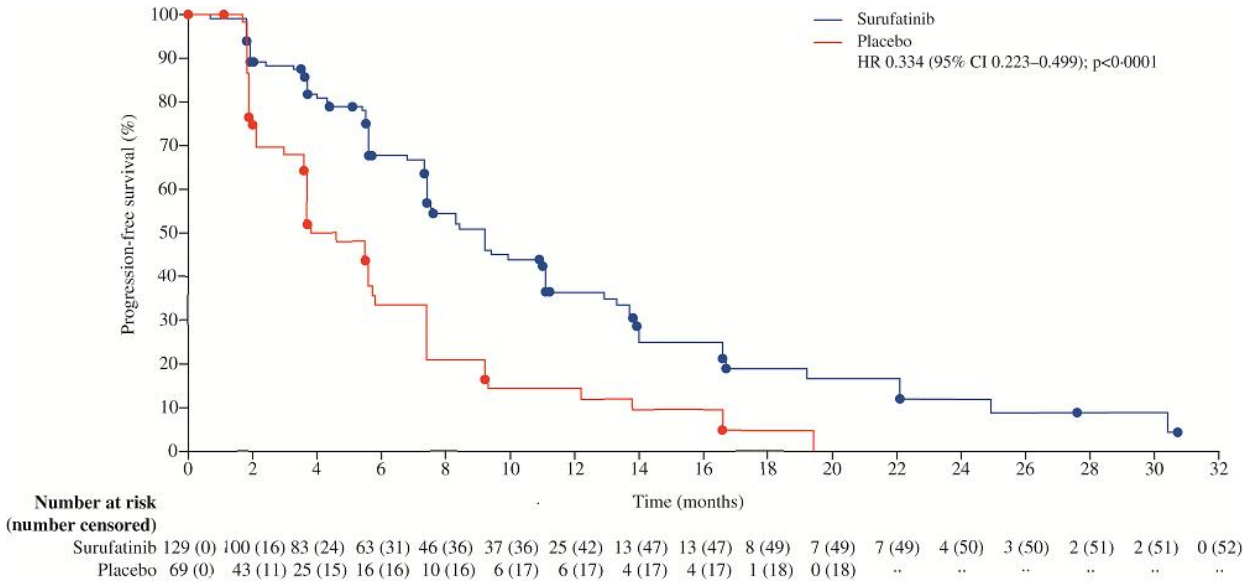
NET = neuroendocrine tumor.

SANET-ep study: Phase III study of surufatinib monotherapy in non-pancreatic NETs (Status: completed and product launched in China; NCT02588170)

In 2015, we initiated the SANET-ep study, which is a Phase III study in China in patients with grade 1 and 2 advanced non-pancreatic NETs. In this study, patients were randomized at a 2:1 ratio to receive either an oral dose of 300 mg of surufatinib or a placebo once daily on a 28-day treatment cycle. The primary endpoint was PFS, with secondary endpoints including ORR, disease control rate, time to response, duration of response, OS, safety and tolerability.

A 198-patient interim analysis was conducted on SANET-ep in mid-2019, leading the independent data monitoring committee, or IDMC, to determine that it had met the pre-defined primary endpoint of PFS and should be stopped early. The positive results of this trial were highlighted in an oral presentation at the 2019 European Society for Medical Oncology Congress, and subsequently published in *The Lancet Oncology* in September 2020. Median PFS per investigator assessment was 9.2 months for patients treated with surufatinib, as compared to 3.8 months for patients in the placebo group (HR 0.334; 95% CI: 0.223, 0.499; p<0.0001). Efficacy was also supported by a blinded independent image review committee assessment. Surufatinib was well-tolerated in this study and the safety profile was consistent with observations in prior clinical studies. CTC grade 3 or above TEAEs in this study with greater than 5% incidence were hypertension (36%), proteinuria (19%) and anemia (7%).

SANET-ep Clearly Succeeded in Meeting Primary Endpoint of PFS



Notes: P-value is obtained from the stratified one-sided log-rank test; Hazard ratio is obtained from stratified Cox model; CI = confidence interval; and HR = hazard ratio.

Source: Xu J, Shen L, Zhou Z, et al. Surufatinib in advanced extrapancreatic neuroendocrine tumours (SANET-ep): a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol. 2020;21(11):1500-1512. doi:10.1016/S1470-2045(20)30496-4.

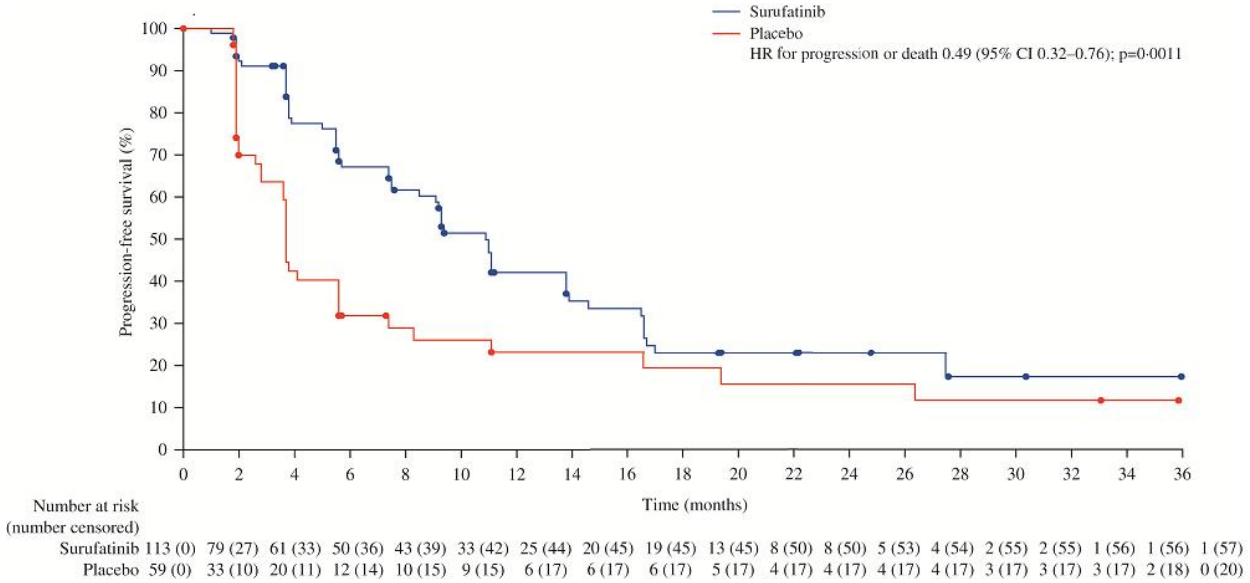
In late 2020, surufatinib was granted approval for drug registration by the NMPA for the treatment of non-pancreatic NET and launched in mid-January 2021 within three weeks of approval. We believe the benefits of surufatinib as a monotherapy to patients with non-pancreatic NETs in China could be significant as compared to the minimal treatment alternatives currently available to them.

SANET-p study: Phase III study of surufatinib monotherapy in pancreatic NETs (Status: completed and product launched in China for treatment of pancreatic NETs; NCT02589821)

In 2016, we initiated the SANET-p study, which is a Phase III study in China in patients with low- or intermediate-grade, advanced pancreatic NETs. In this study, patients are randomized at a 2:1 ratio to receive either an oral dose of 300 mg of surufatinib or a placebo once daily on a 28-day treatment cycle. The primary endpoint is PFS, with secondary endpoints including ORR, disease control rate, time to response, duration of response, OS, safety and tolerability.

In early 2020, an interim analysis was conducted on SANET-p, leading the IDMC to recommend that the study stop early as the pre-defined primary endpoint of PFS had already been met. Investigator-assessed median PFS was 10.9 months for patients treated with surufatinib, as compared to 3.7 months for patients in the placebo group (HR 0.491; 95% CI: 0.319-0.755; p=0.0011). ORRs were 19.2% for the efficacy evaluable patients in the surufatinib group versus 1.9% for the placebo group, with a DCR of 80.8% versus 66.0%, respectively. Most patients in the trial had Grade 2 disease with heavy tumor burden, including liver metastasis and multiple organ involvement. Efficacy was also supported by blinded independent image review committee assessment, with a median PFS of 13.9 months for surufatinib as compared to 4.6 months for placebo (HR 0.339; 95% CI 0.209-0.549; p<0.0001). The safety profile of surufatinib was manageable and consistent with observations in prior studies. Treatment was well tolerated for most patients, with discontinuation rates as a result of TEAEs of 10.6% in the surufatinib group as compared to 6.8% in the placebo group. CTC grade 3 or above TEAEs in this study with greater than 5% incidence were hypertension (38%), proteinuria (10%) and hypertriglyceridemia (7%).

SANET-p Clearly Succeeded in Meeting Primary Endpoint of PFS



Notes: P-value is obtained from the stratified one-sided log-rank test; Hazard ratio is obtained from stratified Cox model; CI = confidence interval; and HR = hazard ratio.

Source: Xu J, Shen L, Bai C, et al. Surufatinib in advanced pancreatic neuroendocrine tumours (SANET-p): a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol. 2020;21(11):1489-1499. doi:10.1016/S1470-2045(20)30493-9.

Surufatinib was granted approval for drug registration by the NMPA for the treatment of advanced pancreatic NET and launched in June 2021. We believe the benefits of surufatinib as a monotherapy to patients with pancreatic NETs in China could be significant as compared to the alternatives currently available to them. We believe that surufatinib is currently the only approved targeted therapy that can address and treat all subtypes of NETs.

Global development of surufatinib in NET: U.S. NDA and EU MAA under review

The U.S. NDA and EU MAA are supported by data from two positive Phase III studies of surufatinib in patients with pancreatic and extra-pancreatic NET in China (SANET-p and SANET-ep both previously reported in *The Lancet Oncology*), and a surufatinib Phase Ib study conducted in U.S. NET patients (N=107 for safety and N=67 for efficacy).

In June 2021, the U.S. FDA accepted our filing of the NDA for surufatinib for the treatment of pancreatic and extra-pancreatic (non-pancreatic) NETs. Surufatinib received fast track designation in April 2020 for the treatment of pancreatic and extra-pancreatic NET. Orphan Drug Designation for pancreatic NET was also granted in November 2019. In addition, we have initiated an expanded access program in the United States for compassionate use by patients with NET with limited therapeutic options. Regulatory clearance of this program has been granted by the U.S. FDA and this program is open for site activation.

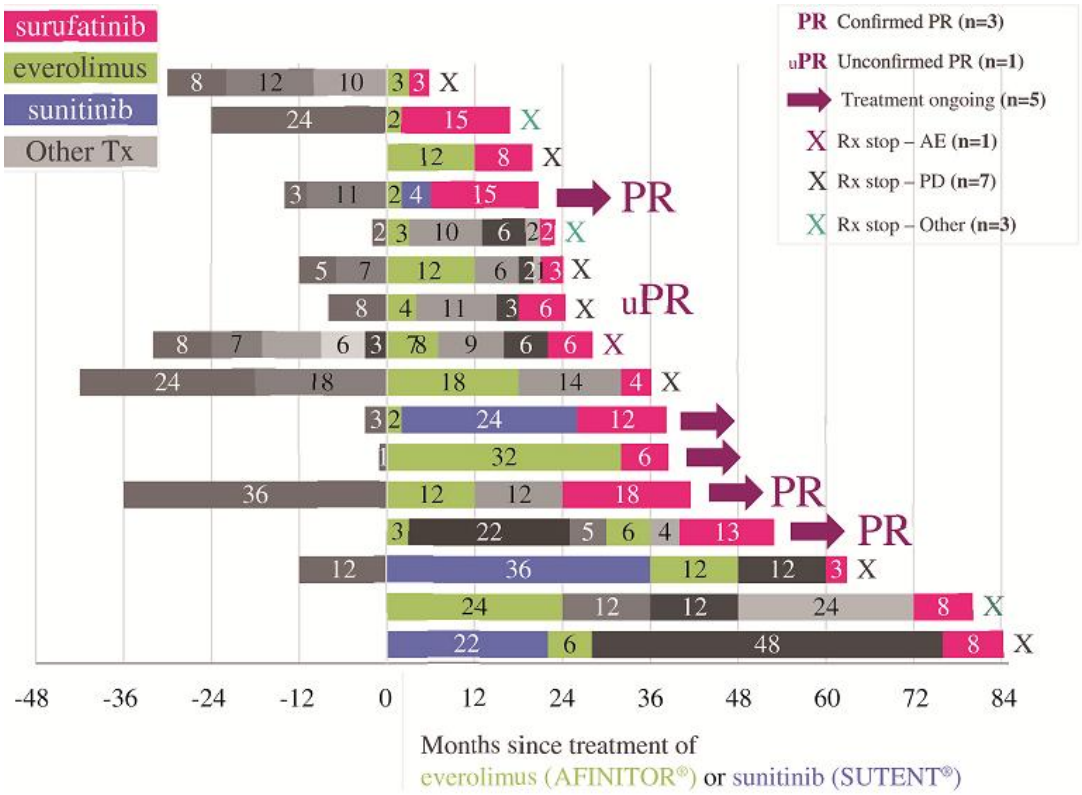
U.S. FDA NDA review, as well as the clinical site inspections and pre-approval inspections of our manufacturing facilities, are ongoing. The PDUFA goal date for the FDA's completion of review is April 30, 2022. Timing of completion of the NDA review is subject to FDA scheduling limitations which are contingent on COVID–19 travel restrictions and security requirements for foreign visitors. Remaining inspections must be completed before regulatory action can be taken.

We have also submitted the EMA MAA for surufatinib, which was validated and accepted in July 2021, for the treatment of both pancreatic and non-pancreatic NET. The 120-day assessment has been completed, and we are now entering the later stages of MAA review. In addition, we initiated a registration-enabling bridging study in NET patients in Japan in September 2021.

Phase Ib study of surufatinib monotherapy in heavily pretreated progressive NETs (Status: ongoing; NCT02549937)

We are conducting a multi-center, open-label, Phase Ib clinical study to evaluate the safety, tolerability and pharmacokinetics of surufatinib in U.S. patients, which has established the U.S. recommended Phase II dose, or RP2D, to be 300 mg, the same as that in China. At the 2021 ASCO annual meeting, preliminary data presented from the two NET cohorts in the ongoing U.S. Phase Ib trial for surufatinib demonstrated efficacy comparable to China data in heavily pretreated patients, including Afinitor and Sutent, with pancreatic or non-pancreatic NETs. The safety profile was also consistent with the larger pool of surufatinib safety data. As of June 30, 2020, 16 patients with pancreatic NET were treated for a median of 8.5 months (range 2-23) and 16 patients with non-pancreatic NET were treated for a median of 8 months (range of 2-15). All 32 patients have pretreated progressive NETs (median prior lines of treatment: 3; range 1-8). Confirmed response was observed in 18.8% of pancreatic, NET, and disease control was observed in 87.5% of patients. In the non-pancreatic NET cohort, confirmed response was observed in 6.3% of the patients and disease control was observed in 93.8% of patients. Median PFS was 11.5 months for patients in both cohorts (95% confidence interval: 6.5-17.5).

US Phase Ib: Encouraging Preliminary Efficacy in Afinitor and Sutent Refractory/Intolerant NET



Notes: Data cut-off as of April 21, 2020. PR = partial response; AE = adverse event; PD = progressive disease; Rx = treatment; Tx = treatment; and n = number of patients.

Source: Dasari, et al. Efficacy and safety of surufatinib in United States (US) patients (pts) with neuroendocrine tumors (NETs). Journal of Clinical Oncology 2020 38:15_suppl, 4610-4610.

Bridging study of surufatinib monotherapy in heavily pretreated progressive NETs (Status: ongoing; NCT05077384)

In September 2021, we initiated a Japan registration-enabling bridging study for surufatinib to support the registration of surufatinib in the treatment of patients with advanced NETs. Based on dialogue with the PMDA, it was agreed that the surufatinib Japanese NDA for the treatment of advanced NETs include results from a pivotal study to be conducted in Japan, to complement the registration data package supporting the NDA to the U.S. FDA and the MAA to the EMA.

This Japan study is a two-stage, open label study of surufatinib where approximately 34 patients are expected to be recruited. In part 1 of the study, the safety and tolerability of surufatinib 300mg once daily after 28 days of treatment will be assessed in patients with relapsed/refractory non-hematological malignancies; pharmacokinetics and anti-tumor activity of surufatinib are secondary endpoints. In Part 2 of the study, efficacy will be assessed in patients with locally advanced or metastatic NETs; the primary outcome measure is ORR. The secondary outcome measures include DCR, PFS, DoR, safety, and pharmacokinetics.

Biliary Tract Cancer

BTC (also known as cholangiocarcinoma) is a heterogeneous group of rare malignancies arising from the biliary tract epithelia. Gemzar, a type of chemotherapy, is the currently approved first-line therapy for BTC patients, with median survival of less than 12 months for patients with unresectable or metastatic disease at diagnosis. As a result, this is an unmet medical need for patients who have progressed on chemotherapy. There is currently no standard of care for these patients. Surufatinib may offer a new targeted treatment option in this tumor type. The table below shows a summary of the clinical studies that we have conducted for surufatinib in BTC patients. Based on the emerging data from our Phase II cohort of the surufatinib combination plus Tuoyi in BTC, we are now prioritizing the combination over surufatinib monotherapy for further development.

Clinical Trials of Surufatinib in BTC

Treatment	Sponsors/Partners	Name, Line, Patient Focus	Sites	Phase	Status/Plan	NCT #
Surufatinib monotherapy	HUTCHMED	BTC	China	Ib/IIa	Completed; data presented at ASCO 2021	NCT02966821
Surufatinib monotherapy	HUTCHMED	BTC	China	IIb	Completed	NCT03873532

Notes: Chemotherapy refractory = resistant to prior chemotherapy treatment; and BTC = biliary tract cancer.

Phase Ib/IIa surufatinib monotherapy in chemotherapy refractory BTC – China (Status: completed; NCT02966821)

In early 2017, we began a Phase Ib/IIa proof-of-concept study in patients with BTC. Preliminary efficacy led us to begin the Phase II/III study discussed below.

At the 2021 ASCO annual meeting, results of this study were disclosed. Surufatinib demonstrated moderate efficacy and favorable tolerability profile. After 16 weeks of treatment, 46% of the patients did not experience progression of their disease. Median PFS was 3.7 months and median OS was 6.9 months. The most common Grade 3 or higher treatment-related adverse events were blood bilirubin increase (21%), hypertension (18%), and proteinuria (13%).

Phase IIb study of surufatinib monotherapy in second line BTC – China (Status: completed; NCT03873532)

In March 2019, based on preliminary Phase Ib/IIa data, we initiated a registration-intent Phase IIb/III study comparing surufatinib with capecitabine in patients with unresectable or metastatic BTC. Enrollment for the Phase IIb portion (80 patients) of this study was completed in late 2020.

Surufatinib Combinations with Checkpoint Inhibitors

Surufatinib's ability to inhibit angiogenesis, block the accumulation of tumor associated macrophages and promote infiltration of effector T cells into tumors, could help improve the anti-tumor activity of PD-1 antibodies.

The table below shows a summary of the clinical trials that we have underway or in planning for surufatinib in combination with checkpoint inhibitors.

Clinical Trials of Surufatinib with Checkpoint Inhibitors

Treatment	Sponsors/Partners	Name, Line, Patient Focus	Sites	Phase	Status/Plan	NCT #
Surufatinib and Tuoyi (PD-1)	HUTCHMED and Junshi	SURTORI-01: neuroendocrine carcinoma	China	III	Ongoing	NCT05015621
Surufatinib and Tuoyi (PD-1)	HUTCHMED and Junshi	Neuroendocrine neoplasms	China	II	Ongoing; data presented at ASCO 2021 and ESMO IO 2021.	NCT04169672
Surufatinib and Tuoyi (PD-1)	HUTCHMED and Junshi	BTC	China	II	Ongoing	NCT04169672
Surufatinib and Tuoyi (PD-1)	HUTCHMED and Junshi	Gastric cancer	China	II	Ongoing; data presented at ASCO 2021 and updated at ESMO IO 2021	NCT04169672
Surufatinib and Tuoyi (PD-1)	HUTCHMED and Junshi	Thyroid cancer	China	II	Ongoing	NCT04169672
Surufatinib and Tuoyi (PD-1)	HUTCHMED and Junshi	Small cell lung cancer	China	II	Ongoing; data presented at ESMO IO 2021	NCT04169672
Surufatinib and Tuoyi (PD-1)	HUTCHMED and Junshi	Soft tissue sarcoma	China	II	Ongoing	NCT04169672
Surufatinib and Tuoyi (PD-1)	HUTCHMED and Junshi	Endometrial cancer	China	II	Ongoing	NCT04169672
Surufatinib and Tuoyi (PD-1)	HUTCHMED and Junshi	Esophageal cancer	China	II	Ongoing; data presented at ESMO IO 2021.	NCT04169672
Surufatinib and Tuoyi (PD-1)	HUTCHMED and Junshi	NSCLC	China	II	Ongoing	NCT04169672
Surufatinib and tislelizumab (PD-1)	HUTCHMED and BeiGene	Solid tumors	U.S./ Europe	Ib/II	Ongoing	NCT04579757

In late 2018, we entered into a global collaboration with Junshi to evaluate the combination of surufatinib with Tuoyi. We completed a Phase I dose-finding study and presented the data at the AACR Conference in April 2020. The data showed that surufatinib plus Tuoyi were well tolerated with no unexpected safety signals observed. At the recommend Phase 2 dose, a DCR of 100% and ORR of 63.6% were reported for 11 efficacy evaluable patients, with 2 unconfirmed partial responses. Surufatinib plus Tuoyi showed encouraging antitumor activity in patients with advanced solid tumors. A Phase II China study is enrolling approximately 260 patients in nine solid tumor indications, including NENs, BTC, gastric cancer, thyroid cancer, small cell lung cancer, soft tissue sarcoma, endometrial cancer, esophageal cancer and NSCLC. In 2021, we presented encouraging preliminary data on several of these surufatinib-Tuoyi combination cohorts at CSCO and ESMO IO. These have led to the initiation of the first Phase III trial combining surufatinib with a PD-1 antibody, the SURTORI-01 study in NEC, and we are currently considering further registration studies in gastric cancer, small cell lung cancer and esophageal cancer.

NEC (subset of NENs) cohort – At the 2021 CSCO annual meeting, we presented data, with a cutoff date of July 30, 2021 for all 21 enrolled NEC patients that were efficacy evaluable. Average duration of treatment was 4.9 months (range 1-19) and median OS was 10.3 months (95% CI: 9.1-not reached). The median PFS was 4.14 months (95% CI: 1.5-5.5) and median DoR was 4.1 months (95% CI: 3.0-not reached). The confirmed ORR was 23.8% (95% CI: 8.2-47.2) and DCR was 71.4% (95% CI: 47.8-88.7). All patients experienced treatment-related adverse events, including 9 (42.9%) who experienced grade 3 or above treatment-related adverse events. 1 (4.8%) patient reported treatment-related serious adverse events. Hyperglycemia (3 patients, 14.3%), hypertension (2 patients, 9.5%) and hypertriglyceridemia (2 patients, 9.5%) were the most commonly (more than one patient) reported grade 3 or above treatment-related adverse events. No treatment-related adverse events led to treatment discontinuation or treatment-related deaths.

In September 2021, we initiated a Phase III study to evaluate the combination compared with Folfiri to treat patients with advanced NEC who have progression of disease or intolerable toxicity after previous first-line chemotherapy. It is a randomized, controlled, open-label, multi-center study where approximately 200 patients are expected to be enrolled. For the study group, all patients will receive study treatment in a 21-day cycle. The primary outcome measure is OS. We are the sponsor and responsible for the study's execution. We and Junshi Biosciences are jointly funding the study.

At the 2021 ASCO annual meeting, encouraging preliminary data were disclosed for the surufatinib and Tuoyi combination in the NEC and GC cohorts. For the 20 patients in the NEC cohort who received an average of 5 cycles of treatments and are efficacy evaluable, ORR was 20% while DCR was 70%. Median PFS was 3.9 months (95% confidence interval: 1.3-NR). Grade 3 or higher treatment-related adverse events occurred in 33% of patients. Median duration of treatment for the GC cohort was 3 months, with 15 patients efficacy evaluable at the time of the analysis. For these 15 patients, confirmed ORR was 13% and an additional 20% of patients had unconfirmed OR. DCR was 73% and median PFS was 3.7 months (95% confidence interval: 1.4-NR). Grade 3 or higher treatment-related adverse events occurred in 14% of patients.

In 2022, we plan to initiate SURTORI-02, a Phase III study of surufatinib in combination with Tuoyi in esophageal cancer in China. We also plan to submit further Phase II data for presentation from the surufatinib and Tuoyi combination for biliary tract, esophageal, small cell lung cancers and sarcoma cohorts in 2022.

In addition, in May 2020, we entered into a global clinical collaboration agreement to evaluate the safety, tolerability and efficacy of combining surufatinib with BeiGene's anti-PD-1 antibody, tislelizumab, for the treatment of various solid tumor cancers in the United States, Europe, China and Australia. In March 2021, we dosed the first patient in an open-label, Phase Ib/II study of surufatinib in combination with tislelizumab in the United States and Europe, evaluating the safety, tolerability, pharmacokinetics and efficacy in patients with advanced solid tumors, including CRC, NET, small cell lung cancer, gastric cancer and soft tissue sarcoma. The dose finding phase of the study is now complete, and the expansion phase is ongoing.

Surufatinib Exploratory Development

In China, we support an investigator initiated trial, or IIT, program for surufatinib, with about 50 IITs in various solid tumor settings being conducted for both combination and single agent regimens. These trials explore and answer important medical questions in addition to our own company-sponsored clinical trials.

Overview of Sulanda Commercial Launch

Surufatinib capsules, sold under the brand name Sulanda, were approved for marketing in China by the NMPA in December 2020 and June 2021 for the treatment of advanced non-pancreatic NETs and pancreatic NETs, respectively. In 2021, Sulanda was sold as a self-pay drug whereby patients paid for treatment out-of-pocket. We used means-test early access and patient access programs to help patients afford Sulanda, and we estimate that approximately 4,800 new patients were treated. Following negotiations with the China National Healthcare Security Administration, Sulanda was included on China's NRDL at a 52% discount on our main 50mg dosage form, relative to the 2021 self-pay price, for two years starting on January 1, 2022.

During 2021, we introduced Sulanda through a campaign of local, regional and national launch events involving approximately 12,000 healthcare professionals. We have also confirmed a total of around 50 investigator-initiated studies in a broad range of exploratory solid tumor indications all of which are expected to gradually expand awareness of Sulanda in China.

3. Fruquintinib (HMPL-013), VEGFR 1, 2 and 3 Inhibitor

Fruquintinib is a VEGFR inhibitor that we believe is highly differentiated due to its superior kinase selectivity compared to other small molecule VEGFR inhibitors, which can be prone to excessive off-target toxicities. Fruquintinib's selectivity on VEGFR 1, 2 and 3 results in fewer off-target toxicities, thereby allowing for better target coverage, as well as possible use in combination with other agents such as chemotherapies, targeted therapies and immunotherapies.

We believe these are meaningful points of differentiation compared to other approved small molecule VEGFR inhibitors such as Sutent, Nexavar and Stivarga, and can potentially significantly expand the use and market potential of fruquintinib. Consequently, we believe that fruquintinib has the potential to become a global small molecule VEGFR inhibitor with the best selectivity for many types of solid tumors.

We received full approval for launch of fruquintinib (under the brand name Elunate) in CRC in September 2018. In partnership with Eli Lilly, we launched fruquintinib in China in late November 2018. Elunate is indicated for the treatment of patients with mCRC that have been previously treated with fluoropyrimidine, oxaliplatin and irinotecan, including those who have previously received anti-VEGF, therapy and/or anti-EGFR therapy (Ras wild type). We manufacture all commercial supplies of Elunate in our factory in Suzhou and have expanded our role in the commercialization of Elunate since October 1, 2020. For more information regarding the Elunate product launch, see "—Overview of Elunate Commercial Launch."

Mechanism of Action

During the development of cancer, tumors at an advanced stage can secrete large amounts of VEGF, a protein ligand, to stimulate formation of excessive vasculature (angiogenesis) around the tumor in order to provide greater blood flow, oxygen, and nutrients to fuel the rapid growth of the tumor. Since essentially all solid tumors require angiogenesis to progress beyond a few millimeters in diameter, VEGFR drugs have demonstrated benefits in a wide variety of tumor types. VEGF and other ligands can bind to three VEGF receptors, VEGFR 1, 2 and 3, each of which has been shown to play a role in angiogenesis. Therefore, inhibition of the VEGF/VEGFR signaling pathway can act to stop the growth of the vasculature around the tumor and thereby starve the tumor of the nutrients and oxygen it needs to grow rapidly.

This therapeutic strategy has been well validated with several first-generation VEGF inhibitors having been approved globally since 2005 and 2006. These include both small molecule multi-kinase inhibitor drugs such as Nexavar and Sutent as well as monoclonal antibodies such as Avastin. The success of these drugs validated VEGFR inhibition as a new class of therapy for the treatment of cancer.

Fruquintinib Pre-clinical Evidence

Pre-clinical trials have demonstrated that fruquintinib is a highly selective VEGFR 1, 2 and 3 inhibitor with high potency and low cell toxicity at the enzymatic and cellular levels. In a kinase selectivity screening, fruquintinib was found to be approximately 250 times more selective to VEGFR 3 than to the next non-VEGFR kinase.

As a result of off-target side effects, existing VEGFR inhibitors are often unable to be dosed high enough to completely inhibit VEGFR, the intended target. In addition, the complex off-target toxicities resulting from inhibition of multiple signaling pathways are often difficult to manage in clinical practice. Combining such drugs with chemotherapy can lead to severe toxicities that can cause more harm than benefit to patients. To date, the first generation VEGFR TKI have been rarely used in combination with other therapies, thereby limiting their potential. Because of the potency and selectivity of fruquintinib, we believe that it has the potential to be safely combined with other oncology drugs, which could significantly expand its clinical potential.

Fruquintinib Clinical Trials

Colorectal Cancer

The table below shows a summary of the clinical trials we have recently completed, are underway or are in planning for fruquintinib in CRC patients. We have two additional trials in progress for fruquintinib in CRC in combination with a checkpoint inhibitor as discussed in more detail below under "— Fruquintinib Combinations with Checkpoint Inhibitors."

Current Clinical Trials of Fruquintinib in CRC

Treatment	Sponsors/Partners	Name, Line, Patient Focus	Sites	Phase	Status/Plan	NCT #
Fruquintinib monotherapy	HUTCHMED and Eli Lilly	FRESCO: ≥3L CRC; chemotherapy refractory	China	III	Approved and launched	NCT02314819
Fruquintinib monotherapy [(1)]	HUTCHMED	FRESCO-2: mCRC	U.S./Europe/ Japan/Australia	III	Fully enrolled	NCT04322539
Fruquintinib monotherapy	HUTCHMED	CRC, TN & HR+/HER2- breast cancer	U.S.	Ib	Ongoing	NCT03251378

Notes: (1) The FDA granted fast track designation for the development of fruquintinib for the treatment of patients with mCRC in June 2020.

CRC = colorectal cancer; ≥3L= third line or above; refractory = resistant to prior treatment ; TN = triple-negative; HR+ = hormone receptor-positive; and HER2 = human epidermal growth factor receptor 2.

FRESCO study; Phase III study of fruquintinib monotherapy in third-line CRC (Status: completed and product launched; NCT02314819)

In 2014, we initiated the FRESCO study, which is a randomized, double-blind, placebo-controlled, multi-center, Phase III pivotal trial in China in patients with locally advanced or mCRC who had failed at least two prior systemic antineoplastic therapies, including fluoropyrimidine, Eloxatin and Camptosar. No drugs had been approved in third-line CRC in China with best supportive care being the general standard of care. This study followed a Phase II proof-of-concept trial in third-line CRC that met its primary endpoint of PFS in 2014.

Enrollment was completed in May 2016, and 519 patients were screened. The intent-to-treat population of 416 patients was randomized at a 2:1 ratio to receive either: 5 mg of fruquintinib orally once daily, on a three-weeks-on/one-week-off cycle, plus best supportive care (278 patients) or placebo plus best supportive care (138 patients). Randomization was stratified for prior anti-VEGF therapy and K-RAS gene status. The trial concluded in January 2017.

In June 2017, we presented the results of the FRESCO study in an oral presentation at the ASCO annual meeting. Results showed that FRESCO met all primary and secondary endpoints including significant improvements in OS and PFS with a manageable safety profile and lower off-target toxicities compared to other targeted therapies. The primary endpoint of median OS was 9.30 months (95% confidence interval: 8.18-10.45 months) in the fruquintinib group versus 6.57 months (95% confidence interval: 5.88-8.11 months) in the placebo group, with a hazard ratio of 0.65 (95% confidence interval: 0.51-0.83; two-sided $p<0.001$). The secondary endpoint of median PFS was 3.71 months (95% confidence interval: 3.65-4.63 months) in the fruquintinib group versus 1.84 months (95% confidence interval: 1.81-1.84 months) in the placebo group, with a hazard ratio of 0.26 (95% confidence interval: 0.21-0.34; two-sided $p<0.001$). Significant benefits were also seen in other secondary endpoints. The disease control rate in the fruquintinib group was 62% versus 12% for placebo ($p<0.001$), while the ORR based on confirmed responses was 5% versus 0% for placebo ($p=0.012$).

We have not performed a head-to-head clinical trial of fruquintinib versus Stivarga. While it is difficult to directly evaluate and compare clinical results across separate trials, data from the FRESCO study compare favorably to the data from the CONCUR study, a Phase III study of Stivarga monotherapy in CRC conducted in Asia, and the CORRECT study, a global Phase III study of Stivarga in CRC. In particular, in the Chinese patient subgroup of the CONCUR study, Stivarga had a disease control rate of 46% versus 7% in the placebo group. Median PFS was 2.0 months in the Stivarga group versus 1.7 months in the placebo group, and median OS was 8.4 months in the Stivarga group versus 6.2 months in the placebo group. In the CORRECT study, Stivarga had a disease control rate of 41% versus 15% in the placebo group. Median PFS was 1.9 months in the Stivarga group versus 1.7 months for the placebo group, and median OS was 6.4 months in the Stivarga group versus 5.0 months in the placebo group.

In terms of safety, results showed that fruquintinib had a manageable safety profile with lower off-target toxicities compared to Stivarga, the other VEGFR TKI approved for third-line CRC. Of particular interest was that the CTC grade 3 or above hepatotoxicity was similar for the fruquintinib group as compared to the placebo group, which was in contrast to Stivarga which was markedly higher and often difficult to manage in the Chinese patient population in the CONCUR study. Adverse events led to dose interruptions in 69% of patients in the Chinese patient subgroup of the CONCUR study, compared to 35% in the FRESCO study. The most frequently reported fruquintinib-related CTC grade 3 or above TEAEs included hypertension (21%), hand-foot skin reaction (11%), proteinuria (3%) and diarrhea (3%), all possibly associated with VEGFR inhibition. No other CTC grade 3 or above TEAEs exceeded 2% in the fruquintinib population, including hepatic function adverse events such as elevations in bilirubin (1%), alanine aminotransferase (<1%) or aspartate aminotransferase (<1%).

In terms of tolerability, dose interruptions or reductions occurred in only 35% and 24% of patients in the fruquintinib arm, respectively, and only 15% of patients discontinued treatment of fruquintinib due to adverse events versus 6% for placebo. The FRESCO study was published in the Journal of the American Medical Association in June 2018.

Subgroup analysis

In June 2018, a further subgroup analysis of data from the FRESCO Phase III study was presented at the ASCO annual meeting. This analysis explored possible effects of prior target therapy on the efficacy and safety of fruquintinib by analyzing the subgroups of patients with prior target therapy and those without prior target therapy.

Results showed that the benefits of fruquintinib were generally consistent across all subgroups. Among a total of 278 fruquintinib-treated patients, 111 had received prior target therapy while 55 of the 138 placebo-treated patients had received prior target therapy. In the prior target therapy subgroup, fruquintinib significantly prolonged OS and PFS. Median OS was 7.69 months for patients treated with fruquintinib versus 5.98 months for placebo (hazard ratio = 0.63; $p = 0.012$). Median PFS was 3.65 months for patients treated with fruquintinib versus 1.84 months for placebo (hazard ratio = 0.24; $p < 0.001$).

Among these 278 patients, the results showed that a subgroup of 84 patients who had received prior anti-VEGF treatment also benefited from fruquintinib. In this subgroup, the median OS was 7.20 months for fruquintinib versus 5.91 months for placebo (hazard ratio = 0.68; p=0.066) and the median PFS was 3.48 months for fruquintinib versus 1.84 months for placebo (hazard ratio = 0.24; $p < 0.001$).

In the subgroup of 250 patients without prior targeted therapies, the median OS was 10.35 months for 167 patients treated with fruquintinib versus 6.93 months for 83 patients treated with placebo (hazard ratio = 0.63; $p = 0.003$), and the median PFS for patients treated with fruquintinib was 3.81 months versus 1.84 months for placebo (hazard ratio = 0.28; $p < 0.001$).

Additional data showed that there were no observed cumulative CTC grade 3 or above TEAEs in the subgroup of patients with prior target therapy. The CTC grade 3 or above TEAEs rates of fruquintinib were similar in the subgroups with prior target therapy (61.3%) and without prior target therapy (61.1%). This subgroup analysis is consistent with the previously reported results from the FRESCO study's intent-to-treat population.

The results of this analysis showed that fruquintinib had clinically meaningful benefits in third-line mCRC patients regardless of prior target therapy without observed cumulative toxicity.

Quality-adjusted survival analysis

At the 2018 ASCO Annual Meeting, an analysis was presented that aimed to compare the quality-adjusted survival between the two arms of the FRESCO study using quality-adjusted time without symptoms or toxicity, or Q-TWiST, methodology and to investigate the Q-TWiST benefit of fruquintinib treatment among subgroups. Q-TWiST is a tool to evaluate relative clinical benefit-risk from a patient's perspective and has been widely used in oncology treatment assessment. The survival time for each patient was divided into three portions: time with CTC grade 3 or above toxicity before progression, time without symptoms or CTC grade 3 or above toxicity, and time from progression or relapse until death or end of follow-up.

Patients treated with fruquintinib had longer Q-TWiST periods compared to patients treated with placebo. Q-TWiST benefits were observed regardless of prior lines of chemotherapy and prior anti-VEGF or anti-EGFR targeted therapy. The relative improvement of Q-TWiST with fruquintinib represents a clinically important quality-of-life benefit for mCRC patients.

Supported by data from the successful FRESCO study, we submitted an NDA for fruquintinib in June 2017. Fruquintinib was subsequently awarded priority review status by the NMPA in view of its clinical value in September 2017, and in September 2018, the NMPA approved fruquintinib for the treatment of patients with advanced CRC and was launched in November 2018. For more information regarding the Elunate product launch, see "—Overview of Elunate Commercial Launch."

Phase III study of fruquintinib monotherapy in mCRC – Global (Status: enrollment completed; NCT04322539)

We initiated a global Phase III registration study, known as the FRESCO-2 study, in refractory metastatic CRC. The first patient was dosed in September 2020 in the United States and the enrollment was completed in December 2021, where 691 patients from over 150 sites in 14 countries were enrolled.

The U.S. FDA has acknowledged the totality of the fruquintinib clinical data, including the FRESCO-2 study (if positive), the prior positive Phase III FRESCO study demonstrating improvement in OS that led to fruquintinib approval for metastatic CRC in China in 2018, and additional completed and ongoing supporting studies in metastatic CRC, could potentially support an NDA for the treatment of patients with metastatic CRC in the third-line setting. The EMA and PMDA have reviewed and endorsed the FRESCO-2 study design. The primary endpoint of the study is OS.

We expect to report outcome of this study in the second half of 2022 when the event-driven primary endpoint, OS, is reached. If positive, we plan to initiate a simultaneous submission program to apply for fruquintinib marketing authorization with the U.S. FDA, the EMA and the PMDA.

Phase Ib study of fruquintinib monotherapy in metastatic colorectal and breast cancers – U.S. (Status: ongoing; NCT03251378)

We are conducting a multi-center, open-label, Phase Ib clinical study to evaluate the safety, tolerability and pharmacokinetics of fruquintinib in U.S. patients, which has established the U.S. RP2D to be 5 mg, the same as that in China. This dose is being further evaluated in patients with mCRC and breast cancers.

Preliminary efficacy and safety data of fruquintinib in patients with refractory, metastatic CRC were presented at the ASCO Gastrointestinal Cancers Symposium in early 2022. In patients who had progressed on all standard therapies, including Lonsurf and/or Stivarga, the DCR was 68.3% and the median duration of treatment was 19.3 weeks. In patients who had not received Lonsurf or Stivarga, the DCR was 57.5% and the median duration of treatment was 14.1 weeks. The safety profile in both patient populations was consistent with what has previously been reported.

Gastric Cancer

Advanced gastric cancer is a major medical need, particularly in Asian populations, with limited treatment options for patients who have failed first-line standard chemotherapy with 5-fluorouracil and platinum doublets. The table below shows a summary of the clinical study we have underway for fruquintinib in gastric cancer patients.

Clinical Trials of Fruquintinib in Gastric Cancer

Treatment	Sponsors/Partners	Name, Line, Patient Focus	Sites	Phase	Status/Plan	NCT #
Fruquintinib and Taxol	HUTCHMED and Eli Lilly	FRUTIGA: 2L gastric cancer	China	III	Ongoing; completed second interim analysis	NCT03223376

Notes: 2L = second line.

FRUTIGA study: Phase III study of fruquintinib in combination with Taxol in gastric cancer (second-line) (Status: Completed second interim analysis; NCT03223376)

In October 2017, we initiated the FRUTIGA study, a pivotal Phase III clinical trial of fruquintinib in combination with Taxol for the treatment in advanced gastric or gastroesophageal junction adenocarcinoma patients in China. This randomized, double-blind, placebo-controlled, multi-center trial is being conducted in patients with advanced gastric cancer who have progressed after first-line standard chemotherapy. All subjects will receive fruquintinib or placebo combined with paclitaxel. Patients will be randomized at a 1:1 ratio and stratified according to factors such as stomach versus gastroesophageal junction tumors and ECOG performance status, a scale established by the Eastern Cooperative Oncology Group which determines ability of patient to tolerate therapies in serious illness, specifically for chemotherapy. The study is expected to enroll approximately 700 patients. Its co-primary endpoints are PFS and OS.

In June 2020, the IDMC of the FRUTIGA study completed a second planned interim data review and, based on the preset criteria, the IDMC and Joint Steering Committees recommended that the trial continue with a sample size increase to ~700 patients. We expect to complete enrollment of FRUTIGA in 2022.

Fruquintinib Combinations with Checkpoint Inhibitors

The table below shows a summary of the clinical trials we have ongoing and in planning for fruquintinib in combination with checkpoint inhibitors.

Clinical Trials of Fruquintinib with Checkpoint Inhibitors

Treatment	Sponsors/Partners	Name, Line, Patient Focus	Sites	Phase	Status/Plan	NCT #
Fruquintinib and Tyvyt (PD-1)	Chinese PLA General Hospital and Innovent	CRC	China	II	Ongoing; data presented at ASCO 2021	NCT04179084
Fruquintinib and Tyvyt (PD-1)	HUTCHMED and Innovent	Hepatocellular carcinoma	China	Ib/II	Ongoing; data presented at CSCO 2021	NCT03903705
Fruquintinib and Tyvyt (PD-1)	HUTCHMED and Innovent	Endometrial cancer	China	II registration-intent	Ongoing; Ib data presented at CSCO 2021	NCT03903705
Fruquintinib and Tyvyt (PD-1)	HUTCHMED and Innovent	RCC	China	Ib/II	Ongoing; data at CSCO 2021	NCT03903705
Fruquintinib and Tyvyt (PD-1)	HUTCHMED and Innovent	Gastrointestinal tumors	China	Ib/II	Ongoing	NCT03903705
Fruquintinib and tislelizumab (PD-1)	HUTCHMED and BeiGene	TN breast cancer & endometrial cancer	U.S.	Ib/II	Ongoing	NCT04577963
Fruquintinib and tislelizumab (PD-1)	BeiGene and HUTCHMED	Solid tumors	Korea / China	Ib/II	Ongoing	NCT04716634

Notes: CRC = colorectal cancer; NSCLC = non-small cell lung cancer.

In November 2018, we entered into two collaboration agreements to evaluate the safety, tolerability and efficacy of fruquintinib in combination with checkpoint inhibitors. These include a global collaboration with Innovent to evaluate the combination of fruquintinib with Innovent's Tyvyt, a PD-1 monoclonal antibody approved in China, and a collaboration in China with Genor to evaluate the fruquintinib combination with geptanolimab, a PD-1 monoclonal antibody being developed by Genor. We are now approaching completion of the Phase I dose-finding study in China of fruquintinib in combination with Tyvyt, with the Phase I dose-expansion study already underway in five solid tumor indications. Phase Ib studies of fruquintinib in combination with geptanolimab in second-line CRC and NSCLC are ongoing. In 2022, we plan to initiate Phase III studies of fruquintnib plus Tyvyt combination in HCC, RCC and endometrial cancer in China.

Advanced endometrial cancer registration-intent cohort

Platinum-based systemic chemotherapy is the standard first-line treatment for advanced endometrial cancer. However, patients who progress following first-line chemotherapy have limited treatment options, and the prognosis remains poor. As disclosed at CSCO 2021, as of the data cutoff date of August 31, 2021, 35 patients were enrolled (NCT03903705), including 7 treatment-naïve and 28 pretreated patients. Of them, 29 were efficacy evaluable, 4 were treatment-naïve and 25 were pretreated. All 4 treatment-naïve patients experienced confirmed tumor response, for ORR of 100% (95% CI: 39.8-100.0), and median PFS was not reached. Among the 25 pretreated patients, the confirmed ORR was 32.0% (95% CI: 14.9-53.5), DCR was 92.0% (95% CI: 74.0-99.0) and the median PFS was 6.9 months (95% CI: 4.1-NR). Among the 19 proficient mismatch repair (pMMR) patients in the pretreated cohort, the confirmed ORR was 36.8% (95% CI: 16.3-61.6), DCR was 94.7% (95% CI: 74.0-99.9), median PFS was 6.9 months (95% CI: 4.1-NR), and the median OS was not reached. Among the 35 enrolled patients, treatment-related adverse events of grade 3 or above that occurred in more than 10% of patients were hypertension (4 patients, 11.4%) and proteinuria (4 patients, 11.4%). 5 (14.3%) patients reported treatment-related serious adverse events.

Following discussion with the NMPA in late 2021, the cohort is now targeting to enroll over 130 patients to meet the requirements to be a single-arm, registration-intent Phase II study.

CRC registration strategy for mCRC under discussion

Encouraging preliminary data presented at ASCO 2021 for fruquintinib in combination with two PD-1 inhibitors, Tyvyt and geptanolimab, in advanced CRC showed a five-fold increase in ORR and a doubling of median PFS as compared to the FRESCO study for fruquintinib as a monotherapy.

In the Tyvyt combination study (NCT04179084), 44 patients were enrolled into the CRC cohort, 22 of whom received the RP2D. ORR was 23% for all patients and 27% for those who received the RP2D. DCR was 86% for all patients and 96% for those who received the RP2D. Median PFS was 5.6 months for all patients, and 6.9 months for those who received the RP2D. Median OS was 11.8 months for all patients.

In the geptanolimab combination study (NCT03977090), for the 15 patients in the CRC cohort ORR was 26.7% (including 1 patient with unconfirmed PR) and 33% in the group that received the RP2D. DCR for all evaluable patients was 80% and median PFS was 7.3 months (95% CI: 1.9-NR). Grade 3 treatment-related adverse events occurred in 47% of patients, and no incidences of grade 4 or 5 treatment-related adverse events were observed.

Tislelizumab combinations (NCT04577963 & NCT04716634)

In August 2021, we initiated an open-label, multi-center, non-randomized Phase Ib/II study in the U.S. to assess fruquintinib in combination with tislelizumab in patients with locally advanced triple negative breast cancer or advanced endometrial cancer. In addition, a Phase II study in China and Korea for fruquintinib in combination with tislelizumab was initiated and is being led by BeiGene for the treatment of advanced or metastatic, unresectable gastric cancer, CRC or NSCLC.

Fruquintinib Exploratory Development

We are conducting multiple Phase Ib expansion cohorts in the United States to explore fruquintinib in CRC and breast cancer. In China, there are about 40 ongoing investigator-initiated studies in various solid tumor settings.

Overview of Elunate Commercial Launch

Fruquintinib capsules, sold under the brand name Elunate, were approved for marketing in China by the NMPA in September 2018 and commercially launched in late November 2018. We also received marketing approval for Elunate in Macau in February 2022. Elunate is for the treatment of patients with mCRC that have been previously treated with fluoropyrimidine, oxaliplatin and irinotecan, including those who have previously received anti-VEGF therapy and/or anti-EGFR therapy (RAS wild type).

Starting on January 1, 2020, Elunate was included on China's NRDL at a 63% discount to its initial retail price for two years, paving the way to significantly broaden access for advanced CRC patients and rapidly build penetration in China over the coming years. The inclusion was renewed pursuant to which we agreed to a discount of 5% relative to the 2021 NRDL price, and Elunate will continue to be included in the NRDL starting January 2022 for another two years.

The revenues we generate from Elunate are comprised of royalty revenue, revenue from the sales of Elunate to Eli Lilly which we manufacture and sell at cost and, starting in October 2020, revenue from promotion and marketing services. In 2019, we generated $10.8 million in total revenue from Elunate, of which $2.7 million was royalty revenue and $8.1 million was revenue from sales to Eli Lilly. In 2020, we generated $20.0 million in total revenue from Elunate, of which $4.9 million was royalty revenue, $11.3 million was revenue from sales of goods primarily to Eli Lilly and $3.8 million was revenue from promotion and marketing services to Eli Lilly. In 2021, we generated $53.5 million in total revenue from Elunate, of which $10.3 million was royalty revenue, $15.8 million was revenue from sales of goods primarily to Eli Lilly and $27.4 million was revenue from promotion and marketing services to Eli Lilly.

Partnership with Eli Lilly

In October 2013, we entered into a license and collaboration agreement with Eli Lilly in order to accelerate and broaden our fruquintinib development program in China. As a result, we were able to quickly expand the clinical development of fruquintinib into indications with unmet medical needs in China including CRC and gastric cancer, as discussed above. In December 2018, we amended our license and collaboration agreement with Eli Lilly. This amendment gives us, among other things, all planning, execution and decision making responsibilities for life cycle indication development of fruquintinib in China. Support from Eli Lilly has also helped us to establish our own manufacturing (formulation) facility in Suzhou, China, which now produces clinical and commercial supplies of fruquintinib. In July 2020, we reached an agreement with Eli Lilly to take over development and execution of all on-the-ground medical detailing, promotion and local and regional marketing activities for Elunate in China starting on October 1, 2020. Under the terms of the new agreement, we will share gross profits linked to sales target performance. Subject to meeting pre-agreed sales targets, Eli Lilly will pay us an estimated total of 70% to 80% of Elunate in-market sales in the form of royalties, manufacturing costs and service payments.

For more information regarding our partnership with Eli Lilly, see "—Overview of Our Collaborations—Eli Lilly."

4. Amdizalisib (HMPL-689), PI3Kδ Inhibitor

Amdizalisib is a novel, highly selective oral inhibitor targeting the isoform PI3Kδ, a key component in the B-cell receptor signaling pathway. Amdizalisib's pharmacokinetic properties have been found to be favorable with good oral absorption, moderate tissue distribution and low clearance in pre-clinical studies. We also expect that amdizalisib will have low risk of drug accumulation and drug-drug interactions. In 2021, registration-intent studies for amdizalisib were initiated and Breakthrough Therapy Designation was granted for relapse or refractory follicular lymphoma in China.

Mechanism of Action

Targeting the B-cell signaling pathway is emerging as a potential means to treat both hematological cancer and immunological diseases. Inhibiting different kinases found along the B-cell signaling pathway has proven to have clinical efficacy in hematological cancers, with breakthrough therapies having been recently approved by the FDA.

The high efficacy and successful approvals of Bruton's tyrosine kinase, or BTK, inhibitors and PI3Kδ inhibitors are evidence that modulation of the B-cell signaling pathway is critical for the effective treatment of B-cell malignancies.

Class I phosphatidylinositide-3-kinases, or PI3Ks, are lipid kinases that, through a series of intermediate processes, control the activation of several important signaling proteins including the serine/threonine kinase AKT.

There are multiple sub-families of PI3K kinases, and PI3Kδ is a lipid kinase that, through a series of intermediate processes, controls the activation of several important signaling proteins, including the serine/threonine kinase B, or AKT. In most cells, AKT is a key PI3Kδ affector that regulates cell proliferation, carbohydrate metabolism, cell motility and apoptosis and other cellular processes. Upon an antigen binding to B-cell receptors, PI3Kδ can be activated through the Lyn and Syk signaling cascade.

Aberrant B-cell function has been observed in multiple immunological diseases and B-cell mediated malignancies. Therefore, PI3Kδ is considered to be a promising target for drugs that aim to prevent or treat hematologic cancer, autoimmunity and transplant organ rejection and other related inflammation diseases.

Amdizalisib Pre-clinical Evidence

Compared to other PI3Kδ inhibitors, amdizalisib shows higher potency and selectivity.

Enzyme Selectivity (IC_{50}, in nM) of amdizalisib Versus Competing PI3Kδ Inhibitors; This Shows amdizalisib is Approximately Five-fold More Potent than Zydelig on Whole Blood Level and, unlike Copiktra, does not Inhibit PI3K-γ.

Enzyme IC_{50} (nM)	HMPL-689	Zydelig	Copiktra	Aliqopa
PI3Kδ	0.8 (n = 3)	2	1	0.7
PI3Kγ (fold vs. PI3Kδ)	114 (142x)	104 (52x)	2 (2x)	6.4 (9x)
PI3Kα (fold vs. PI3Kδ)	>1,000 (>1,250x)	866 (433x)	143 (143x)	0.5 (1x)
PI3Kδ human whole blood CD63+	3	14	15	n/a
PI3Kβ (fold vs. PI3Kδ)	87 (109x)	293 (147x)	8 (8x)	3.7 (5x)

Source: Company.

Amdizalisib Clinical Development

The table below shows a summary of the clinical studies for amdizalisib.

Clinical Trials of Amdizalisib

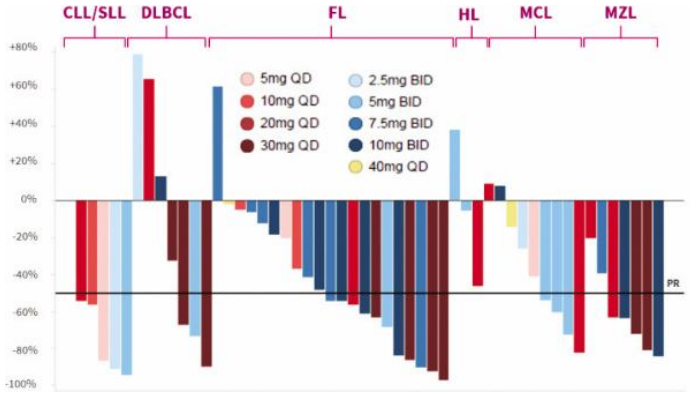
Treatment	Sponsors/Partners	Name, Line, Patient Focus	Sites	Phase	Status/Plan	NCT #
Amdizalisib monotherapy	HUTCHMED	Indolent non-Hodgkin's lymphoma PTCL	China	Ib	Ongoing; expansion data presented at ESMO 2021	NCT03128164
Amdizalisib monotherapy	HUTCHMED	Relapsed/refractory follicular lymphoma	China	II registration-intent	Ongoing: initiated in April 2021. Breakthrough Therapy Designation	NCT04849351
Amdizalisib monotherapy	HUTCHMED	Relapsed/refractory marginal zone lymphoma	China	II registration-intent	Ongoing: initiated in April 2021	NCT04849351
Amdizalisib monotherapy	HUTCHMED	Indolent non-Hodgkin's lymphoma	U.S./ Europe	I/Ib	Dose expansion portion initiated in the second half of 2021	NCT03786926

Phase Ib study of amdizalisib in patients with Indolent non-Hodgkin's lymphoma in China (Status: ongoing; NCT03128164)

Our Phase I/Ib study of amdizalisib in China has successfully established a Phase II dose and has now expanded into multiple sub-categories of indolent non-Hodgkin's lymphoma.

In December 2020, we presented preliminary results from a Phase I dose escalation study of amdizalisib in Chinese patients with relapsed/refractory lymphoma at the American Society of Hematology (ASH) Annual Meeting. A total of 56 patients were enrolled resulting in an ORR of 51.9% (27/52) and complete response rate of 11.5% (6/52) in efficacy evaluable patients. The median time to response and duration of response were 1.8 months (1.8-1.9) and 9.2 months (3.9-NR), respectively. One patient with follicular lymphoma who achieved complete response (per post hoc independent radiologic review) was on treatment for over 19 months. In the nine efficacy evaluable patients treated with the RP2D of 30mg QD orally, efficacy was encouraging with an ORR of 100% (4/4) in follicular lymphoma, 100% in marginal zone lymphoma (2/2) and 67% (2/3) in diffuse large B cell lymphoma.

Phase 1 Dose Escalation Study: Promising Amdizalisib Single-agent Clinical Activity in Relapsed/refractory B-cell Lymphoma Patients



Intent-to-treat population (n=56)	
Best Response	
Complete Response, %	11 (4-22)
Partial Response, %	37
Stable Disease, %	34
Progressive Disease, %	11
Overall Response Rate	48% (35-62)
Clinical Benefit Rate	82% (70-91)
Time on Treatment	5.6 months (0.7–23.2)
Time to Response	1.8 months (1.8–1.9)
Duration of Response	9.2 months (3.9–NA)
Progression Free Survival	10.1 months (5.5–15.7)
1-year PFS rate	40% (27–57)

Notes: CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; HL = Hodgkin's lymphoma; MCL = mantle cell lymphoma; MZL = marginal zone lymphoma; BID = twice daily; QD = once daily; PR = partial response; n = number of patients; PFS = progression free survival; and NA = not available.

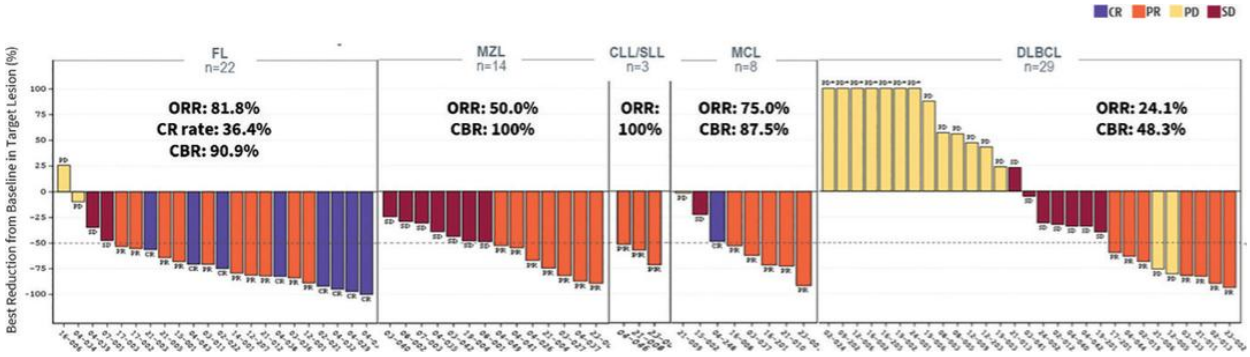
Source: Cao JN, et al. "Results from a Phase 1 Dose Escalation Study of Amdizalisib, a Selective Oral Phosphoinositide 3-Kinase-Delta Inhibitor, in Chinese Patients with relapsed/refractory (R/R) Lymphoma" Presented at the 62nd American Society of Hematology (ASH) Annual Meeting and Exposition on December 5, 2020. Abstract #1135.

Amdizalisib was well tolerated at the RP2D exhibiting dose-proportional pharmacokinetics and a manageable toxicity profile. Grade 3 or more non-hematologic TEAEs occurring in more than two patients were pneumonia, rash, hypertension, and increased lipase. Grade 3 or more hematologic TEAEs occurring in more than two patients were neutropenia, and no Grade 5 TEAEs were reported.

In ESMO 2021, we presented results from the Phase Ib study. In the efficacy evaluable population of 76 patients, the median time of follow-up was 5.6 months (95% CI: 5.5-8.3). Objective response rate was 53.9%, completed response rate was 11.8%, and clinical benefit rate was 76.3%. Median duration of response was not reached, and 6-months duration of response rate was 84.5% (95% CI: 62.9-94.1). Median time to response was 1.9 months (95% CI: 1.8-1.9). Amdizalisib showed promising single-agent clinical activity in patients with relapsed/refractory B-cell lymphoma, with high objective response rate and complete response rates noted particularly for follicular lymphoma patients.

In the 22 follicular lymphoma patients with efficacy evaluable, the median time of follow-up was 8.3 months (95% CI: 2.0-11.0). Objective response rate was 81.8%, complete response rate was 36.4% and clinical benefit rate was 90.9%. Median time to response was 1.8 months (95% CI: 1.8-1.9), 1-year duration of response was 59.7%, and progression-free survival rate was 75.8%. 77% of the patients remain on therapy.

Phase Ib Study of Amdizalisib in Chinese Patients with Relapsed/Refractory Lymphoma:
Best response of target lesion (N=76)



Notes: Data cut-off as of June 15, 2021. Target lesion SPD (sum of the product of perpendicular diameters) increased more over 100%. Efficacy evaluable population: received at least one tumor assessment. FL = follicular lymphoma; MZL = marginal zone lymphoma; CLL/SLL = chronic lymphocytic leukemia / small lymphocytic lymphoma; MCL = mantle cell lymphoma; DLBCL = diffuse large B cell lymphoma; n = number of patients; CR = complete response; PR = partial response; PD = progressive disease; SD = stable disease; ORR = objective response rate; CBR = clinical benefit rate (CR + PR + SD)

Source: CaoJN, et al. "A phase Ib study result of HMPL-689, a PI3Kδ inhibitor, in Chinese patients with relapsed/refractory lymphoma." Presented at the 2021 European Society for Medical Oncology (ESMO) Virtual Congress on September 20, 2021. Presentation #833O

Amdizalisib was well tolerated and demonstrated a manageable safety profile. The most frequent treatment-emergent adverse event was neutrophil count decreased (28.9%), and most frequent, non-hematologic, Grade 3 or above treatment-emergent adverse events were pneumonia (13.3%) and rash (5.6%). All liver enzyme elevation was mild to moderate (Grade 1-2). Grade 3 diarrhea was low (2.2%) and there were no colitis cases as of the data cut-off. Treatment discontinuation rate due to adverse events was 5.6%.

Phase II registration-intent study of amdizalisib in patients with relapsed/refractory follicular lymphoma and relapsed/refractory marginal zone lymphoma in China (Status: enrolling; NCT04849351)

Based on the highly promising preliminary results from the above Phase Ib expansion study, in April 2021, we commenced a registration-intent Phase II trial of amdizalisib in China in patients with relapsed or refractory follicular lymphoma and marginal zone lymphoma, two subtypes of non-Hodgkin's lymphoma. The clinical trial is a multi-center, single-arm, open-label clinical study to evaluate the efficacy and safety of amdizalisib once a day oral monotherapy in approximately 100 patients with relapsed/refractory follicular lymphoma and approximately 80 patients with relapsed/refractory marginal zone lymphoma. Relapsed/refractory is defined when a patient has not achieved response (complete response or partial response) after the latest line of systemic treatment, or has progressive disease or relapse after achieving response. The primary endpoint is ORR, with secondary endpoints including CR rate, PFS, TTR and duration of response. The trial is being conducted in over 35 sites in China.

Phase I/Ib study of amdizalisib in patients with Indolent non-Hodgkin's lymphoma in the United States and Europe (Status: enrolling; NCT03786926)

In August 2019, we initiated an international Phase I/Ib study of amdizalisib in patients with relapsed or refractory lymphoma. The international clinical study, with 17 sites in the United States and Europe, is a multi-center, open-label, two-stage study, including dose escalation and expansion, investigating the effects of amdizalisib administered orally to patients with relapsed or refractory lymphoma. The primary outcome measures are safety and tolerability. Secondary outcomes include pharmacokinetic measurements and preliminary efficacy such as ORR.

5. Sovleplenib (HMPL-523), Syk Inhibitor

The result of our over six-year program of discovery and pre-clinical work against Syk is sovleplenib, a highly selective Syk inhibitor with a unique pharmacokinetic profile which provides for higher drug exposure in the tissue than on a whole blood level. We designed sovleplenib intentionally to have high tissue distribution because it is in the tissue that the B-cell activation associated with rheumatoid arthritis and lupus occurs most often. Furthermore, and somewhat counter intuitively, in hematological cancer the vast majority of cancer cells nest in tissue, with a small proportion of cancer cells releasing and circulating in the blood where they cannot survive for long. We assessed that an effective small molecule Syk inhibitor would need to have superior tissue distribution.

In January 2022, the Center for Drug Evaluation of the NMPA granted Breakthrough Therapy Designation to sovleplenib for the treatment of chronic adult primary immune thrombocytopenia patients who have received at least one prior therapy.

Mechanism of Action

Syk is a key kinase upstream to PI3Kδ and BTK within the B-cell signaling pathway and therefore thought to be an important target for modulating B-cell signaling.

Syk, a target for autoimmune diseases

The central role of Syk in signaling processes is not only in cells of immune responses but also in cell types known to be involved in the expression of tissue pathology in autoimmune, inflammatory and allergic diseases. Therefore, interfering with Syk could represent a possible therapeutic approach for treating these disorders. Indeed, several studies have highlighted Syk as a key player in the pathogenesis of a multitude of diseases, including rheumatoid arthritis, systemic lupus erythematosus and multiple sclerosis.

Syk, a target for oncology

In hematological cancer, we believe Syk is a high potential target. In hematopoietic cells, Syk is recruited to the intracellular membrane by activated membrane receptors like B-cell receptors or another receptor called Fc and then binds to the intracellular domain of the receptors. Syk is activated after being phosphorylated by certain kinases and then further induces downstream intracellular signals including B-cell linker, PI3Kδ, BTK and Phospholipase C-y2 to regulate B-cell proliferation, growth, differentiation, homing, survival, maturation, and immune responses. Syk not only involves the regulation of lymphatic cells but also signal transduction of non-lymphatic cells such as mast cells, macrophages, and basophils, resulting in different immunological functions such as degranulation to release immune active substances, leading to immunological reaction and disease. Therefore, regulating B-cell signal pathways through Syk is expected to be effective for treating lymphoma.

Syk is upstream of both BTK and PI3Kδ, and we believe it could deliver the same outcome as inhibitors of BTK and PI3Kδ, assuming no unintentional toxicities are derived from Syk inhibition.

Sovleplenib Research Background

The threshold of safety for a Syk inhibitor in chronic disease is extremely high, with no room for material toxicity. The failure of Tavalisse in a global Phase III registration study in rheumatoid arthritis provided important insights for us in the area of toxicity. While Tavalisse clearly showed patient benefit in rheumatoid arthritis, a critical proof-of-concept for Syk modulation, it also caused high levels of hypertension which is widely believed to be due to the high levels of off-target kinase insert domain receptor inhibition. In addition, Tavalisse has also been shown to strongly inhibit the Ret kinase, and in pre-clinical trials it was demonstrated that inhibition of the Ret kinase was associated with developmental and reproductive toxicities.

The requirement for Syk kinase activity in inflammatory responses was first evaluated with Tavalisse, which was co-developed by AstraZeneca/Rigel Pharmaceuticals, Inc. In 2013, AstraZeneca announced results from pivotal Phase III clinical trials that Tavalisse statistically significantly improved ACR20 (a 20% improvement from baseline based on the study criteria) response rates of patients inadequately responding to conventional disease-modifying anti-rheumatic drugs and a single anti-TNFα (a key pro-inflammatory cytokine involved in rheumatoid arthritis pathogenesis) antagonist at 24 weeks, but failed to demonstrate statistical significance in comparison to placebo at 24 weeks. As a result, AstraZeneca decided not to proceed. Rigel Pharmaceuticals subsequently chose to develop Tavalisse for immune thrombocytopenia instead, for which it was approved by the FDA in 2018 and the EMA in 2020.

Tavalisse was also in trials for B-cell lymphoma and T-cell lymphoma. It demonstrated some clinical efficacy in diffused large B-cell lymphoma patients with an ORR of 22%. Entospletinib has features of high potency and good selectivity toward kinases. However, while the Phase II study discussed above showed that it had significant efficacy in patients with chronic lymphocytic leukemia and small lymphocytic lymphoma, its poor solubility and permeability into intestinal epithelial cells resulted in unsatisfactory oral absorption and a great variation of individual drug exposure. In addition, entospletinib shows some inhibition of the CYP3A4, CYP2D6, and CYP1A2 enzymes involved in the metabolism of certain drugs, and therefore their inhibition could increase the risk of drug-to-drug interaction when used in combined therapy.

Sovleplenib Pre-clinical Evidence

The safety profile of sovleplenib was evaluated in multiple in vitro and in vivo pre-clinical trials under good laboratory practice guidelines and found to be well tolerated following single dose oral administration. Toxic findings were seen in repeat dose animal safety evaluations in rats and dogs at higher doses and found to be reversible. These findings can be readily monitored in the clinical trials and fully recoverable upon drug withdrawal. The starting dose in humans was suggested to be 5 mg. This dose level is approximately 5% of the human equivalent dose extrapolated from the pre-clinical “no observed adverse event levels,” which is below the 10% threshold recommended by FDA guidelines.

Sovleplenib Clinical Trials

As discussed below, we currently have various clinical trials of sovleplenib ongoing in Australia, the United States, Europe and China as a monotherapy. We plan to complete U.S. IND and initiate Phase I study in the United States in patients with immune thrombocytopenia purpura in 2022. The table below shows a summary of the clinical trials that we currently have for sovleplenib.

Current Clinical Trials of Sovleplenib

Treatment	Sponsors/Partners	Name, Line, Patient Focus	Sites	Phase	Status/Plan	NCT #
Sovleplenib monotherapy	HUTCHMED	ESLM-01: Immune thrombocytopenia	China	III	Ongoing: initiated in October 2021. Breakthrough Therapy Designation	NCT05029635
Sovleplenib monotherapy	HUTCHMED	Immune thrombocytopenia purpura	China	I/Ib	Completed: data presented at ASH 2021	NCT03951623
Sovleplenib monotherapy	HUTCHMED	Indolent non-Hodgkin's lymphoma	Australia	Ib	Active, not recruiting	NCT02503033
Sovleplenib monotherapy	HUTCHMED	Indolent non-Hodgkin's lymphoma	U.S./ Europe	I/Ib	Ongoing; preliminary data presented at ASH 2021	NCT03779113
Sovleplenib monotherapy	HUTCHMED	Multiple sub-types of B-cell malignancies	China	I/Ib	Completed	NCT02857998
Sovleplenib monotherapy	HUTCHMED	wAIHA	China	II	In planning	N/A

Phase I/Ib study of sovleplenib in patients with immune thrombocytopenia (Status: ongoing; NCT03951623)

In mid-2019, we initiated a Phase I study of sovleplenib in patients with immune thrombocytopenia purpura. Immune thrombocytopenia purpura is an autoimmune disorder characterized by low platelet count and an increased bleeding risk. Despite availability of several treatments with differing mechanisms of action, a significant proportion of patients develop resistance to treatment and are prone to relapse. In addition, there is a significant population of patients who have limited sensitivity to currently available agents and are in need of a new approach to treatment.

The study is a randomized, double-blinded, placebo-controlled Phase Ib clinical trial investigating the safety, tolerability, pharmacokinetics and preliminary efficacy of sovleplenib in adult patients with immune thrombocytopenia purpura. The primary endpoint is the number of patients with any adverse event. The secondary endpoints are maximum plasma concentration, area under the concentration-time curve in a selected time interval, and rate of clinical remission at week eighty. The trial is comprised of a dose escalation stage and a dose expansion stage. Approximately 50 to 60 patients are expected to be enrolled. Encouraging results from the Phase Ib study were presented at the ASH 2021 annual meeting.

As of the data cutoff date, 34 patients had received sovleplenib and 11 received placebo. Among 16 patients who received the RP2D of 300mg once daily, 11 (68.8%) experienced response (defined by at least one incident of platelet count being $\geq 50x10^9/L$ in the initial 8-week double blinded phase of the study), compared to one placebo patient (9.1%). One additional patient at the RP2D experienced response during the subsequent 16-week open-label phase of the study, and all four placebo patients that crossed over to receive treatment at RP2D after the initial 8-week double blinded phase experienced response. In total, 16 out of 20 patients (80%) experienced response during both phases of the study. Durable response (defined as platelet count being $\geq 50x10^9/L$ in at least 4 out of 6 last scheduled visits) was reported in 8 out of 20 patients (40%) who received RP2D in both phases of the study.

Safety data were presented for all 41 patients (31 sovleplenib, 10 placebo). The median duration of treatment was 142 days (range: 23-170). No patients discontinued treatment due to treatment-related adverse event, and no cases of treatment-related serious adverse events were reported. There were 30 patients (73%) who experienced treatment-related adverse events, including 3 (7.3%) who experienced grade 3 or above treatment-related adverse events, one of whom received the RP2D. No treatment-related adverse events of grade 3 or above occurred in more than one patient.

Phase Ib Study of Sovleplenib in Adult Patients with Primary Immune Thrombocytopenia

	Initial 8-week double-blind treatment					Subsequent 16-week open-label treatment
	Placebo	100mg	200mg	300mg	400mg	300mg*
Overall response %(n)	9% (1/11)	50% (3/6)	33% (2/6)	69% (11/16)	33% (2/6)	80% (16/20)
Durable response %(n)	9% (1/11)	0	0	31% (5/16)	0	40% (8/20)

Notes: Data cut-off as of September 30, 2021. Overall Response was defined as at least one incident of platelet count being ≥ 50×10^9/L in the initial 8-week double blinded phase of the study. Durable Response was defined as platelet count being ≥ 50×10^9/L in at least 4 out of 6 last scheduled visits.

*The 300mg QD cohort includes 4 patients who, after receiving placebo in the first 8 weeks of double blind treatment, received sovleplenib 300mg QD in a 16-week open-label treatment period. QD= once daily

Source: Yang R, et al. "Safety, Pharmacokinetics and Preliminary Efficacy of HMPL-523 in Adult Patients with Primary Immune Thrombocytopenia: A Randomized, Double-Blind and Placebo-Controlled Phase Ib Study." Presented at the 63rd American Society of Hematology (ASH) Annual Meeting and Exposition on December 11, 2021. Abstract #149895.

Phase III study of sovleplenib in patients with immune thrombocytopenia (Status: ongoing; NCT05029635)

Based on encouraging data from the Phase Ib study of sovleplenib in adult patients with immune thrombocytopenia, we initiated a Phase III study of sovleplenib in October 2021. The study is a randomized, double blinded, placebo-controlled Phase III clinical trial evaluating the efficacy and safety of sovleplenib in treating adult patients with ITP. The primary endpoint of the study is the durable response rate. Secondary and exploratory endpoints include ORR, incidence of treatment emergent adverse events, and patient quality of life improvement. Approximately 180 patients are expected to be enrolled. Sovleplenib received Breakthrough Therapy Designation in China in January 2022.

Phase I/Ib studies in multiple subtypes of B-cell malignancies (Status: ongoing; NCT02503033/NCT02857998)

Our Phase I/Ib dose escalation and expansion studies in Australia and China have now enrolled over 200 patients in a broad range of hematological cancers and have identified indications of interest for future development.

Phase I/Ib study of sovleplenib in indolent non-Hodgkin's lymphoma (Status: enrolling; NCT03779113)

Based on extensive proof-of-concept clinical data in China and Australia, we have initiated a Phase I/Ib study in the United States and Europe. We presented preliminary results from this study at the ASH 2021 annual meeting, which support progressing sovleplenib into the ongoing dose expansion phase of the study to evaluate its safety and efficacy in multiple subtypes of B-cell and T-cell lymphoma at the RP2D of 700mg.

6. Tazemetostat, EZH2 Inhibitor

Tazemetostat is an inhibitor of EZH2 developed by Epizyme that is approved by the U.S. FDA for the treatment of certain epithelioid sarcoma and follicular lymphoma patients. It received accelerated approval from the FDA based on ORR and DoR in January and June 2020 for epithelioid sarcoma and follicular lymphoma, respectively. Tazemetostat is currently marketed as Tazverik in the United States. We entered into a strategic collaboration with Epizyme pursuant to which we received a license to research, develop, manufacture and commercialize Tazemetostat in Greater China, including mainland China, Hong Kong, Macau and Taiwan.

We plan to seek approval for tazemetostat in various hematological and solid tumors, including epithelial sarcoma, follicular lymphoma and diffuse large b-cell lymphoma (DLBCL) in Greater China. We are participating in Epizyme's SYMPHONY-1 (EZH-302) study, leading it in Greater China. The parties also intend to conduct additional global studies jointly. Tazemetostat's mechanism of action is highly complementary and potentially synergistic with HUTCHMED's portfolio of cancer drug candidates. We will generally be responsible for funding all clinical trials of tazemetostat in Greater China including the portion of global trials conducted there. We are responsible for the research, manufacturing and commercialization of tazemetostat in Greater China.

Mechanism of Action

EZH2 is one member of a class of histone methyltransferases ("HMTs"). It catalyzes the methylation of histone H3 at lysine 27 (H3K27) which controls expression of various genes and in turn plays a role in the normal physiology of many cell types. Dysregulation of EZH2 has been seen in a wide range of cancers and is associated with poor clinical prognosis and outcomes. Tazemetostat inhibits EZH2 which allows transcription of genes involved in functions such as cell cycle control and terminal differentiation and thus inhibits cancer cell proliferation.

Tazemetostat Clinical Trials

The table below shows a summary of the clinical trials that we have recently underway for tazemetostat.

Clinical Trials of Tazemetostat

Treatment	Sponsors/Partners	Name, Line, Patient Focus	Sites	Phase	Status/Plan	NCT #
Tazemetostat and R² (lenalidomide and rituximab)	HUTCHMED / Epizyme	SYMPHONY-1: 2L follicular lymphoma	Global	III	HUTCHMED is leading China portion of global Phase III trial	NCT04224493
Tazemetotat monotherapy	HUTCHMED	Relapsed/refractory 3L+ follicular lymphoma	China	II registration-intent (bridging)	In planning	Pending
Tazemetotat combinations	HUTCHMED	Indolent lymphoma combinations	China	II	In planning	N/A

SYMPHONY-1 is a global, multicenter, randomized, double-blind, active-controlled, 3-stage, biomarker-enriched, Phase Ib/III study of tazemetostat in combination with R² (lenalidomide and rituximab) in patients with relapsed or refractory follicular lymphoma after at least one prior line of therapy. Epizyme conducted the Phase Ib portion of the study in 2021, which determined the recommended Phase III dose ("RP3D") and also demonstrated potential efficacy in second-line follicular lymphoma. The safety profile of the combination was consistent with the previously reported safety information in the U.S. prescribing information for both Tazverik and R², respectively.

In the Phase III portion of the trial, approximately 500 patients are randomly assigned to receive the RP3D of tazemetostat + R² or placebo + R². The study will also include a maintenance arm with tazemetostat or placebo following the first year of treatment with tazemetostat + R² or placebo + R². We anticipate the first patient enrollment in the first half of 2022 in the China Phase III portion of SYMPHONY-1.

We intend to initiate a bridging study in follicular lymphoma to support China registration as well as several combination studies of Tazemetostat with HUTCHMED assets.

7. HMPL-306, IDH1 and 2 Inhibitor

HMPL-306 is a novel small molecule dual-inhibitor of IDH1 and 2 enzymes. IDH1 and IDH2 mutations have been implicated as drivers of certain hematological malignancies and solid tumors, particularly among acute myeloid leukemia patients.

Mechanism of Action

IDHs are critical metabolic enzymes that help to break down nutrients and generate energy for cells. When mutated, IDH creates a molecule that alters the cell's genetic programming and prevents cells from maturing, 2-hydroxyglutarate ("2-HG"). Reduction in 2-HG levels can be used as a marker of target engagement by an IDH inhibitor. IDH1 or IDH2 mutations are common genetic alterations in various types of blood and solid tumors, including acute myeloid leukemia, with approximately 20% of patients having mutant IDH genes, myelodysplastic syndrome (MDS), myeloproliferative neoplasms (MPNs), low-grade glioma and intrahepatic cholangiocarcinoma. Mutant IDH isoform switching, either from cytoplasmic mutant IDH1 to mitochondrial mutant IDH2, or vice versa, is a mechanism of acquired resistance to IDH inhibition in acute myeloid leukemia and cholangiocarcinoma.

Cytoplasmic mutant IDH1 and mitochondrial mutant IDH2 have been known to switch to the other form when targeted by an inhibitor of IDH1 mutant alone or IDH2 mutant alone. By targeting both IDH1 and IDH2 mutations, HMPL-306 could potentially provide therapeutic benefits in cancer patients harboring either IDH mutation and may address acquired resistance to IDH inhibition through isoform switching.

Currently, the FDA has approved one drug for IDH1 mutation and one drug for IDH2 mutation, but no dual inhibitor targeting both IDH1 and IDH2 mutants has been approved.

HMPL-306 Clinical Trials

The table below shows a summary of the clinical trials that we have recently underway or in planning for HMPL-306.

Clinical Trials of HMPL-306

Treatment	Sponsors/Partners	Name, Line, Patient Focus	Sites	Phase	Status/Plan	NCT #
HMPL-306 monotherapy	HUTCHMED	Hematological malignancies	China	I	Ongoing: close to establishing the RP2D, dose expansion in mid-2022	NCT04272957
HMPL-306 monotherapy	HUTCHMED	Solid tumors including but not limited to gliomas, chondrosarcomas or cholangiocarcinomas	U.S.	I	Ongoing: initiated in March 2021. Dose expansion phase is expected to start in mid-2022	NCT04762602
HMPL-306 monotherapy	HUTCHMED	Hematological malignancies	U.S	I	Ongoing: initiated in May 2021	NCT04764474

Phase I HMPL-306 monotherapy–China (Status: ongoing; NCT04272957)

In July 2020, we initiated our Phase I development in China. This is a multi-center study to evaluate the safety, pharmacokinetics, pharmacodynamics and efficacy of HMPL-306 in patients of relapsed or refractory hematological malignancies with an IDH1 and/or IDH2 mutation. We plan to submit presentation data from the dose escalation portion of the study in China in mid-2022.

Phase I HMPL-306 monotherapy in solid tumors–U.S. and Europe (Status: ongoing; NCT04762602)

In March 2021, we initiated our Phase I development in the United States and Europe. This is a multi-center study to evaluate the safety, tolerability pharmacokinetics, pharmacodynamics and preliminary efficacy of HMPL-306 in solid tumors, including but not limited to gliomas, chondrosarcomas or cholangiocarcinomas. We plan to initiate the dose expansion portion of the study in relapsed or refractory solid tumors in mid-2022.

Phase I HMPL-306 monotherapy in hematological malignancies–U.S. and Europe (Status: ongoing; NCT04764474)

In the United States, IND applications for solid tumors and hematologic malignancies were cleared in October 2020. In May 2021, we dosed the first patient with IDHm+ hematological malignancies.

8. HMPL-760, BTK Inhibitor

HMPL-760 is an investigational, non-covalent, third-generation BTK inhibitor. It is a highly potent, selective, and reversible inhibitor with long target engagement against BTK, including wild-type and C481S-mutated BTK.

Mechanism of Action

BTK is a key component of the B-cell receptor signaling pathway and is an important regulator of cell proliferation and cell survival in various lymphomas. The abnormal activation of B-cell receptor signaling is closely related to the development of B-cell type hematological cancers, which represent approximately 85% of all NHL cases. BTK is considered a validated target for drugs that aim to treat certain hematological cancers, however C481S mutation of BTK is a known resistance mechanism for first and second generation BTK inhibitors.

HMPL-760 Clinical Trials

The table below shows a summary of the clinical trials that we have recently underway or in planning for HMPL-760.

Clinical Trials of HMPL-760

Treatment	Sponsors/Partners	Name, Line, Patient Focus	Sites	Phase	Status/Plan	NCT #
HMPL-760 monotherapy	HUTCHMED	CLL, SLL, other NHL	China	I	Ongoing: initiated in January 2022	NCT05190068
HMPL-760 monotherapy	HUTCHMED	CLL, SLL, other NHL	U.S.	I	Initiating	NCT05176691

We currently retain all rights to HMPL-760 worldwide. We have an ongoing Phase I study in China and are in the process of initiating a Phase I study in the United States. Both of these are multi-center and open-label studies to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary efficacy profile of HMPL-760 in patients with previously treated chronic lymphocytic leukemia/small lymphocytic lymphoma or other types of non-Hodgkin lymphoma.

9. HMPL-453, FGFR Inhibitor

Mechanism of Action

FGFR belongs to a subfamily of receptor tyrosine kinases. Four different FGFRs (FGFR1-4) and at least 18 ligand FGFs constitute the FGF/FGFR signaling system. Activation of the FGFR pathway through the phosphorylation of various downstream molecules ultimately leads to increased cell proliferation, migration and survival. FGF/FGFR signaling regulates a wide range of basic biological processes, including tissue development, angiogenesis, and tissue regeneration. Given the inherent complexity and critical roles in physiological processes, dysfunction in the FGF/FGFR signaling leads to a number of developmental disorders and is consistently found to be a driving force in cancer. Deregulation of the FGFR can take many forms, including receptor amplification, activating mutations, gene fusions, and receptor isoform switching, and the molecular alterations are found at relatively low frequencies in most tumors. The incidence of FGFR aberrance in various cancer types is listed in the table below.

Common FGFR Alterations in Certain Tumor Types

	Gene amplification	Gene translocation	Gene mutation
FGFR1	Lung squamous (7-15%) H&N squamous (10-17%) Esophageal squamous (9%) Breast (10-15%)	Lung squamous (n/a) Glioblastoma (n/a) Myeloproliferative syndrome (n/a) Breast (n/a)	Gastric (4%) Pilocytic astrocytoma (5-8%)
FGFR2	Gastric (5-10%) Breast (5-10%)	Intra-hepatic biliary tract cancer (14%) Breast (n/a)	Endometrial (12-14%) Lung squamous (5%)
FGFR3	Bladder (3%) Salivary adenoid cystic (n/a) Breast (1%)	Bladder (3-6%) Lung squamous (3%) Glioblastoma (3-7%) Myeloma (15-20%)	Bladder (60-80% NMIBC; 15-20% MIBC) Cervical (5%)

Notes: H&N = head and neck; NMIBC = non-muscle invasive bladder cancer; MIBC = muscle invasive bladder cancer; and n/a = data not available.

Source: M. Touat et al., "Targeting FGFR Signaling in Cancer," Clinical Cancer Research (2015); 21(12); 2684-94.

HMPL-453 Research Background

We noted a growing body of evidence has demonstrated the oncogenic potential of FGFR aberrations in driving tumor growth, promoting angiogenesis, and conferring resistance mechanisms to oncology therapies. Targeting the FGF/FGFR signaling pathway has therefore attracted attention from biopharmaceutical companies and has become an important exploratory target for new anti-tumor target therapies.

The main FGFR on-target toxicities observed to date in these compounds are all mild and manageable, including hyperphosphatemia, nail and mucosal disorder, and reversible retinal pigmented epithelial detachment. However, there are still many challenges in the development of FGFR-directed therapies. Uncertainties include the screening and stratifying of patients who are most likely to benefit from FGFR targeted therapy. Intra-tumor heterogeneity observed in FGFR amplified cancer may compromise the anti-tumor activity. In addition, the low frequency of specific FGFR molecular aberrance in each cancer type may hinder clinical trial enrollment.

HMPL-453 Pre-clinical Evidence

HMPL-453 is a highly selective and potent, small molecule that targets FGFR 1/2/3 with an IC_{50} in the low nanomolar range. Its good selectivity was revealed in the screening against 292 kinases. HMPL-453 exhibited strong anti-tumor activity that correlated with target inhibition in tumor models with abnormal FGFR activation.

HMPL-453 has good pharmacokinetic properties characterized by rapid absorption following oral dosing, good bioavailability, moderate tissue distribution and moderate clearance in all pre-clinical animal species. HMPL-453 was found to have little inhibitory effect on major cytochrome P450 enzymes, indicating low likelihood of drug-to-drug interaction issues.

HMPL-453 Clinical Development

The table below shows a summary of the clinical trials that we have recently completed and underway for HMPL-453.

Clinical Trials of HMPL-453

Treatment	Sponsors/Partners	Name, Line, Patient Focus	Sites	Phase	Status/Plan	NCT #
HMPL-453 monotherapy	HUTCHMED	2L Cholangiocarcinoma (IHCC with FGFR fusion)	China	II	Ongoing. ~10-15% of IHCC pts' tumors harbor FGFR2 fusion	NCT04353375
HMPL-453 with chemotherapies	HUTCHMED	Advanced solid tumors	China	I/II	Ongoing; initiated in January 2022	NCT05173142
HMPL-453 with Tuoyi (PD-1)	HUTCHMED	Advanced solid tumors	China	I/II	Ongoing; initiated in January 2022	NCT05173142

Phase II HMPL-453 monotherapy in advanced IHCC–China (Status: ongoing; NCT04353375)

In September 2020, we initiated a Phase II, single-arm, multi-center, open-label study, evaluating the efficacy, safety and pharmacokinetics of HMPL-453 in patients with advanced IHCC with FGFR2 fusion that had failed at least one line of systemic therapy. IHCC is a cancer that develops within the bile ducts, the second most common primary hepatic malignancy after hepatocellular carcinoma. Approximately 10-15% of IHCC patients have tumors that harbor FGFR2 fusion.

Phase Ib/II HMPL-453 in combination with chemotherapies or toripalimab in advanced solid tumors–China (Status: ongoing; NCT05173142)

In January 2022, we initiated a Phase Ib/II, multi-center, two-stage, open-label clinical trial of HMPL-453 in combination with chemotherapy or the anti-PD-1 therapy, toripalimab, to evaluate the safety, tolerability, pharmacokinetics and preliminary efficacy profile of HMPL-453 combination therapy in patients with specific advanced or metastatic solid tumors. The first stage of the study is a dose escalation phase to determine the dose limiting toxicity (DLT) and recommended Phase II dose of HMPL-453 in combination with chemotherapy (gemcitabine and cisplatin) or toripalimab. The second stage of the study is a dose expansion phase in solid tumor patients with either gastric cancer, intrahepatic cholangiocarcinoma, or urothelial carcinoma, harboring specific FGFR gene alterations. Each solid tumor cohort will be treated with a specific combination of HMPL-453 and a chemotherapy or anti-PD-1 therapy to further evaluate the preliminary efficacy, safety and tolerability at the recommended Phase II dose.

10. HMPL-295, ERK Inhibitor

HMPL-295, a novel ERK inhibitor, is our tenth in-house discovered small molecule oncology drug candidate. ERK is a downstream component of the RAS-RAF-MEK-ERK signaling cascade (MAPK pathway). This is our first of multiple candidates in discovery addressing the MAPK pathway.

Mechanism of Action

RAS-MAPK pathway is dysregulated in human diseases, particularly cancer, in which mutations or nongenetic events hyperactivate the pathway in more than 50% of cancers. Activating mutations in RAS genes occur in more than 30% of cancers. RAS and RAF mutations predict worse clinical prognosis in a wide variety of tumor types, mediate resistance to targeted therapies, and decrease the response to the approved standards of care, namely, targeted therapy and immunotherapy. On the MAPK pathway, KRAS inhibitors are under clinical evaluation, and acquired resistance develops for RAF/MEK targeted therapies. ERK inhibition has the potential to overcome or avoid the intrinsic or acquired resistance from the inhibition of RAS, RAF and MEK upstream mechanisms.

HMPL-295 Clinical Trials

The table below shows a summary of the clinical trial that we have underway for HMPL-295.

Clinical Trial of HMPL-295

Treatment	Sponsors/Partners	Name, Line, Patient Focus	Sites	Phase	Status/Plan	NCT #
HMPL-295 monotherapy	HUTCHMED	Solid tumors	China	I	Ongoing: initiated in July 2021	NCT04908046

We currently retain all rights to HMPL-295 worldwide. We initiated our Phase I development in China in July 2021. This is a multi-center and open-label study to evaluate the safety, tolerability, pharmacokinetics and preliminary efficacy profile of HMPL-295, and to determine the maximum tolerated dose and RP2D in patients with advanced malignant solid tumors.

11. HMPL-653, CSF-1R Inhibitor

HMPL-653 is an investigational novel, highly selective, and potent CSF-1R inhibitor designed to target malignant driven tumors as a monotherapy or in combination with other drugs.

Mechanism of Action

CSF-1R is usually expressed on the surface of macrophages and can promote growth and differentiation of macrophages. Studies have shown that blocking the CSF-1R signaling pathway could effectively modulate the tumor microenvironment, relieve tumor immunosuppression, and synergize with other anti-cancer therapies such as immune checkpoint inhibitors to achieve tumor inhibition. It has been demonstrated in several clinical studies that CSF-1R inhibitors could treat tenosynovial giant cell tumors and treat a variety of malignancies combined with immuno-oncology or other therapeutic agents.

HMPL-653 Clinical Trials

The table below shows a summary of the clinical trial that we have recently underway for HMPL-653.

Clinical Trial of HMPL-653

Treatment	Sponsors/Partners	Name, Line, Patient Focus	Sites	Phase	Status/Plan	NCT #
HMPL-653 monotherapy	HUTCHMED	Solid tumors & tenosynovial giant cell tumors	China	I	Ongoing: initiated in January 2022, ~110 patients expected to be enrolled	NCT05190068

We currently retain all rights to HMPL-653 worldwide. We initiated our Phase I development in China in January 2022, and the study is a multi-center, open-label and single-armed study to evaluate the safety, tolerability, pharmacokinetics and preliminary efficacy of HMPL-653 in patients with advanced or metastatic solid tumors and tenosynovial giant cell tumors. We expect to enroll around 110 patients in this study.

12. Epitinib and theliatinib, EGFR Inhibitors

Our strategy has been to create targeted therapies in the EGFR area that would go beyond the already approved EGFRm+ patient population to address certain areas of unmet medical needs that represent market opportunities, including: (i) brain metastasis and/or primary brain tumors with EGFRm+, which we seek to address with epitinib; and (ii) tumors with EGFR gene amplification or EGFR overexpressed, which we seek to address with theliatinib.

Epitinib (also known as HMPL-813) is a potent and selective oral EGFR inhibitor designed to optimize brain penetration. A significant portion of patients with EGFR activating mutations go on to develop brain metastasis. Patients with brain metastasis suffer from poor prognosis and low quality of life with limited treatment options. EGFR inhibitors have revolutionized the treatment of NSCLC with EGFR activating mutations. However, many approved EGFR inhibitors cannot penetrate the blood-brain barrier effectively, leaving the majority of patients with primary brain tumors or brain metastasis without an effective targeted therapy.

Furthermore, tumors with wild-type EGFR activation, for instance through gene amplification or protein over-expression, are less sensitive to many EGFR tyrosine kinase inhibitors due to sub-optimal binding affinity. Theliatinib (also known as HMPL-309) is a novel oral EGFR inhibitor that has been designed with strong affinity to the wild-type EGFR kinase and has demonstrated five to ten times the potency than Tarceva in pre-clinical trials. This holds importance because tumors with wild-type EGFR activation have been found to be less sensitive to current EGFR inhibitors and is notable in certain cancer types such as esophageal cancer, where 15-28% have EGFR gene amplification and 50-70% have EGFR overexpressed. As a result, we believe that theliatinib could potentially be more effective than existing EGFR tyrosine kinase inhibitor products and benefit patients with tumor types with a high incidence of wild-type EGFR activation.

We have completed Phase I and II trials for both epitinib (NSCLC with brain metastases; glioblastoma) and theliatinib (solid tumors; esophageal cancer) and have observed efficacy. However, we have decided not to continue their development as monotherapies at this time.

Our Research and Development Approach

Our core research and development philosophy is to take a holistic approach to the treatment of cancer and immunological diseases, through multiple modalities and mechanisms, including targeted therapies, immunotherapies and other pathways. A primary objective of our research efforts has been to develop next generation drug candidates with:

- unique selectivity to limit target-based toxicity;
- high potency to optimize the dose selection with the objective to lower the required dose and thereby limit compound-based toxicity;
- chemical structures deliberately engineered to improve drug exposure in the targeted tissue; and
- ability to be combined with other therapeutic agents, including targeted therapies, immunotherapies and chemotherapies.

We have built a drug discovery engine, with which we strive to create differentiated novel oncology and immunology treatments with global potential. These include furthering both small molecule and biologic therapies which address aberrant genetic drivers and cancer cell metabolism; modulate tumor immune microenvironment; and target immune cell checkpoints. We design drug candidates with profiles that enable them to be used in innovative combinations with other therapies, such as chemotherapy, immunotherapy and other targeted therapy in order to attack disease simultaneously through multiple modalities and pathways. We believe that this approach can significantly improve treatment outcomes for patients.

We believe our ability to successfully develop innovative drug candidates through our Oncology/Immunology operations will be the primary factor affecting our long-term competitiveness, as well as our future growth and development. Creating high quality global first-in-class or best-in-class drug candidates requires a significant investment of resources over a prolonged period of time, and a core part of our strategy is to continue making sustained investments in this area. As a result of this commitment, our pipeline of drug candidates has been steadily advancing and expanding, with thirteen clinical-stage drug candidates. See "– Our Clinical Pipeline" for more details.

Beyond these clinical candidates, we continue to conduct research into discovering new types of drug candidates, including among others, small molecules addressing cancer-related apoptosis, cell signaling, epigenetics and protein translation; biologic drug candidates including bispecific antibodies; and novel technologies including antibody-drug conjugates and heterobifunctional small molecules.

Our Collaborations

Collaborations and joint ventures with corporate partners have provided us with significant funding and access to our partners' scientific, development, regulatory and commercial capabilities. Our current oncology collaborations focus on savolitinib (collaboration with AstraZeneca) and fruquintinib (collaboration with Eli Lilly). When we entered into these collaborations, we had already conducted the discovery research and early clinical development of each drug candidate and, following our agreements, continued to conduct the clinical development and manage the engagement with regulatory authorities in China up to and including filing the NDAs with the NMPA. Our collaboration partners fund a significant portion of our research and development costs for drug candidates developed in collaboration with them. In addition, we receive upfront payments upon our entry into these collaboration arrangements and upon the achievement of certain development milestones for the relevant drug candidate. We have received upfront payments, equity contributions and milestone payments totaling approximately $183.5 million mainly from our collaborations with AstraZeneca and Eli Lilly as of December 31, 2021. In return, our collaboration partners are entitled to a significant proportion of any future revenue from our drug candidates developed in collaboration with them, as well as a degree of influence over the clinical development process for such drug candidates. In addition, we have entered into other clinical collaborations for combination studies of fruquintinib and surufatinib with drug candidates belonging to BeiGene, Innovent and/or Junshi. We also have an immunology collaboration with Inmagene with respect to four novel pre-clinical drug candidates discovered by us and an in-licensing collaboration with Epizyme with respect to tazemetostat.

AstraZeneca

In 2008, our in-house teams started research on MET inhibitors, subsequently discovering our drug candidate, savolitinib, and conducting its pre-clinical development in-house. In 2011, we submitted applications for clinical development and initiated Phase I clinical trials. In December 2011, we entered into an agreement with AstraZeneca under which we granted to AstraZeneca co-exclusive, worldwide rights to develop, and exclusive worldwide rights to manufacture and commercialize savolitinib for all diagnostic, prophylactic and therapeutic uses. In August 2016, December 2020 and November 2021, we and AstraZeneca amended the terms of the agreement. We refer to this agreement, including the amendments thereto, as the AstraZeneca Agreement.

AstraZeneca paid $20.0 million upon execution of the AstraZeneca Agreement and agreed to pay royalties and additional amounts upon the achievement of development and sales milestones. Under the original terms of the AstraZeneca Agreement, we and AstraZeneca agreed to share the development costs for savolitinib in China, with AstraZeneca being responsible for the development costs for savolitinib in the rest of the world. With respect to certain clinical trials, we subsequently agreed with AstraZeneca on sharing development costs. As of December 31, 2021, we had received $49.9 million in milestone payments in addition to approximately $57.1 million in reimbursements for certain development costs. We may potentially receive future clinical development and first sales milestones payments for clinical development and initial sales of savolitinib, plus significant further milestone payments based on sales. Subject to approval of savolitinib in treating PRCC, under the amended AstraZeneca Agreement, AstraZeneca is obligated to pay us increased tiered royalties from 14% to 18% annually on all sales made of any product outside of China, which represents a five percentage point increase over the original terms, subject to a potential downward adjustment on such point increase based on the amount of any contribution by AstraZeneca to the Phase III development in patients with such indication. After total aggregate additional royalties have reached five times our contribution to the Phase III development in patients with such indication, this royalty will step down over a two-year period, to an ongoing royalty rate of 10.5% to 14.5%. AstraZeneca is also obligated to pay us a fixed royalty of 30% on all sales made of any product in China.

Development and collaboration under this agreement are overseen by a joint steering committee that is comprised of three of our senior representatives as well as three senior representatives from AstraZeneca. AstraZeneca is responsible for the development of savolitinib and all regulatory matters related to this agreement in all countries and territories other than China, and we are responsible for the development of savolitinib and all regulatory matters related to this agreement in China. Since entering the AstraZeneca Agreement, we have continued to lead the development of savolitinib in China.

Subject to earlier termination, the AstraZeneca Agreement will continue in full force and effect on a country-by-country basis as long as any collaboration product is being developed or commercialized. The AstraZeneca Agreement is terminable by either party upon a breach that is uncured, upon the occurrence of bankruptcy or insolvency of either party, or by mutual agreement of the parties. The AstraZeneca Agreement may also be terminated by AstraZeneca for convenience with 180 days' prior written notice. Termination for cause by us or AstraZeneca or for convenience by AstraZeneca will have the effect of, among other things, terminating the applicable licenses granted by us. Termination for convenience by AstraZeneca will have the effect of obligating AstraZeneca to grant to us all of its rights to regulatory approvals and other rights necessary to commercialize savolitinib. Termination by AstraZeneca for convenience will not have the effect of terminating any license granted by AstraZeneca to us.

Eli Lilly

In 2007, our in-house research into VEGFR inhibitors led to the discovery of our drug candidate, fruquintinib. We conducted pre-clinical development in-house and initiated a Phase I clinical trial in 2010. In October 2013, we entered into an agreement with Eli Lilly whereby we granted Eli Lilly an exclusive license to develop, manufacture and commercialize fruquintinib for all uses in China and Hong Kong. In December 2018, following the commercial launch of fruquintinib in China, we and Eli Lilly amended the terms of the agreement and further amended the terms of the agreement in July 2020. We refer to this agreement, including the amendments thereto, as the Eli Lilly Agreement.

Subsequent to the entering of the Eli Lilly Agreement, we continued to lead the development of fruquintinib, including all clinical trial development. Eli Lilly reimbursed us for a majority of the development costs and provided input over the course of the development of fruquintinib. Development, collaboration and manufacture of the products under this agreement are overseen by a joint steering committee comprised of equal numbers of representatives from each party.

Eli Lilly paid a $6.5 million upfront fee following the execution of the Eli Lilly Agreement in 2013, and agreed to pay royalties and additional amounts upon the achievement of development and regulatory approval milestones. As of December 31, 2021, Eli Lilly had paid us $37.2 million in milestone payments in addition to approximately $57.7 million in reimbursements for certain development costs.

We could potentially receive future milestone payments for the achievement of development and regulatory approval milestones in China. Additionally, Eli Lilly is obligated to pay us tiered royalties from 15% to 20% annually on sales made of fruquintinib in China and Hong Kong, the rate to be determined based upon the dollar amount of sales made for all products in that year. Under the terms of our 2018 amendment, upon the first commercial launch of fruquintinib in China in a new life cycle indication, these tiered royalties increased to 15% to 29%. Under the terms of our 2020 amendment, we and Eli Lilly share gross profits linked to sales target performance. Subject to meeting pre-agreed sales targets, Eli Lilly will pay us an estimated total of 70% to 80% of Elunate in-market sales in the form of royalties, manufacturing costs and service payments.

Under the terms of our 2018 amendment, we are entitled to determine and conduct future life cycle indication development of fruquintinib in China beyond the three initial indications specified in the original Eli Lilly Agreement. After the 2018 amendment, we assumed responsibility for all development activities and costs for fruquintinib in China in new life cycle indications, and we have the liberty to collaborate with third-parties to explore combination therapies of fruquintinib with various immunotherapy agents. Under the terms of our 2020 amendment, we took over development and execution of all on-the-ground medical detailing, promotion and local and regional marketing activities for Elunate in China.

We are responsible in consultation with Eli Lilly for the supply of, and have the right to supply, all clinical and commercial supplies for fruquintinib pursuant to an agreed strategy for manufacturing. For the term of the Eli Lilly Agreement, such supplies will be provided by us at a transfer price that accounts for our cost of goods sold.

The Eli Lilly Agreement is terminable by either party for breach that is uncured. The Eli Lilly Agreement is also terminable by Eli Lilly for convenience with 120 days' prior written notice or if there is a major unexpected safety issue with respect to a product. Termination by either us or Eli Lilly for any reason will have the effect of, among other things, terminating the applicable licenses granted by us, and will obligate Eli Lilly to transfer to us all regulatory materials necessary for us to continue development efforts for fruquintinib.

BeiGene

In May 2020, we entered into a clinical collaboration agreement with BeiGene to evaluate the safety, tolerability and efficacy of combining surufatinib and fruquintinib with BeiGene's anti-PD-1 antibody tislelizumab, for the treatment of various solid tumor cancers, in the United States, Europe, China and Australia. Under the terms of the agreement, we and BeiGene each plan to explore development of the combination of surufatinib with tislelizumab or fruquintinib with tislelizumab in different indications and regions. We have agreed to provide mutual drug supply and other support.

Inmagene

In January 2021, we and Inmagene entered into a strategic partnership to further develop four novel pre-clinical drug candidates (HMPL-A28, HMPL-727, HMPL-662 and HMPL-958) discovered by us for the potential treatment of multiple immunological diseases. We will work together to move the drug candidates towards IND submission. If successful, Inmagene will then move the drug candidates through global clinical development.

Under the terms of the agreement, we have granted Inmagene exclusive options to four drug candidates solely for the treatment of immunological diseases. If Inmagene exercises an option, it will have the right to further develop, manufacture and commercialize that specific drug candidate worldwide, while we retain first right to co-commercialization in China. For each of the drug candidates, we will be entitled to development milestones of up to $95 million and up to $135 million in commercial milestones, as well as up to double-digit royalties upon commercialization.

Epizyme

In August 2021, we entered into a licensing agreement with Epizyme pursuant to which we obtained a co-exclusive license to develop, an exclusive license to commercialize and a co-exclusive license to manufacture tazemetostat in China, Hong Kong, Taiwan and Macau for all therapeutic and palliative uses in epithelioid sarcoma, follicular lymphoma (second line and third line), diffuse large b-cell lymphoma and any other indications that are approved according to the terms of the licensing agreement.

To date, we have paid Epizyme a $25.0 million upfront payment. We may be required to pay an additional aggregate amount of up to $110 million in development and regulatory milestone payments and up to an additional $175 million in sales milestone payments. Epizyme is also eligible to receive, across up to eight potential indications, certain tiered royalties (from mid-teen to low-twenties-percentage) based on annual net sales of tazemetostat in the licensed territory. In addition, we received a four-year warrant to acquire up to $65 million of Epizyme shares at a price of $11.50 per share.

We have the right to manufacture the licensed product for development and commercialization in the licensed territory and are generally responsible for funding all clinical trials of tazemetostat, including the portion of global trials conducted in the licensed territory. The agreement with Epizyme will remain in effect until, on a licensed product-by-licensed product basis, the expiration of the royalty term for each licensed product in the licensed territory. We have the right to terminate the agreement for convenience at any time, subject to a certain notice period. Either party has the right to terminate the agreement if the other party or its affiliates challenge its patents. In addition, either party may terminate the agreement with written notice for the other party's material breach, subject to a certain cure period, or for the other party's bankruptcy or insolvency.

Other Collaborations

In October and November 2018, we entered into multiple collaborations to evaluate combinations of fruquintinib and surufatinib. These include a global collaboration with Innovent to evaluate the combination of fruquintinib with Tyvyt and a global collaboration with Junshi to evaluate the combination of surufatinib with Tuoyi. In September 2019, we expanded our global collaboration agreement with Innovent to evaluate the safety and efficacy of Tyvyt in combination with surufatinib.

Other Ventures

Other Ventures is our large-scale, profitable drug marketing and distribution platform covering about 290 cities and towns in China with approximately 2,900 manufacturing and commercial personnel as of December 31, 2021. Built over the past 20 years, it has been focused on the sale of prescription drug products and consumer health products conducted through the following entities:

Shanghai Hutchison Pharmaceuticals

Shanghai Hutchison Pharmaceuticals, our non-consolidated joint venture, primarily engages in the manufacture and sale of prescription drug products originally contributed by our joint venture partner, as well as third-party prescription drugs with a focus on cardiovascular medicine. Shanghai Hutchison Pharmaceuticals' proprietary products are sold under the "Shang Yao" brand, literally meaning "Shanghai pharmaceuticals," a trademark that has been used for over 50 years in the pharmaceutical retail market, primarily in Eastern China. In early 2019, Shanghai Hutchison Pharmaceuticals was awarded the 2018 State Scientific and Technological Progress Award – Second Prize, which was presented by President Xi Jinping, Premier Li Keqiang and other state leaders of the PRC at the National Science and Technology Awards Ceremony. This award was one of only two such awards given that year to studies in the botanical drug industry.

Its key product is She Xiang Bao Xin pills, a vasodilator for the long-term treatment of coronary artery and heart disease and for rapid control and prevention of acute angina pectoris, a form of chest pain. There are over one million deaths due to coronary artery disease per year in China. She Xiang Bao Xin pill is the third largest botanical prescription drug in this indication in China, with market share in 2021 of 19.6% (2020 of 18.2%) nationally and 43.6% (2020: 47.5%) in Shanghai. She Xiang Bao Xin pills' sales represented 92% of all Shanghai Hutchison Pharmaceuticals sales in 2021.

She Xiang Bao Xin pills were first approved in 1983 and subsequently enjoyed 22 proprietary commercial protections under the prevailing regulatory system in China. In 2005, Shanghai Hutchison Pharmaceuticals was able to attain "Confidential State Secret Technology" status protection, as certified by China's Ministry of Science and Technology and State Secrecy Bureau, which extended proprietary protection in China until late 2016. The Science and Technology Commission of Shanghai Municipality has subsequently extended such protection. Shanghai Hutchison Pharmaceuticals holds an invention patent in China covering its formulation, which extends proprietary protection through 2029. She Xiang Bao Xin pill is one of less than two dozen proprietary prescription drugs represented on China's National Essential Medicines List, which means that all Chinese state-owned health care institutions are required to carry it. She Xiang Bao Xin pill is fully reimbursed in all of China.

Shanghai Hutchison Pharmaceuticals manufactures its products at its 78,000 square meter production facility located in Feng Pu district outside the center of Shanghai. Shanghai Hutchison Pharmaceuticals holds 74 drug product manufacturing licenses, of which 17 are included in the National Essential Medicines List, and three are in active production. The factory is operated by over 530 manufacturing staff.

As of December 31, 2021, Shanghai Hutchison Pharmaceuticals had a commercial team of about 2,200 medical sales representatives allowing for the promotion and scientific detailing of our products not just in hospitals in provincial capitals and medium-sized cities, but also in the majority of county-level hospitals in China. Shanghai Hutchison Pharmaceuticals, through its GSP-certified subsidiary, sells its products and its third-party licensed prescription drugs directly to distributors who on-sell such products to hospitals and clinics, pharmacies and other retail outlets in their respective areas, as well as to other local distributors. As of December 31, 2021, Shanghai Hutchison Pharmaceuticals engaged a group of approximately 550 primary distributors to cover China. These primary distributors in turn used over 2,000 secondary distributors to work directly with hospitals, on a local level, to manage logistics. Shanghai Hutchison Pharmaceuticals' own prescription drugs sales representatives promote its products to doctors and purchasing managers in hospitals, clinics and pharmacies as part of its marketing efforts.

Hutchison Sinopharm

Hutchison Sinopharm is our consolidated joint venture with Sinopharm. Based in Shanghai, Hutchison Sinopharm focuses on providing logistics services to, and distributing and marketing prescription drugs in China. As of December 31, 2021, Hutchison Sinopharm had a dedicated team of over 130 commercial staff focused on two key areas of operation—a commercial team that markets approximately 1,100 third-party prescription drug and other products directly to about 700 public and private hospitals in the Shanghai region and through a network of approximately 50 distributors to cover all other provinces in China, and a second commercial team that markets our Zhi Ling Tong infant nutrition brand through a network of over 32,000 promoters in over 7,700 outlets in China.

Starting in 2015, Hutchison Sinopharm had been the exclusive marketing agent for Seroquel tablets in China. In June 2018, AstraZeneca sold and licensed its rights to Seroquel to Luye Pharma Group, Ltd., including its rights in China. The terms of our agreement with AstraZeneca were assigned to Luye Pharma Hong Kong Ltd., or Luye Pharma HK. In May 2019, we received a notice from Luye Pharma HK purporting to terminate our agreement. We believe that Luye Pharma HK had no basis for termination and commenced confidential legal proceedings to seek damages. In December 2021, the Hong Kong International Arbitration Centre made a final award in favor of Hutchison Sinopharm against Luye Pharma Hong Kong in the amount of RMB253.2 million plus costs we incurred in the legal proceedings and interest. We expect the award to be paid in 2022. We did not have any revenue from the distribution of Seroquel for the years ended December 31, 2019, 2020 and 2021.

In 2019, we began building an in-house oncology commercial sales and marketing team at Hutchison Sinopharm to support the launch of certain of our innovative oncology drugs. By December 31, 2021, this team had grown to over 630 commercial sales and marketing staff.

In 2021, a substantial portion of Hutchison Sinopharm's sales were made directly to hospitals and clinics, with the remaining sales being made through distributors. As of December 31, 2021, Hutchison Sinopharm had approximately 740 customers of which approximately 6% were distributors, and the revenue generated from these distributors accounted for approximately 26% of the revenue of Hutchison Sinopharm for the year ended December 31, 2021.

Hutchison Baiyunshan

Hutchison Baiyunshan was our non-consolidated joint venture until we disposed of our interest in it in September 2021. It focused primarily on the manufacture, marketing and distribution of over-the-counter pharmaceutical products, including Banlangen granules for the treatment of viral flu, fever, and respiratory tract infections and Fu Fang Dan Shen tablets for the treatment of chest congestion and angina pectoris.

Hutchison Hain Organic

Hutchison Hain Organic is a consolidated joint venture with Hain Celestial, a Nasdaq-listed, natural and organic food and personal care products company. Hutchison Hain Organic distributes a broad range of over 500 imported organic and natural products. Pursuant to its joint venture agreement, Hutchison Hain Organic has rights to manufacture, market and distribute Hain Celestial's products within nine Asian territories. We believe the key strategic product for Hutchison Hain Organic is Earth's Best organic baby products, a leading brand in the United States. Hutchison Hain Organic's other products are distributed to hypermarkets, specialty stores and other retail outlets in Hong Kong, China and across seven other territories in Asia mainly through third-party local distributors, including retail chains owned by affiliates of CK Hutchison.

Hutchison Healthcare

Hutchison Healthcare is our wholly owned subsidiary and is primarily engaged in the manufacture and sale of health supplements. Hutchison Healthcare's major product is Zhi Ling Tong DHA capsules, a health supplement made from algae DHA oil for the promotion of brain and retinal development in babies and young children, which is distributed by Hutchison Sinopharm.

The majority of Hutchison Healthcare's products are contract manufactured at a dedicated and certified manufacturing facility operated by a third party.

HUTCHMED Science Nutrition

HUTCHMED Science Nutrition is our wholly owned subsidiary that is primarily engaged in the distribution of third-party consumer products in Asia.

Competition

Oncology/Immunology Competition

The biotechnology and pharmaceutical industries are highly competitive. While we believe that our highly selective drug candidates, experienced development team and chemistry-focused scientific approach provide us with competitive advantages, we face potential competition from many different sources, including major pharmaceutical, specialty pharmaceutical and biotechnology companies. Any drug candidates that we successfully develop and commercialize will compete with existing drugs and/or new drugs that may become available in the future.

We compete in the segments of the pharmaceutical, biotechnology and other related markets that address inhibition of key biological pathways in cancer and immunological diseases. There are other companies working to develop kinase inhibitors and monoclonal antibodies as targeted therapies for cancer and immunological diseases. These companies include divisions of large pharmaceutical companies and biotechnology companies of various sizes.

Many of our competitors, either alone or with their strategic partners, have substantially greater financial, technical and human resources than we do and significantly greater experience in the discovery and development of drug candidates, obtaining regulatory approvals of products and the commercialization of those products. Accordingly, our competitors may be more successful than we may be in obtaining approval for drugs and achieving widespread market acceptance. Our competitors' drugs may be more effective, or more effectively marketed and sold, than any drug we may commercialize and may render our drug candidates obsolete or non-competitive before we can recover the expenses of developing and commercializing any of our drug candidates. We anticipate that we will face intense and increasing competition as new drugs enter the market and advanced technologies become available.

Below is a summary of existing therapies and therapies currently under development that may become available in the future which may compete with each of our clinical-stage drug candidates.

Savolitinib

While there are currently no approved selective MET inhibitors on the market in China, two selective MET inhibitors are on the market in the US and Japan: Tepmetko (tepotinib) and Tabrecta (capmatinib) are approved for MET exon 14 skipping NSCLC with additional programs underway focused on lung cancer. Market Authorization Applications for Tabrecta and Tepmetko are both under review by the European Medicines Agency (EMA) for use in the treatment of MET exon 14 skipping NSCLC. Other selective MET inhibitors in development include telisotuzumab vedotin (in Phase II for advanced solid tumors, including NSCLC), elzovantinib (TPX-0022, in Phase I/II development for advanced solid tumors), AMG 337 (in Phase II for advanced or metastatic clear cell sarcoma harboring the EWSR1-ATF1 gene fusion), and glumetinib (in Phase I/II in China for advanced solid tumors, including MET-altered NSCLC). Sym-015 is a bi-specific antibody that binds to non-overlapping epitopes on the extracellular domain of the Met receptor tyrosine kinase (in Phase IIa development).

Approved compounds that inhibit MET as well as other kinases include Xalkori (crizotinib) (ALK, ROS1 and MET inhibitor marketed for NSCLC) and Cabometyx (cabozantinib) (VEGFR/MET/Ret inhibitor approved for RCC and liver cancer as well as in development for genitourinary cancers). Amivantamab (JNJ-61186372) (EGFR/MET bi-specific antibody) is approved for NSCLC harboring EGFR exon 20 insertion mutation and in late-stage development for EGFRm+ NSCLC.

Surufatinib

Sutent (VEGFR inhibitor) and Afinitor (mTOR inhibitor) have been approved for the treatment of pancreatic NETs. Somatuline Depot (Lanreotide) is a growth hormone release inhibitor that has been approved for the treatment of gastroenteropancreatic NETs. Sandostatin (octreotide) is a growth hormone and insulin-like growth factor-1 inhibitor that has also been approved for NETs. Lutathera (Lu-dotatate), a somatostatin receptor targeting radiotherapy, has been approved by the FDA for the treatment of somatostatin receptor positive gastroenteropancreatic NETs. Furthermore, small molecules, monoclonal antibodies and radiotherapies are being developed for the treatment of NETs. Compounds undergoing development for NETs include Inlyta (axitinib, tyrosine kinase inhibitor), and Vargatef (nintedanib, a tyrosine kinase inhibitor). Cometriq (an additional brand name for cabozantinib) has been marketed for thyroid cancer and is being studied for NETs. In addition, Avastin is an anti-VEGF monoclonal antibody being studied for NETs.

Fruquintinib

Approved VEGF inhibitors on the market for the treatment of CRC include Avastin (anti-VEGF monoclonal antibody), Cyramza (anti-VEGFR2 monoclonal antibody), Stivarga (VEGFR/TIE2 inhibitor) and Zaltrap (ziv-aflibercept) (VEGF inhibitor). Cyramza is additionally approved for the treatment of NSCLC, gastric cancer, and a certain type of liver cancer. Avastin is approved for NSCLC and nintedanib is approved for the treatment of lung disease associated with fibrosis (under the name Ofev) as well asadeno-NSCLC in Europe (under the name Vargatef). Other VEGFR inhibitors being developed for the treatment of NSCLC include Cabometyx, Lenvima (lenvatinib), lucitanib and Caprelsa. VEGFR inhibitors being developed for the treatment of gastric cancer include dovitinib, telatinib and Stivarga. In China, Aitan (apatinib) has been approved for the treatment of third-line gastric cancer and Focus-V (anlotinib) has been approved for the treatment of third-line NSCLC.

Sovleplenib and Amdizalisib

There has been extensive research on oral small-molecule Syk inhibitors due to the major unmet medical need in inflammation and oncology. However, many Syk inhibitors have failed in the development stage due to their off-target toxicity as a result of lower kinase selectivity and possibly poor pharmacokinetic properties. The only small molecule drug candidate targeting Syk specifically has been approved to date is Tavalisse for the treatment of chronic immune thrombocytopenia. Lanraplenib (GS-9876) is a Syk inhibitor that has been studied for autoimmune diseases, but not currently in active development for autoimmune diseases. Syk inhibitors currently in clinical studies for hematological cancers include entospletinib (AML harboring NPM1c or FLT3 mutations), lanraplenib and cerdulatinib (lymphoma).

Currently there are three PI3K inhibitors approved and on the market. In February 2021, Ukoniq (umbralisib) was approved for the treatment of relapsed or refractory marginal zone lymphoma and follicular lymphoma, although the FDA is currently investigating possible increased risk of death associated with umbralisib. Aliqopa (copanlisib, pan-PI3K inhibitor) was approved for relapsed follicular lymphoma as a monotherapy and is being studied in combination with rituximab as well as rituximab and chemotherapy in NHL. Copiktra (duvelisib, PI3K-δ/γ dual inhibitor) is currently approved for relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma as a monotherapy. In January 2022, Incyte announced that it is withdrawing its NDA for parsaclisib due to the investment required to complete a post marketing confirmatory study within the timeframe required by the FDA. In addition, several drug candidates that inhibit PI3Kδ are in clinical development for hematological cancers, including zandelisib (ME-401), ACP 319 and YY-20394.

Tazemetostat

The most common treatments for follicular lymphoma are chemotherapies, usually combined with the monoclonal antibody Rituxan, or Gazyva, which is an antibody that acts against the same target as Rituxan, CD20. While Rituxan and a number of other widely used anti-cancer agents are labeled broadly for follicular lymphoma, no therapies are approved specifically for the treatment of tumors associated with EZH2 activating mutations. There are a number of companies currently evaluating investigational agents in the relapsed and refractory follicular lymphoma patient setting.

In the relapsed and refractory follicular lymphoma patient setting, both current and near-term competition exists. Current competition includes CD20 combinations along with multiple PI3K inhibitors. Near term competition includes companies currently evaluating investigational agents with varying mechanisms of action.

Other than tazemetostat, there are no therapies which have been approved specifically for the treatment of epithelioid sarcoma. Epithelioid sarcoma, an INI1-negative tumor, is typically treated with surgical resection when it presents as localized disease. When epithelioid sarcoma recurs or metastasizes, it may be treated with systemic chemotherapy or investigational agents because, other than tazemetostat, there are no approved systemic therapies specifically indicated for this disease. To the best of our knowledge there are no competitive products in development specifically for epithelioid sarcoma. However, we are aware of several clinical trials run by competitors that recruit patients with soft tissue sarcoma, which is inclusive of epithelioid sarcoma.

HMPL-306

Tilbsovo (ivosidenib) is an approved therapy that specifically inhibits IDH1 while Idhifa (enasidenib) is an approved therapy that specifically inhibits IDH2. To date, there are no approved therapies that inhibit both IDH1 and IDH2, which could be advantageous in deferring resistance to therapy. A pan-IDH inhibitor, vorasidenib, is currently in late stage development for glioma. An IDH 1/2 inhibitor, LY3410738, is in Phase 1 development for both hematological malignancies and solid tumors. Other IDH1 inhibitors in development include olutasidenib (FT-2102), BAY1436032, and DS-1001b.

HMPL-760

Approved first and second generation BTK inhibitors include Imbruvica, Calquence, Tirabrutinib, Brukinsa and orelabrutinib. Rolling NDA submission started for pirtobruntinib in mantle cell lymphoma in December 2021. Nemtabrutinib, orelabrutinib, TG-1701 and JNJ-64264681 are in development for cancer. A number of other BTK inhibitors, such as evobrutinib, remibrutinib, tolebrutinib, rilzabrutinib, SAR444727 and fenebrutinib, are in development for immunological diseases.

HMPL-453

To date, Balversa, Pemazyre and Truseltiq are the only approved therapies that specifically target the FGFR signaling pathway. Late-stage studies are underway for futibatinib and derazantinib. Additionally, a FGFR specific monoclonal antibody, bemarituzumab, is in Phase III development for gastric cancer and gastroesophageal junction (GEJ) adenocarcinoma. Several small molecule FGFR TKI are in clinical trials for solid tumors, including AZD4547, rogaratinib, fisogatinib (BLU-554), famitinib, Debio 1347, E7090, ICP-192, ICP-105, ASP5878, FGF401, RLY-4008 and HH185.

HMPL-295

To date, no ERK inhibitor drug has been approved. A number of ERK inhibitors, including BVD-523, LY3214996 and LLT462, among others are being developed in clinical settings as a single agent and/or in combination with various therapeutical agents.

HMPL-653

Turalio is the only FDA approved CSF-1R inhibitor drug and currently there is no CSF-1R inhibitors approved in China. CSF-1R inhibitors in development globally include axatilimab, BLZ945, vimseltinib, AMB-05X, NMS-03592088, ARRY-382, JNJ-40346527, emactuzumab, AMG820 and IMC-CS4.

Other Ventures Competition

Our Other Ventures operations which focus on prescription drugs compete in the pharmaceutical industry in China, which is highly competitive and is characterized by a number of established, large pharmaceutical companies, as well as some smaller emerging pharmaceutical companies. This business faces competition from other pharmaceutical companies in China engaged in the development, production, marketing or sales of prescription drugs, in particular cardiovascular drugs.

The barrier to entry for the PRC pharmaceutical industry primarily relates to regulatory requirements in connection with the production of pharmaceutical products and new product launches. The identities of the key competitors with respect to our prescription drugs business vary by product, and, in certain cases, different competitors that have greater financial resources than us may elect to focus these resources on developing, importing or in-licensing and marketing products in the PRC that are substitutes for our products and may have broader sales and marketing infrastructure with which to do so.

We believe that we compete primarily on the basis of brand recognition, pricing, sales network, promotion activities, product efficacy, safety and reliability. We believe our Other Ventures' continued success will depend on our business's capability to: maintain profitability of its products, obtain and maintain regulatory approvals, develop drug candidates with market potential, maintain an efficient operational model, apply technologies to production lines, attract and retain talented personnel, maintain high quality standards, and effectively market and promote the products sold by our prescription drugs business.

Our Other Ventures operations which focus on consumer health products competes in a highly fragmented market in Asia, particularly in our primary market in China. We believe that this business competes primarily on the basis of brand recognition, pricing, sales network, promotion activities, product safety and reliability. We believe our continued success will depend on our business's capability to: successfully market and distribute in-licensed products such as Earth's Best infant formula, maintain an efficient operational model, attract and retain talented personnel, maintain high quality standards, and effectively market and promote the products sold by our business.

Patents and Other Intellectual Property

Our commercial success depends in part on our ability to obtain and maintain proprietary or intellectual property protection for our Oncology/Immunology drugs and drug candidates, our Other Ventures' products and other know-how. Our policy is to seek to protect our proprietary and intellectual property position by, among other methods, filing patent applications in various jurisdictions related to our proprietary technology, inventions and improvements that are important to the development and implementation of our business. We also rely on trade secrets, know-how and continuing technological innovation to develop and maintain our proprietary and intellectual property position.

Patents

We and our joint ventures file patent applications directed to our Oncology/Immunology drugs and drug candidates and our Other Ventures' products in an effort to establish intellectual property positions with regard to new small molecule compounds and/or extracts of natural herbs, their compositions as well as their medical uses in the treatment of diseases. In relation to our Oncology/Immunology operations, we also file patent applications directed to crystalline forms, formulations, processes, key intermediates, and secondary uses as clinical trials for our drug candidates evolve. We file such patent applications in major market jurisdictions, including but not limited to the United States, Europe, Japan and China.

Our Oncology/Immunology Patents

As of December 31, 2021, we had 270 issued patents, including 21 Chinese patents, 24 U.S. patents and 14 European patents, 184 patent applications pending in the above major market jurisdictions, and 13 pending PCT patent applications relating to the drugs and drug candidates of our Oncology/Immunology operations. The intellectual property portfolios for our most advanced drug candidates are summarized below. With respect to most of the pending patent applications covering our drug candidates, prosecution has yet to commence. Prosecution is a lengthy process, during which the scope of the claims initially submitted for examination by the relevant patent office is often significantly narrowed by the time when they issue, if they issue at all. We expect this to be the case for our pending patent applications referred to below.

Savolitinib—The intellectual property portfolio for savolitinib contains two patent families.

The first patent family for savolitinib is directed to novel small molecule compounds as well as methods of treating cancers with such compounds. As of December 31, 2021, we owned 56 patents in this family, including patents in China, the United States, Europe and Japan, each expiring in 2030, and we also had 11 patent applications pending in various other jurisdictions.

The second patent family is directed to the method for the preparation of savolitinib. As of December 31, 2021, we had 17 patent applications pending in this family in various jurisdictions, including China, the United States, Europe, and Japan, each of which, if issued, would have an expiration date in 2039. This patent family is co-owned by us and AstraZeneca.

Our collaboration partner AstraZeneca is responsible for maintaining and enforcing the intellectual property portfolio for savolitinib.

Surufatinib—The intellectual property portfolio for surufatinib contains nine patent families.

The first patent family for surufatinib is directed to novel small molecule compounds as well as methods of treating tumor angiogenesis-related disorders with such compounds. As of December 31, 2021, in this patent family we owned one Chinese patent expiring in 2027 and 12 patents in various other jurisdictions, including the United States expiring in 2031, and Europe and Japan, each expiring in 2028. As of December 31, 2021, we also had one patent application pending in Brazil.

The second patent family is directed to the crystalline forms of surufatinib as well as methods of treating tumor angiogenesis-related disorders with such forms. As of December 31, 2021, in this patent family we owned two patents in China expiring in 2029 and 2030, respectively, and we owned 15 patents in other jurisdictions, including the United States expiring in 2031 and Europe expiring in 2030. As of December 31, 2021, we also had one patent application pending in Brazil.

The third patent family is directed to the formulation of a micronized active pharmaceutical ingredient used in surufatinib as well as methods of treating tumor angiogenesis-related disorders with such formulation. As of December 31, 2021, we owned 11 patents in this family in various jurisdictions, including China, Europe and Japan, each of which will expire in 2036. We also had 8 patent applications pending in various other jurisdictions, each of which, if issued, would have an expiration date in 2036.

The fourth patent family is directed to clinical indications of surufatinib. With respect to this patent family, we had one patent application pending in Japan, which, if issued, would have an expiration date in 2036.

The fifth patent family is subject to confidential review by the patent authorities. With respect to this family, we had one patent application pending in China, which, if issued, would have an expiration date in 2040.

The sixth patent family is directed to the pharmaceutical combinations of toripalimab and surufatinib. With respect to this family, we had one PCT and one Taiwan applications pending, each of which, if issued, would have an expiration date in 2041. This patent family is co-owned by us and Shanghai Junshi Biosciences Co., Ltd.

The seventh patent family is subject to confidential review by the patent authorities. With respect to this family, we had one patent application pending in the United States, which, if issued, would have an expiration date in 2041.

The eighth and ninth patent families are each subject to confidential review by the patent authorities. With respect to each of these families, we had one patent application pending in China, which, if issued, would have an expiration date in 2041.

Fruquintinib—The intellectual property portfolio for fruquintinib contains six patent families.

The first patent family for fruquintinib is directed to novel small molecule compounds as well as methods of treating tumor angiogenesis-related disorders with such compounds. As of December 31, 2021, we owned three U.S. patents, one Chinese patent and one Taiwanese patent in this family, each of which will expire in 2028. We also owned 15 patents in other jurisdictions including Europe and Japan, each of which will expire in 2029. As of December 31, 2021, we also had one patent application pending in Brazil.

The second patent family is directed to crystalline forms of fruquintinib as well as methods of treating tumor angiogenesis-related disorders with such forms. As of December 31, 2021, we owned 22 patents in this family in various jurisdictions, including the United States, China, Europe and Japan, each of which will expire in 2035, and we had 5 patent applications pending in various other jurisdictions.

The third patent family is directed to the method of preparing one of the critical intermediates used in the manufacturing process of fruquintinib. With respect to this patent family, we had one patent in China expiring in 2034.

The fourth patent family is directed to the pharmaceutical composition of fruquintinib. As of December 31, 2021, we had 7 patent applications pending in this patent family in various jurisdictions, including China, the United States, Europe and Japan, each of which, if issued, would have an expiration date in 2039.

The fifth patent family is directed to the pharmaceutical combinations of geptanolimab and fruquintinib. With respect to this family, we had one patent application pending in China, which, if issued, would have an expiration date in 2040. We also had one PCT application pending in this family, which, if issued, would have an expiration date in 2041. This patent family is co-owned by us and Genor Biopharma Co. Ltd.

The sixth patent family is directed to the pharmaceutical combinations of sintilimab and fruquintinib. With respect to this family, we had one PCT and one Taiwan application pending, each of which, if issued, would have an expiration date in 2041. This patent family is co-owned by us and Innovent Biologics (Suzhou) Co. Ltd.

Sovleplenib—The intellectual property portfolio for sovleplenib contains two patent families.

The first patent family is directed to novel small molecule compounds as well as methods of treating cancers, inflammatory diseases, allergic diseases, cell-proliferative diseases, and immunological diseases with such compounds. As of December 31, 2021, we owned 24 patents in this family in various jurisdictions, including the United States, China, Europe and Japan, each of which will expire in 2032. As of December 31, 2021, we also had one patent application pending in India.

The second patent family is directed to the salts of sovleplenib as well as crystalline forms thereof. As of December 31, 2021, we had 24 patent applications pending in this patent family in various jurisdictions, including China, the United States, Europe and Japan, each of which, if issued, would have an expiration date in 2038.

Amdizalisib—The intellectual property portfolio for amdizalisib contains three patent families.

The first patent family is directed to novel small molecule compounds as well as uses of such compounds. As of December 31, 2021, we owned 25 patents in this family in various jurisdictions, including the United States, Europe, China and Japan, each of which will expire in 2035. As of December 31, 2021, we also had two patent applications pending in this family in Argentina and Brazil.

The second patent family is directed to crystalline forms of amdizalisib. As of December 31, 2021, we had 23 patent applications pending in this family in various jurisdictions, including China, the United States, Europe and Japan, each of which, if issued, would have an expiration date in 2039.

The third patent family is directed to the method of preparing one of the critical intermediates used in the manufacturing process of amdizalisib. With respect to this patent family, we had one patent in China expiring in 2038.

Tazemetostat — The intellectual property portfolio for Tazemetostat is licensed from Epizyme, Inc.

We entered into a licensing agreement with Epizyme pursuant to which we obtained a co-exclusive license to develop, an exclusive license to commercialize and a co-exclusive license to manufacture tazemetostat in China, Hong Kong, Taiwan and Macau for all therapeutic and palliative uses in epithelioid sarcoma, follicular lymphoma (second line and third line), diffuse large B-cell lymphoma and any other indications that are approved according to the terms of the licensing agreement. For more details, please see "—Our Collaborations—Epizyme."

HMPL-306 — The intellectual property portfolio for HMPL-306 contains one patent family.

The patent family is directed to novel small molecule compounds as well as methods of treating cancers with the compounds. As of December 31, 2021, we had 24 patent applications pending in this patent family in various jurisdictions, including China, the United States, Europe and Japan, each of which, if issued, would have an expiration date in 2038.

HMPL-760 — The intellectual property portfolio for HMPL-760 contains one patent family.

The patent family is directed to novel small molecule compounds as well as methods of treating cancers, inflammatory diseases or auto-immune diseases with such compounds. As of December 31, 2021, in this patent family we had PCT, the United States, Argentina and Taiwan applications pending, each of which, if issued, would have an expiration date in 2041.

HMPL-453 — The intellectual property portfolio for HMPL-453 contains two patent families.

The first patent family is directed to novel small molecule compounds as well as methods of treating cancers with the compounds. As of December 31, 2021, we owned 22 patents in this family in various jurisdictions, including China, Europe, Japan and the United States, each of which will expire in 2034. As of December 31, 2021, we had three patent applications pending in various other jurisdictions.

The second patent family is directed to the salts of HMPL-453. With respect to this family, we had PCT, Argentina and Taiwan applications pending, each of which, if issued, would have an expiration date in 2040.

HMPL-295 — The intellectual property portfolio for HMPL-295 contains one patent family.

The patent family is directed to novel small molecule compounds as well as methods of treating cancers or auto-immune diseases with such compounds. As of December 31, 2021, in this patent family we had 23 patent applications pending in various jurisdictions, including China, the United States, Europe and Japan, each of which, if issued, would have an expiration date in 2040.

HMPL-653 — The intellectual property portfolio for HMPL-653 contains one patent family.

The patent family is directed to novel small molecule compounds as well as methods of treating cancers, inflammatory diseases or auto-immune diseases with such compounds. As of December 31, 2021, in this patent family we had PCT, Argentina and Taiwan applications pending, each of which, if issued, would have an expiration date in 2041.

Epitinib—The intellectual property portfolio for epitinib contains two patent families.

The first patent family is directed to novel small molecule compounds as well as methods of treating cancers with such compounds. As of December 31, 2021, we owned two patents in China and Taiwan expiring in 2028, one patent in the United States expiring in 2031 and 14 patents in other jurisdictions, including Europe, each expiring in 2029.

The second patent family is directed to the salts and solvates of epitinib and crystalline forms thereof, as well as methods of treating cancers with such forms. As of December 31, 2021, we had one patent application pending in this family in China, which, if issued, would have an expiration date in 2038.

Theliatinib—The intellectual property portfolio for theliatinib contains two patent families.

The first patent family is directed to novel small molecule compounds as well as methods of treating cancers with such compounds. As of December 31, 2021, we owned 19 patents in this family in various jurisdictions, including China and Japan, each of which will expire in 2031.

The second patent family is directed to the salts and solvates of theliatinib and crystalline forms thereof. With respect to this family, we had one Chinese application pending, which, if issued, would have an expiration date in 2038.

Other Ventures Patents

As of December 31, 2021, our joint venture Shanghai Hutchison Pharmaceuticals had 60 issued patents and 37 pending patent applications in China, including patents for its key prescription products described below.

She Xiang Bao Xin Pills. As of December 31, 2021, Shanghai Hutchison Pharmaceuticals held an invention patent in China directed to the formulation of the She Xiang Bao Xin pill. Under PRC law, invention patents are granted for new technical innovations with respect to products or processes. Invention patents in China have a maximum term of 20 years. This patent will expire in 2029. The "Confidential State Secret Technology" status protection on the She Xiang Bao Xin pill technology held by Shanghai Hutchison Pharmaceuticals, as certified by China's Ministry of Science and Technology and State Secrecy Bureau, is currently active.

Danning Tablets. As of December 31, 2021, Shanghai Hutchison Pharmaceuticals also held an invention patent in China directed to the formulation of the Danning tablet. This patent will expire in 2027.

Patent Term

The term of a patent depends upon the laws of the country in which it is issued. In most jurisdictions, a patent term is 20 years from the earliest filing date of a non-provisional patent application. In the United States, a patent's term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the USPTO in examining and granting a patent, or may be shortened if a patent is terminally disclaimed over an earlier filed patent. The term of a patent that covers a drug or biological product may also be eligible for patent term extension when FDA approval is granted, provided statutory and regulatory requirements are met. In the future, if and when our drug candidates receive approval by the FDA or other regulatory authorities, we expect to apply for patent term extensions on issued patents covering those drugs, depending upon the length of the clinical trials for each drug and other factors. There can be no assurance that any of our pending patent applications will be issued or that we will benefit from any patent term extension.

As with other pharmaceutical companies, our or our joint ventures' ability to maintain and solidify our proprietary and intellectual property position for our drugs and drug candidates or our or their products and technologies will depend on our or our joint ventures' success in obtaining effective patent claims and enforcing those claims if granted. However, our or our joint ventures' pending patent applications and any patent applications that we or they may in the future file or license from third parties may not result in the issuance of patents. We also cannot predict the breadth of claims that may be allowed or enforced in our or our joint ventures' patents. Any issued patents that we may receive in the future may be challenged, invalidated or circumvented. For example, we cannot be certain of the priority of filing covered by pending third-party patent applications. If third parties prepare and file patent applications in the United States, China or other markets that also claim technology or therapeutics to which we or our joint ventures have rights, we or our joint ventures may have to participate in interference proceedings, which could result in substantial costs to us, even if the eventual outcome is favorable to us, which is highly unpredictable. In addition, because of the extensive time required for clinical development and regulatory review of a drug candidate we may develop, it is possible that, before any of our drug candidates can be commercialized, any related patent may expire or remain in force for only a short period following commercialization, thereby limiting protection such patent would afford the respective product and any competitive advantage such patent may provide.

Trade Secrets

In addition to patents, we and our joint ventures rely upon unpatented trade secrets and know-how and continuing technological innovation to develop and maintain our or their competitive position. We and our joint ventures seek to protect our proprietary information, in part, by executing confidentiality agreements with our collaborators and scientific advisors, and non-competition, non-solicitation, confidentiality, and invention assignment agreements with our employees and consultants. We and our joint ventures have also executed agreements requiring assignment of inventions with selected scientific advisors and collaborators. The confidentiality agreements we and our joint ventures enter into are designed to protect our or our joint ventures' proprietary information and the agreements or clauses requiring assignment of inventions to us or our joint ventures, as applicable, are designed to grant us or our joint ventures, as applicable, ownership of technologies that are developed through our or their relationship with the respective counterpart. We cannot guarantee, however, that these agreements will afford us or our joint ventures adequate protection of our or their intellectual property and proprietary information rights.

Trademarks and Domain Names

We conduct our business using trademarks with various forms of the "Hutchison", "Chi-Med", "Hutchison China MediTech", "HUTCHMED", "Elunate", "Sulanda", "Orpathys" and "Tazverik" brands, the logos used by HUTCHMED Limited, as well as domain names incorporating some or all of these trademarks. In April 2006, we entered into a brand license agreement (as amended and restated on June 15, 2021) with Hutchison Whampoa Enterprises Limited, an indirect wholly-owned subsidiary of CK Hutchison, pursuant to which we have been granted a non-exclusive, non-transferrable, royalty-free right to use the "Hutchison", "Hutchison China MediTech", "Chi-Med", "HUTCHMED" trademarks, domain names and other intellectual property rights owned by the CK Hutchison group in connection with the operation of our business worldwide. See "Connected Transactions" for further details. The Elunate and Orpathys trademarks are licensed to us in China by our collaboration partners Eli Lilly and AstraZeneca, respectively. The trademarks for the HUTCHMED Limited logo and "Sulanda" are owned by us. The Tazverik trademark is licensed to us in China, Hong Kong, Taiwan and Macau by our collaboration partner Epizyme.

In addition, our joint ventures seek trademark protection in China for their products. As of December 31, 2021, our joint venture Shanghai Hutchison Pharmaceuticals owned a total of 12 trademarks in China related to products sold by it. For example, the name "Shang Yao" is a registered trademark of Shanghai Hutchison Pharmaceuticals in China for certain uses including pharmaceutical preparations.

Raw Materials and Supplies

Raw materials and supplies are ordered based on our or our joint ventures' respective sales plans and reasonable order forecasts and are generally available from our or our joint ventures' own cultivation operations and various third-party suppliers in quantities adequate to meet our needs. We typically order raw materials on short-term contract or purchase order basis and do not enter into long-term dedicated capacity or minimum supply arrangements.

For our Oncology/Immunology operations, the active pharmaceutical ingredient used in our drug candidates are supplied to us from third-party vendors. Our ability to successfully develop our drug candidates, and to ultimately supply our commercial drugs in quantities sufficient to meet the market demand, depends in part on our ability to obtain the active pharmaceutical ingredients for these drugs in accordance with regulatory requirements and in sufficient quantities for commercialization and clinical testing.

We generally aim to identify and qualify one or more manufacturers to provide such active pharmaceutical ingredients prior to submission of an NDA to the FDA and/or NMPA. We contract with a single supplier to manufacture and supply us with the active pharmaceutical ingredient for fruquintinib for commercial purposes and are in the process of engaging a second supplier. We have already validated the second supplier's cGMP production processes and the application for this second supplier has been approved by the NMPA. We also contract with a single supplier to manufacture and supply us with the active pharmaceutical ingredient for surufatinib for commercial purposes. We contracted with a single supplier to provide active pharmaceutical ingredient and finished product for savolitinib. We manage the risk of price fluctuations and supply disruptions of active pharmaceutical ingredients by purchasing them in bulk quantities as these ingredients have a relatively long shelf life. Other than the foregoing, we do not currently have arrangements in place for a contingent or second-source supply of the active pharmaceutical ingredients for fruquintinib, surufatinib or savolitinib in the event any of our current suppliers of such active pharmaceutical ingredients or finished product cease their operations for any reason, which may lead to an interruption in our production and operations. However, to date, while we have experienced price fluctuations associated with our raw materials, we have not experienced any material disruptions in the supply of the active pharmaceutical ingredients or the other raw materials we and our joint venture partners use. See Item 3.D. "Risk Factors—Certain of our joint venture parties principal products involve the cultivation or sourcing of key raw materials including botanical products, and any quality control or supply failure or price fluctuations could adversely affect our ability to manufacture our products and/or could materially and adversely affect our operating results."

Quality Control and Assurance

We have our own independent quality control system and devote significant attention to quality control for the designing, manufacturing and testing of our products. We have established a strict quality control system in accordance with the NMPA regulations. Our laboratories fully comply with the Chinese manufacturing guidelines and are staffed with highly educated and skilled technicians to ensure quality of all batches of product release. We monitor in real time our operations throughout the entire production process, from inspection of raw and auxiliary materials, manufacture, delivery of finished products, clinical testing at hospitals, to ethical sales tactics. Our quality assurance team is also responsible for ensuring that we are in compliance with all applicable regulations, standards and internal policies. Our senior management team is actively involved in setting quality policies and managing internal and external quality performance of our company and our joint venture Shanghai Hutchison Pharmaceuticals.

Customers and Suppliers

For the years ended December 31, 2019, 2020 and 2021, we generated revenue of $75.7 million, $102.3 million and $188.9 million from our five largest customers, respectively. For the years ended December 31, 2019, 2020 and 2021, revenue from our five largest customers represented approximately 37%, 45% and 53% of our total revenue, respectively, and revenue from our largest customer in those periods represented approximately 13%, 16% and 16% of our revenue in the same periods, respectively. Save for Sinopharm, our five largest customers were independent third parties and none of our directors or their close associates or, to the knowledge of our directors, any shareholders who owned more than 5% of our issued ordinary shares had any interest in any of our five largest customers as of the date of the filing of this annual report.

In 2019, 2020 and 2021, Sinopharm, which jointly owns Hutchison Sinopharm with us, was one of our five largest customers. Sales to Sinopharm and/or its associates contributed 14%, 16% and 12% of our revenue in 2019, 2020 and 2021, respectively. Purchases from Sinopharm and/or its associates contributed less than 1% of our total purchases in 2019, 2020 and 2021, respectively.

For the years ended December 31, 2019, 2020 and 2021, the total purchases from our five largest suppliers were $46.8 million, $58.0 million and $100.6 million, respectively. For the years ended December 31, 2019, 2020 and 2021, our purchases from our five largest suppliers represented 28% of our total purchases. Save for Shanghai Hutchison Pharmaceuticals and Hain Celestial, all of our five largest suppliers were independent third parties and none of our directors or their close associates or, to the knowledge of our directors, any shareholder who owned more than 5% of our issued ordinary shares had any interest in any of our five largest suppliers as of the date of the filing of this annual report.

Contract Research Organizations

Although we or our collaboration partners design the clinical trials for our drug candidates, CROs conduct most of the clinical trials. Our agreements with CROs are usually structured as master service agreements which set out the services to be performed, payment schedule, term and confirmation that all intellectual rights arising out of or made in performance of the services are owned by us. We and our collaboration partners work with major global and Chinese CROs.

Certificates and Permits

HUTCHMED (Suzhou) Limited (formerly Hutchison MediPharma (Suzhou) Limited) holds a pharmaceutical manufacturing permit issued by its local regulatory authority expiring on September 13, 2025. It also complies with applicable GMP standards.

Hutchison Sinopharm holds a pharmaceutical trading license issued by its local regulatory authority expiring on July 30, 2024. Hutchison Sinopharm also holds a good supply practice, or GSP, certificate issued by its local regulatory authority which expires on July 30, 2024.

Shanghai Hutchison Pharmaceuticals holds a pharmaceutical manufacturing permit from its local regulatory authorities expiring on December 31, 2025.

Shanghai Shangyao Hutchison Whampoa GSP Company Limited, a subsidiary of Shanghai Hutchison Pharmaceuticals, holds a pharmaceutical trading license from its local regulatory authority expiring on November 17, 2024. It also holds a GSP certificate issued by its local regulatory authority expiring on November 17, 2024.

Regulations

This section sets forth a summary of the most significant rules and regulations affecting our business activities in China and the United States.

Government Regulation of Pharmaceutical Product Development and Approval

PRC Regulation of Pharmaceutical Product Development and Approval

Since China's entry to the World Trade Organization in 2001, the PRC government has made significant efforts to standardize regulations, develop its pharmaceutical regulatory system and strengthen intellectual property protection.

Regulatory Authorities

In the PRC, the NMPA is the authority that monitors and supervises the administration of pharmaceutical products and medical appliances and equipment as well as cosmetics. The NMPA's predecessor, the State Drug Administration, or the SDA, was established on August 19, 1998 as an organization under the State Council to assume the responsibilities previously handled by the Ministry of Health of the PRC, or the MOH, the State Pharmaceutical Administration Bureau of the PRC and the State Administration of Traditional Chinese Medicine of the PRC. The SDA was replaced by the State Food and Drug Administration, or the SFDA, in March 2003 and was later reorganized into the China Food and Drug Administration, or the CFDA, in March 2013. On March 17, 2018, the First Session of the Thirteenth National People's Congress approved the State Council Institutional Reform Proposal, according to which the duties of the CFDA were consolidated into the State Administration for Market Regulation, or the SAMR, and the NMPA was established under the management and supervision of the SAMR.

The primary responsibilities of the NMPA include:

- monitoring and supervising the administration of pharmaceutical products, medical appliances and equipment as well as cosmetics in the PRC;
- formulating administrative rules and policies concerning the supervision and administration of cosmetics and the pharmaceutical industry; evaluating, registering and approving of new drugs, generic drugs, imported drugs and traditional Chinese medicine;
- undertaking the standard, registration, quality and post marketing risk management of pharmaceutical products, medical appliances and equipment as well as cosmetics; and
- examining, evaluating and supervising the safety of pharmaceutical products, medical appliances and equipment as well as that of cosmetics.

The MOH is an authority at the ministerial level under the State Council and is primarily responsible for national public health. Following the establishment of the SFDA in 2003, the MOH was put in charge of the overall administration of national health in the PRC excluding the pharmaceutical industry. In March 2008, the State Council placed the SFDA under the management and supervision of the MOH. The MOH performs a variety of tasks in relation to the health industry such as establishing social medical institutes and producing professional codes of ethics for public medical personnel. The MOH is also responsible for overseas affairs, such as dealings with overseas companies and governments. In 2013, the MOH and the National Population and Family Planning Commission were integrated into the National Health and Family Planning Commission of the PRC, or the NHFPC. On March 17, 2018, the First Session of the Thirteenth National People's Congress approved the State Council Institutional Reform Proposal, according to which the responsibilities of NHFPC and certain other governmental authorities are consolidated into the National Health Commission, or the NHC, and the NHFPC shall no longer be maintained. The responsibilities of the NHC include organizing the formulation of national drug policies, the national essential medicine system and the National Essential Medicines List and drafting the administrative rules for the procurement, distribution and use of national essential medicines.

Healthcare System Reform

The PRC government has promulgated several healthcare reform policies and regulations to reform the healthcare system. On March 17, 2009, the Central Committee of the PRC Communist Party and the State Council jointly issued the Guidelines on Strengthening the Reform of Healthcare System. On March 18, 2009, the State Council issued the Implementation Plan for the Recent Priorities of the Healthcare System Reform (2009-2011). On July 22, 2009, the General Office of the State Council issued the Five Main Tasks of Healthcare System Reform in 2009.

Highlights of these healthcare reform policies and regulations include the following:

- The overall objective of the reform is to establish a basic healthcare system to cover both urban and rural residents and provide the Chinese people with safe, effective, convenient and affordable healthcare services. The PRC government aims to extend basic medical insurance coverage to at least 90% of the country's population by 2011 and increase the amount of subsidies on basic medical insurance for urban residents and rural cooperative medical insurance to RMB120 ($18.32) per person per year by 2010. By 2020, a basic healthcare system covering both urban and rural residents should be established.

- The reforms aim to promote orderly market competition and improve the efficiency and quality of the healthcare system to meet the various medical needs of the Chinese population. From 2009, basic public healthcare services such as preventive healthcare, maternal and child healthcare and health education will be provided to urban and rural residents. In the meantime, the reforms also encourage innovations by pharmaceutical companies to eliminate low-quality and duplicative products.

- The five key tasks of the reform from 2009 to 2011 are as follows: (1) to accelerate the formation of a basic medical insurance system; (2) to establish a national essential drug system; (3) to establish a basic healthcare service system; (4) to promote equal access to basic public healthcare services; and (5) to promote the reform of public hospitals.

Drug Administration Laws and Regulations

The PRC Drug Administration Law as promulgated by the Standing Committee of the National People's Congress in 1984 and the Implementing Measures of the PRC Drug Administration Law as promulgated by the MOH in 1989 have laid down the legal framework for the establishment of pharmaceutical manufacturing enterprises, pharmaceutical trading enterprises and for the administration of pharmaceutical products including the development and manufacturing of new drugs and medicinal preparations by medical institutions. The PRC Drug Administration Law also regulates the packaging, trademarks and the advertisements of pharmaceutical products in the PRC.

Certain revisions to the PRC Drug Administration Law took effect on December 1, 2001. They were formulated to strengthen the supervision and administration of pharmaceutical products, and to ensure the quality and the safety of pharmaceutical products for human use. The revised PRC Drug Administration Law applies to entities and individuals engaged in the development, production, trade, application, supervision and administration of pharmaceutical products. It regulates and prescribes a framework for the administration of pharmaceutical manufacturers, pharmaceutical trading companies, and medicinal preparations of medical institutions and the development, research, manufacturing, distribution, packaging, pricing and advertisements of pharmaceutical products.

The PRC Drug Administration Law was later amended on December 28, 2013 and April 24, 2015 by the Standing Committee of the National People's Congress. It provides the basic legal framework for the administration of the production and sale of pharmaceutical products in China and covers the manufacturing, distributing, packaging, pricing and advertising of pharmaceutical products.

On August 26, 2019, the Standing Committee of the National People's Congress promulgated the amended PRC Drug Administration Law, which took effect on December 1, 2019. The amendment brought a series of changes to the drug supervision and administration system, including but not limited to the clarification of the MAH system, pursuant to which the MAH shall assume responsibilities for non-clinical studies, clinical trials, manufacturing and marketing, post-marketing studies, monitoring, reporting and handling of adverse reactions of the drug. The amendment also stipulated that the PRC supports the innovation of drugs with clinical value and specific or special effects on human diseases, encourages the development of drugs with new therapeutic mechanisms and promotes the technological advancement of such drugs.

According to the PRC Drug Administration Law, no pharmaceutical products may be produced without a pharmaceutical production license. A manufacturer of pharmaceutical products must obtain a pharmaceutical production license from one of NMPA's provincial level branches in order to commence production of pharmaceuticals. Prior to granting such license, the relevant government authority will inspect the manufacturer's production facilities, and decide whether the sanitary conditions, quality assurance system, management structure and equipment within the facilities have met the required standards.

The PRC Drug Administration Implementation Regulations promulgated by the State Council took effect on September 15, 2002 and were later amended on February 6, 2016 and March 2, 2019 to provide detailed implementation regulations for the revised PRC Drug Administration Law. With respect to the latest revision of the PRC Drug Administration Law, promulgated on August 26, 2019 and effective on December 1, 2019, there are no corresponding revised PRC Drug Administration Implementation Regulations.

Examination and Approval of New Medicines

On January 22, 2020, the NMPA promulgated the Administrative Measures on the Registration of Pharmaceutical Products, or the Registration Measures, which became effective on July 1, 2020. According to the Registration Measures, an applicant who has obtained a drug registration certificate shall be a drug MAH. The approval process for medicines seeking marketing authorization mainly consists of the following steps:

- upon the completion of pharmaceutical, pharmacological and toxicological research and related activities, an application for clinical trial will be submitted to the Center for Drug Evaluation of the NMPA, or the Center for Drug Evaluation, for review. The Center for Drug Evaluation will organize pharmacists, medical personnel and other professionals to review the application for clinical trial. A decision on approval or non-approval of the application for clinical trial of drugs will be made within 60 working days from acceptance of the application, and the applicant shall be notified of the examination and approval result through the website of the Center for Drug Evaluation. If the applicant is not notified within the stipulated period, the application shall be deemed approved. The applicant who is approved to conduct clinical trial shall act as the sponsor for the clinical trial;

- if the application for clinical trial is approved, the sponsor shall, prior to conducting subsequent phases of the clinical trial, formulate a corresponding program for the clinical trial, carry out the clinical trial after the review and approval by the Ethics Committee, and submit the corresponding program for clinical trial and supporting materials on the website of the Center for Drug Evaluation. The applicant may proceed with the relevant clinical research (which is generally conducted in three phases for a new medicine under the Registration Measures) at institutions with appropriate qualification:

    - Phase I refers to the preliminary clinical trial for clinical pharmacology and body safety. It is conducted to observe the human body tolerance for new medicine and pharmacokinetics, so as to provide a basis for determining the prescription plan.

    - Phase I or II refers to the stage of preliminary evaluation of clinical effectiveness. The purpose is to preliminarily evaluate the clinical effectiveness and safety of the medicine used on patients with targeted indication, as well as to provide a basis for determining the Phase III clinical trial research plan and the volume under the prescription plan.

    - Phase III is a clinical trial stage to verify the clinical effectiveness. The purpose is to test and determine the clinical effectiveness and safety of the medicine used on patients with targeted indication, to evaluate the benefits and risks thereof and, eventually, to provide sufficient basis for review of the medicine registration application.

    - Phase IV refers to the stage of surveillance and research after the new medicines is launched. The purpose is to observe the clinical effectiveness and adverse effects of the medicine over a much larger patient population and longer time period than in Phase I to III clinical trials, and evaluate the benefits and risks when it is administered to general or special patient population in larger prescription volume;

- the sponsor shall submit a safety update report during the research and development period on the website of the NMPA on a regular basis. The safety update report during the research and development period shall be submitted once a year, and within two months of every full year after the clinical drug trial is approved. The NMPA may require the sponsor to adjust the reporting period if deemed necessary;

- after (i) completing relevant pharmaceutical, pharmacological and toxicological research, clinical drug trials, and other research supporting the marketing registration of a medicine, (ii) determining medicine quality standards, (iii) completing the verification of commercial scale manufacturing process, and (iv) making preparations for drug registration inspections, the applicant shall file the application for drug marketing authorization with the Center for Drug Evaluation;

- the Center for Drug Evaluation will organize pharmaceutical, medical and other professionals to review accepted drug marketing authorization applications in accordance with relevant requirements;

- upon acceptance of an application for drug registration, the Center for Drug Evaluation will conduct a preliminary examination within 40 working days from acceptance of the application; if there is a need to conduct an examination of manufacturing premises for drug registration, the Center for Drug Evaluation will notify the Centre for Food and Drug Inspection of the NMPA to organize an examination, provide the relevant materials required, and simultaneously notify the applicant as well as the provincial drug administrative authorities where the applicant or the manufacturing enterprise is located. The Centre for Food and Drug Inspection of the NMPA shall in principle complete the examination 40 working days before expiry of the review period, and give feedback to the Center for Drug Evaluation on the status and findings etc. of the examinations; and

- if the application is approved through the comprehensive review process, the drug shall be approved for marketing and a drug registration certificate shall be issued. The drug registration certificate will state the approval number for the drug, the holder of the certificate, and information of the manufacturing enterprise. A drug registration certificate for non-prescription drugs will also state the non-prescription drug category.

Any applicant who is not satisfied with the Center for Drug Evaluation's decision to deny an application during the application of the drug registration period can appeal within 15 working days after it is notified by the Center for Drug Evaluation of such decision. Upon termination for examination and approval of the application for drug registration, if the applicant is dissatisfied with the administrative licensing decision, the applicant may apply for administrative review or file an administrative lawsuit.

In accordance with the Provisions on the Administration of Special Examination and Approval of Registration of New Drugs promulgated by the NMPA, issued and effective on January 7, 2009, an NDA that meets certain requirements as specified below will be handled with priority in the review and approval process, so-called "green-channel" approval. In addition, the applicant is entitled to provide additional materials during the review period besides those requested by the NMPA, and will have access to enhanced communication channels with the NMPA.

Applicants for the registration of the following new drugs are entitled to request priority treatment in review and approval: (i) active ingredients and their preparations extracted from plants, animals and minerals, and newly discovered medical materials and their preparations that have not been sold in the China market, (ii) chemical drugs and their preparations and biological products that have not been approved for sale at its origin country or abroad, (iii) new drugs with obvious clinical treatment advantages for such diseases as AIDS, therioma, and rare diseases, and (iv) new drugs for diseases that have not been treated effectively. Under category (i) or (ii) above, the applicant for drug registration may apply for special examination and approval when applying for the clinical trial of new drugs; under category (iii) or (iv) above, the applicant may only apply for special examination and approval when applying for manufacturing.

In addition, on July 7, 2020, the NMPA released the Priority Review and Approval Procedures for Drug Marketing Authorizations (for Trial Implementation), which further clarified that a fast track process for drug registration will be available to the following drugs with distinctive clinical value: (i) (a) drugs in urgent clinical demand and in shortage and (b) innovative drugs and modified new drugs for prevention and treatment of serious infectious diseases, rare diseases and other diseases; (ii) new varieties, dosage forms and specifications of children's drugs that conform to children's physiological characteristics; (iii) (a) vaccines that are in urgent need for disease prevention and control and (b) innovative vaccines; (iv) drugs that have been included in the procedures for Breakthrough Therapy Designation; (v) drugs that are subject to conditional approval; and (vi) other drugs which the NMPA deems applicable. It also specified that fast track status would be given to clinical trial applications for drugs with patent expiry within three years and manufacturing authorization applications for drugs with patent expiry within one year. Concurrent applications for new drug clinical trials which are already approved in the United States or E.U. are also eligible for fast track NMPA approval.

Drug Technology Transfer Regulations

On August 19, 2009, the NMPA promulgated the Administrative Regulations for Technology Transfer Registration of Drugs to standardize the registration process of drug technology transfer, which includes application for, and evaluation, examination, approval and monitoring of, drug technology transfer. Drug technology transfer refers to the transfer of drug production technology by the owner to a drug manufacturer and the application for drug registration by the transferee according to the provisions in the new regulations. Drug technology transfer includes new drug technology transfer and drug production technology transfer.

Conditions for the application for new drug technology transfer

Applications for new drug technology transfer may be submitted prior to the expiration date of the monitoring period of the new drugs with respect to:

- drugs with new drug certificates only; or
- drugs with new drug certificates and drug approval numbers.

For drugs with new drug certificates only and not yet in the monitoring period, or drug substances with new drug certificates, applications for new drug technology transfer should be submitted prior to the respective expiration date of the monitoring periods for each drug registration category set forth in the new regulations and after the issue date of the new drug certificates.

Conditions for the application of drug production technology transfer

Applications for drug production technology transfer may be submitted if:

- the transferor holds new drug certificates or both new drug certificates and drug approval numbers, and the monitoring period has expired or there is no monitoring period;
- with respect to drugs without new drug certificates, both the transferor and the transferee are legally qualified drug manufacturing enterprises, one of which holds over 50% of the equity interests in the other, or both of which are majority-owned subsidiaries of the same drug manufacturing enterprise;
- with respect to imported drugs with imported drug licenses, the original applicants for the imported drug registration may transfer these drugs to local drug manufacturing enterprises.

Application for, and examination and approval of, drug technology transfer

Applications for drug technology transfer should be submitted to the provincial drug administration. If the transferor and the transferee are located in different provinces, the provincial drug administration where the transferor is located should provide examination opinions. The provincial drug administration where the transferee is located is responsible for examining application materials for technology transfer and organizing inspections on the production facilities of the transferee. Medical examination institutes are responsible for testing three batches of drug samples.

The Center for Drug Evaluation should further review the application materials, provide technical evaluation opinions and form a comprehensive evaluation opinion based on the site inspection reports and the testing results of the samples. The NMPA should determine whether to approve the application according to the comprehensive evaluation opinion of the Center for Drug Evaluation. An approval letter of supplementary application and a drug approval number will be issued to qualified applications. An approval letter of clinical trials will be issued when necessary. For rejected applications, a notification letter of the examination opinions will be issued with the reasons for rejection.

Permits and Licenses for Manufacturing and Registration of Drugs

Production Licenses

To manufacture pharmaceutical products in the PRC, a pharmaceutical manufacturing enterprise must first obtain a Pharmaceutical Manufacturing Permit issued by the relevant pharmaceutical administrative authorities at the provincial level where the enterprise is located. Among other things, such a permit must set forth the permit number, the name, legal representative and registered address of the enterprise, the site and scope of production, issuing institution, date of issuance and effective period.

Each Pharmaceutical Manufacturing Permit issued to a pharmaceutical manufacturing enterprise is effective for a period of five years. The enterprise is required to apply for renewal of such permit within six months prior to its expiry and will be subject to reassessment by the issuing authorities in accordance with then prevailing legal and regulatory requirements for the purposes of such renewal.

Business Licenses

In addition to a Pharmaceutical Manufacturing permit, the manufacturing enterprise must also obtain a business license from the administrative bureau of industry and commerce at the local level. The name, legal representative and registered address of the enterprise specified in the business license must be identical to that set forth in the Pharmaceutical Manufacturing Permit.

Registration of Pharmaceutical Products

All pharmaceutical products that are produced in the PRC must bear a registration number issued by the NMPA, with the exception of Chinese herbs and Chinese herbal medicines in soluble form. The medicine manufacturing enterprises must obtain the medicine registration number before manufacturing any medicine.

Good Manufacturing Practices

The Guidelines on Good Manufacturing Practices, as amended in 1998 and 2010, or the Guidelines, took effect on August 1, 1999 and set the basic standards for the manufacture of pharmaceuticals. These Guidelines cover issues such as the production facilities, the qualification of the personnel at the management level, production plant and facilities, documentation, material packaging and labeling, inspection, production management, sales and return of products and customers' complaints. On October 23, 2003, the NMPA issued the Notice on the Overall Implementation and Supervision of Accreditation of Good Manufacturing Practice Certificates for Pharmaceuticals, which required all pharmaceutical manufacturers to apply for the GMP certificates by June 30, 2004. Those enterprises that failed to obtain the GMP certificates by December 31, 2004 would have their Pharmaceutical Manufacturing Permit revoked by the drug administrative authorities at the provincial level. On October 24, 2007, the NMPA issued Evaluation Standard on Good Manufacturing Practices which became effective on January 1, 2008. On December 1, 2019, per the Announcement of the NMPA on Issues Concerning the Implementation of the PRC Drug Administration Law, GMP certificates were abolished, though manufacturers remain to be obligated to operate in accordance with the applicable requirements of the Guidelines. The Notice of the NMPA on Promulgation of the Administrative Measures for Drug Inspection (for Trial Implementation), or Trial Drug Inspection Measures, was released and effective on May 24, 2021, which regulates the inspection, investigation, evidence collection and disposal and other actions carried out by medical products administrative authorities with respect to the manufacturing, distribution and use of drugs. The Trial Drug Inspection Measures stipulate that where an application for a pharmaceutical manufacturing permit is filed for the first time, on-site inspection shall be carried out in accordance with the applicable requirements of the Guidelines. Where an application for re-issuance of a pharmaceutical manufacturing permit is filed, a compliance inspection may be carried out if necessary based on the principles of risk management, taking into consideration the enterprise's compliance with the laws and regulations on drug administration, the Guidelines, and the running of quality control systems.

Marketing Authorization Holder System

In May 2016, the State Council announced the piloting of the MAH system in ten provinces in China, where the market authorization/drug license holders are no longer required to be the actual manufacturers. The MAH system will allow for more flexibilities in contract manufacturing arrangements.

Under the authorization of the Standing Committee of the National People's Congress, the State Council issued the Pilot Plan for the Drug MAH Mechanism on May 26, 2016, providing a detailed pilot plan for the MAH system in ten provinces in China. Under the MAH system, domestic drug research and development institutions and individuals in the pilot regions are eligible to be holders of drug registrations without having to become drug manufacturers. The MAHs may engage contract manufacturers for manufacturing, provided that the contract manufacturers are licensed and are also located within the pilot regions. Drugs that qualify for the MAH system include: (1) new drugs (including biological products for curative uses of Class I, Class VII and biosimilars under the Administration of Drug Registration) approved after the implementation of the MAH system; (2) generic drugs approved as Category 3 or 4 drugs under the Reform Plan for Registration Category of Chemical Medicine issued by the NMPA on March 4, 2016; (3) previously approved generics that have passed equivalence assessments against their original drugs; and (4) previously approved drugs whose licenses were held by drug manufacturers originally located within the pilot regions but have moved out of the pilot regions due to corporate mergers or other reasons.

On August 15, 2017, the NMPA issued the Circular on the Matters Relating to Promotion of the Pilot Program for the Drug MAH System, clarifying that the MAH shall be responsible for managing the whole manufacturing and marketing chain and the whole life cycle of drugs and shall assume full legal liabilities for the non-clinical drug study, clinical trials, manufacturing, marketing and distribution and adverse drug reaction monitoring. The MAH is permitted to entrust several drug manufacturers under the drug quality management system established by the MAH. The MAH shall submit a report of drug manufacturing, marketing, prescription, techniques, pharmacovigilance, quality control measures and certain other matters to the NMPA within 20 working days after the end of each year.

On December 1, 2019, the latest amendment of Drug Administration Law came into effect, marking the success of the pilot work, and the MAH system has become a national system. Pursuant to the latest amendment, the legal representative and the key person-in-charge of a drug MAH shall be fully responsible for the quality of drugs.

Administrative Protection for New Drugs

The Administrative Measures Governing the Production Quality of Pharmaceutical Products, or the Administrative Measures for Production, provides detailed guidelines on practices governing the production of pharmaceutical products. A manufacturer's factory must meet certain criteria in the Administrative Measures for Production, which include: institution and staff qualifications, production premises and facilities, equipment, hygiene conditions, production management, quality controls, product operation, maintenance of sales records and manner of handling customer complaints and adverse reaction reports.

Distribution of Pharmaceutical Products

According to the PRC Drug Administration Law and its implementing regulations and the Measures for the Supervision and Administration of Circulation of Pharmaceuticals, a manufacturer of pharmaceutical products in the PRC can only engage in the trading of the pharmaceutical products that the manufacturer has produced itself. In addition, such manufacturer can only sell its products to:

- wholesalers and distributors holding Pharmaceutical Distribution Permits;
- other holders of Pharmaceutical Manufacturing Permits; or
- medical practitioners holding Medical Practice Permits.

A pharmaceutical manufacturer in the PRC is prohibited from selling its products to end-users, or individuals or entities other than holders of Pharmaceutical Distribution Permits, the Pharmaceutical Manufacturing Permits or the Medical Practice Permits.

The granting of a Pharmaceutical Distribution Permit to wholesalers shall be subject to approval of the provincial level drug regulatory authorities, while the granting of a retailer permit shall be subject to the approval of the drug regulatory authorities above the county level. Unless otherwise expressly approved, no pharmaceutical wholesaler may engage in the retail of pharmaceutical products, nor may pharmaceutical retailers engage in wholesaling.

A pharmaceutical distributor shall satisfy the following requirements:

- personnel with pharmaceutical expertise as qualified according to law;

- business site, facilities, warehousing and sanitary environment compatible to the pharmaceutical products being distributed;
- quality management system and personnel compatible to the pharmaceutical products being distributed; and
- rules and regulations to ensure the quality of the pharmaceutical products being distributed.

Operations of pharmaceutical distributors shall be conducted in accordance with the Pharmaceutical Operation Quality Management Rules.

Pharmaceutical distributors must keep true and complete records of any pharmaceutical products purchased, distributed or sold with the generic name of such products, specification, approval code, term, manufacturer, purchasing or selling party, price and date of purchase or sale. A pharmaceutical distributor must keep such record at least until one year after the expiry date of such products and in any case, such record must be kept for no less than three years. Penalties may be imposed for any violation of record-keeping.

Pharmaceutical distributors can only distribute pharmaceutical products obtained from those with a Pharmaceutical Manufacturing Permit and a Pharmaceutical Distribution Permit.

On December 26, 2016, the Medical Reform Office of the State Council, the National Health and Family Planning Commission, the NMPA and other five government authorities promulgated the "Two-Invoice System" Opinions, which became effective on the same date. On April 25, 2017, the General Office of the State Council further promulgated the Notice on Issuing the Key Working Tasks for Deepening the Reform of Medicine and Health System in 2017. According to these rules, a two-invoice system is encouraged to be gradually adopted for drug procurement. The two-invoice system generally requires a drug manufacturer to issue only one invoice to its distributor followed by the distributor issuing a second invoice directly to the end customer hospital. Only one distributor is permitted to distribute drug products between the manufacturer and the hospital. The system also encourages manufacturers to sell drug products directly to hospitals. Public medical institutions are required to adopt the two-invoice system, and its full implementation nationwide is targeted for 2018. As of the date of the filing of this annual report, the relevant local rules with respect to the "Two-Invoice System" have been promulgated in some provinces and municipal cities in the PRC, and the reform is still in progress. Private medical institutions are encouraged but not yet required to adopt the two-invoice system. Pharmaceutical manufacturers and distributors who fail to implement the two-invoice system may be disqualified from attending future bidding events or providing distribution for hospitals and blacklisted for drug procurement practices. These rules aim to consolidate drug distribution and reduce drug prices. The impact on our company is that Shanghai Hutchison Pharmaceuticals was required to restructure its distribution and logistics network and Hutchison Sinopharm began to shift its prior Seroquel distribution model to a fee-for-service model. For more details, please refer to Item 4.B. "Business Overview—Other Ventures."

Foreign Investment and "State Secret" Technology Drugs

The interpretation of certain PRC laws and regulations governing foreign investment and "state secret" technology is uncertain. Under the Special Administrative Measures (Negative List) for Foreign Investment Access, or the Negative List, published by the MOFCOM and the China National Development and Reform Commission or the NDRC. Under the Catalogue, "manufacturing of modern Chinese medicines with confidential proprietary formula" has been deemed prohibited for any foreign investment. The technology and know-how of the She Xiang Bao Xin pill is classified as "state secret" technology by China's Ministry of Science and Technology, or the MOST, and the National Administration for the Protection of State Secrets, or NAPSS.

There are currently no PRC laws or regulations or official interpretations, and therefore there can be no assurance, as to whether the use of "state secret" technology constitutes the "manufacturing of Chinese medicines with confidential proprietary formula" under the Negative List. However, under the Rules on Confidentiality of Science and Technology promulgated by the State Science and Technology Commission (the predecessor of the MOST and the NAPSS) on January 6, 1995, cooperation with foreign parties or establishing joint ventures with foreign parties in respect of state secret technology is expressly allowed, provided that such cooperation has been duly approved by the relevant science and technology authorities. The establishment of Shanghai Hutchison Pharmaceuticals as a sino-foreign joint venture, including the re-registration of licenses for She Xiang Bao Xin pills in its name, was approved by the local counterpart of the MOFCOM and the Shanghai Drug Administration in 2001. Subsequently, the "Confidential State Secret Technology" status protection for She Xiang Bao Xin pills was also granted in 2005 to Shanghai Hutchison Pharmaceuticals as a sino-foreign joint venture by the MOST and NAPSS. Consequently, we believe Shanghai Hutchison Pharmaceuticals is in compliance with all applicable PRC laws and regulations governing foreign investment and "state secret" technology. Moreover, we believe that our other joint ventures and wholly-foreign owned enterprises in the PRC are also in compliance with all applicable PRC laws and regulations governing foreign investment.

U.S. Regulation of Pharmaceutical Product Development and Approval

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and the Public Health Service Act, or PHSA, and their implementing regulations. The process of obtaining approvals and the subsequent compliance with appropriate federal, state and local rules and regulations requires the expenditure of substantial time and financial resources. Failure to comply with the applicable U.S. regulatory requirements at any time during the product development process, approval process or after approval may subject an applicant and/or sponsor to a variety of administrative or judicial sanctions, including refusal by FDA to approve pending applications, withdrawal of an approval, imposition of a clinical hold, issuance of warning letters and other types of enforcement correspondence, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement of profits, or civil or criminal investigations and penalties brought by FDA and the U.S. Department of Justice, or DOJ, or other governmental entities. Drugs are also subject to other federal, state and local statutes and regulations.

Our drug candidates must be approved by the FDA through the NDA process before they may be legally marketed in the United States. The process required by the FDA before a drug may be marketed in the United States generally involves the following:

- completion of extensive pre-clinical studies, sometimes referred to as pre-clinical laboratory tests, pre-clinical animal studies and formulation studies all performed in compliance with applicable regulations, including the FDA's good laboratory practice regulations;

- submission to the FDA of an IND application which must become effective before human clinical trials may begin and must be updated annually;

- IRB approval before each clinical trial may be initiated;

- performance of adequate and well-controlled human clinical trials in accordance with study protocols, the applicable GCPs and other clinical trial-related regulations, to establish the safety and efficacy of the proposed drug product for its proposed indication;

- preparation and submission to the FDA of an NDA;

- a determination by the FDA within 60 days of its receipt of an NDA whether the NDA is acceptable for filing; if the FDA determines that the NDA is not sufficiently complete to permit substantive review, it may request additional information and decline to accept the application for filing until the information is provided;

- in-depth review of the NDA by FDA, which may include review by a scientific advisory committee;

- satisfactory completion of an FDA pre-approval inspection of the manufacturing facility or facilities at which the active pharmaceutical ingredient and finished drug product are produced to assess compliance with the FDA's cGMP;

- potential FDA audit of the pre-clinical and/or clinical trial sites that generated the data in support of the NDA;
- payment of user fees and FDA review and approval of the NDA prior to any commercial marketing or sale of the drug in the United States; and
- compliance with any post-approval requirements, such as REMS and post-approval studies required by FDA.

Pre-clinical Studies

The data required to support an NDA is generated in two distinct development stages: pre-clinical and clinical. For new chemical entities, or NCEs, the pre-clinical development stage generally involves synthesizing the active component, developing the formulation and determining the manufacturing process, evaluating purity and stability, as well as carrying out non-human toxicology, pharmacology and drug metabolism studies in the laboratory, which support subsequent clinical testing. The conduct of the pre-clinical tests must comply with federal regulations, including good laboratory practices. The sponsor must submit the results of the pre-clinical tests, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of the IND. An IND is a request for authorization from the FDA to administer an investigational drug product to humans. The central focus of an IND submission is on the general investigational plan and the protocol(s) for human trials. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA raises concerns or questions regarding the proposed clinical trials and places the IND on clinical hold within that 30-day time period. In such a case, the IND sponsor must resolve with the FDA any outstanding concerns or questions before the clinical trial can begin. Some long-term pre-clinical testing, such as animal tests of reproductive adverse events and carcinogenicity, may continue after the IND is submitted. The FDA may also impose clinical holds on a drug candidate at any time before or during clinical trials due to safety concerns or non-compliance. Accordingly, submission of an IND does not guarantee the FDA will allow clinical trials to begin, or that, once begun, issues will not arise that could cause the trial to be suspended or terminated.

Clinical Studies

The clinical stage of development involves the administration of the drug product to human subjects or patients under the supervision of qualified investigators, generally physicians not employed by or under the trial sponsor's control, in accordance with GCPs, which include the requirement that, in general, all research subjects provide their informed consent in writing for their participation in any clinical trial. Clinical trials are conducted under written study protocols detailing, among other things, the objectives of the clinical trial, dosing procedures, subject selection and exclusion criteria, and the parameters to be used to monitor subject safety and assess efficacy. Each protocol, and any subsequent amendments to the protocol, must be submitted to the FDA as part of the IND. Further, each clinical trial must be reviewed and approved by each institution at which the clinical trial will be conducted. An IRB is charged with protecting the welfare and rights of trial participants and considers such items as whether the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to anticipated benefits. The IRB also reviews and approves the informed consent form that must be provided to each clinical trial subject or his or her legal representative and must monitor the clinical trial until completed. There are also requirements governing the reporting of ongoing clinical trials and completed clinical trial results to public registries. For example, information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health for public dissemination on their ClinicalTrials.gov website.

Clinical trials are generally conducted in three sequential phases that may overlap or be combined, known as Phase I, Phase II and Phase III clinical trials.

- Phase I: In a standard Phase I clinical trial, the drug is initially introduced into a small number of subjects who are initially exposed to a range of doses of the drug candidate. The primary purpose of these clinical trials is to assess the metabolism, pharmacologic action, appropriate dosing, side effect tolerability and safety of the drug.
    - Phase Ib: Although Phase I clinical trials are not intended to treat disease or illness, a Phase Ib trial is conducted in patient populations who have been diagnosed with the disease for which the study drug is intended. The patient population typically demonstrates a biomarker, surrogate, or other clinical outcome that can be assessed to show "proof-of-concept." In a Phase Ib study, proof-of-concept typically confirms a hypothesis that the current prediction of a biomarker, surrogate or other outcome benefit is compatible with the mechanism of action of the study drug.

- Phase I/II: A Phase I and Phase II trial for the same treatment is combined into a single study protocol. The drug is administered first to determine a maximum tolerable dose, and then additional patients are treated in the Phase II portion of the study to further assess safety and/or efficacy.

- Phase II: The drug is administered to a limited patient population to determine dose tolerance and optimal dosage required to produce the desired benefits. At the same time, safety and further pharmacokinetic and pharmacodynamic information is collected, as well as identification of possible adverse effects and safety risks and preliminary evaluation of efficacy.

- Phase III: The drug is administered to an expanded number of patients, generally at multiple sites that are geographically dispersed, in well-controlled clinical trials to generate enough data to demonstrate the efficacy of the drug for its intended use, its safety profile, and to establish the overall benefit/risk profile of the drug and provide an adequate basis for drug approval and labeling of the drug product. Phase III clinical trials may include comparisons with placebo and/or other comparator treatments. The duration of treatment is often extended to mimic the actual use of a drug during marketing. Generally, two adequate and well-controlled Phase III clinical trials are required by the FDA for approval of an NDA. A pivotal study is a clinical study that adequately meets regulatory agency requirements for the evaluation of a drug candidate's efficacy and safety such that it can be used to justify the approval of the drug. Generally, pivotal studies are also Phase III studies but may be Phase II studies if the trial design provides a well-controlled and reliable assessment of clinical benefit, particularly in situations where there is an unmet medical need. Phase IV clinical trials are conducted after initial regulatory approval, and they are used to collect additional information from the treatment of patients in the intended therapeutic indication or to meet other regulatory requirements. In certain instances, FDA may mandate the performance of Phase IV clinical trials.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA, and more frequently if serious adverse events occur. Written IND safety reports must be submitted to the FDA and the investigators for serious and unexpected adverse events or any finding from tests in laboratory animals that suggests a significant risk to human subjects. The FDA, the IRB, or the clinical trial sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. The FDA will typically inspect one or more clinical sites to assure compliance with GCPs and the integrity of the clinical data submitted. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients. Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board or committee. This group provides authorization for whether or not a trial may move forward at designated check points based on access to certain data from the trial. Concurrent with clinical trials, companies usually complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the drug as well as finalize a process for manufacturing the drug in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the drug candidate and, among other things, cGMPs impose extensive procedural, substantive and recordkeeping requirements to ensure and preserve the long-term stability and quality of the final drug product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the drug candidate does not undergo unacceptable deterioration over its shelf life.

NDA Submission and FDA Review Process

Following trial completion, trial results and data are analyzed to assess safety and efficacy. The results of pre-clinical studies and clinical trials are then submitted to the FDA as part of an NDA, along with proposed labeling for the drug, information about the manufacturing process and facilities that will be used to ensure drug quality, results of analytical testing conducted on the chemistry of the drug, and other relevant information. The NDA is a request for approval to market the drug and must contain adequate evidence of safety and efficacy, which is demonstrated by extensive pre-clinical and clinical testing. The application includes both negative or ambiguous results of pre-clinical and clinical trials as well as positive findings. Data may come from company-sponsored clinical trials intended to test the safety and efficacy of a use of a drug, or from a number of alternative sources, including studies initiated by investigators. To support regulatory approval, the data submitted must be sufficient in quality and quantity to establish the safety and efficacy of the investigational drug product to the satisfaction of the FDA. Under federal law, the submission of most NDAs is subject to the payment of an application user fees; a waiver of such fees may be obtained under certain limited circumstances. FDA approval of an NDA must be obtained before a drug may be offered for sale in the United States.

In addition, under the Pediatric Research Equity Act of 2003, or PREA, an NDA or supplement to an NDA must contain data to assess the safety and efficacy of the drug for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. The FDA may grant deferrals for submission of data or full or partial waivers.

Under the Prescription Drug User Fee Act, or PDUFA, as amended, each NDA must be accompanied by an application user fee. The FDA adjusts the PDUFA user fees on an annual basis. According to the FDA's fee schedule, effective through September 30, 2021, the user fee for an application requiring clinical data, such as an NDA, is $2,875,842. PDUFA also imposes a program fee for prescription human drugs $336,432. Fee waivers or reductions are available in certain circumstances, including a waiver of the application fee for the first application filed by a small business. Additionally, no user fees are assessed on NDAs for products designated as orphan drugs, unless the product also includes a non-orphan indication. The FDA reviews all NDAs submitted before it accepts them for filing and may request additional information rather than accepting an NDA for filing. The FDA conducts a preliminary review of an NDA within 60 days of receipt and informs the sponsor by the 74th day after FDA's receipt of the submission to determine whether the application is sufficiently complete to permit substantive review. Once the submission is accepted for filing, the FDA begins an in-depth review of the NDA. Under the goals and policies agreed to by the FDA under PDUFA, the FDA has 10 months from the filing date in which to complete its initial review of a standard NDA and respond to the applicant, and six months from the filing date for a "priority review" NDA. The FDA does not always meet its PDUFA goal dates for standard and priority review NDAs, and the review process is often significantly extended by FDA requests for additional information or clarification.

After the NDA submission is accepted for filing, the FDA reviews the NDA to determine, among other things, whether the proposed drug is safe and effective for its intended use, and whether the drug is being manufactured in accordance with cGMP to assure and preserve the drug's identity, strength, quality and purity. The FDA may refer applications for drugs or drug candidates that present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions. The FDA may re-analyze the clinical trial data, which can result in extensive discussions between the FDA and us during the review process.

Before approving an NDA, the FDA will conduct a pre-approval inspection of the manufacturing facilities for the new drug to determine whether they comply with cGMPs. The FDA will not approve the drug unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the drug within required specifications. In addition, before approving an NDA, the FDA may also audit data from clinical trials to ensure compliance with GCP requirements. After the FDA evaluates the application, manufacturing process and manufacturing facilities where the drug product and/or its active pharmaceutical ingredient will be produced, it may issue an approval letter or a Complete Response Letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. A Complete Response Letter indicates that the review cycle of the application is complete and the application is not ready for approval. A Complete Response Letter usually describes all of the specific deficiencies in the NDA identified by the FDA. The Complete Response Letter may require additional clinical data and/or an additional pivotal clinical trial(s), and/or other significant, expensive and time-consuming requirements related to clinical trials, pre-clinical studies or manufacturing. If a Complete Response Letter is issued, the applicant may either resubmit the NDA, addressing all of the deficiencies identified in the letter, or withdraw the application. Even if such data and information is submitted, the FDA may ultimately decide that the NDA does not satisfy the criteria for approval. Data obtained from clinical trials are not always conclusive and the FDA may interpret data differently than we interpret the same data.

If a drug receives regulatory approval, the approval may be limited to specific diseases and dosages or the indications for use may otherwise be limited. Further, the FDA may require that certain contraindications, warnings or precautions be included in the drug labeling or may condition the approval of the NDA on other changes to the proposed labeling, development of adequate controls and specifications, or a commitment to conduct post-market testing or clinical trials and surveillance to monitor the effects of approved drugs. For example, the FDA may require Phase IV testing which involves clinical trials designed to further assess a drug's safety and effectiveness and may require testing and surveillance programs to monitor the safety of approved drugs that have been commercialized. The FDA may also place other conditions on approvals including the requirement for a REMS to ensure that the benefits of a drug or biological product outweigh its risks. If the FDA concludes a REMS is needed, the sponsor of the NDA must submit a proposed REMS. The FDA will not approve the NDA without an approved REMS, if required. A REMS could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. Any of these limitations on approval or marketing could restrict the commercial promotion, distribution, prescription or dispensing of drugs. Drug approvals may be withdrawn for non-compliance with regulatory standards or if problems occur following initial marketing.

Section 505(b)(2) NDAs

NDAs for most new drug products are based on two full clinical studies which must contain substantial evidence of the safety and efficacy of the proposed new product. These applications are submitted under Section 505(b)(1) of the FDCA. The FDA is, however, authorized to approve an alternative type of NDA under Section 505(b)(2) of the FDCA, which authorizes FDA to approve an NDA based on safety and effectiveness data that were not developed by the applicant. Section 505(b)(2) allows the applicant to rely, in part, on the FDA's previous findings of safety and efficacy for a similar product, or published literature. Specifically, Section 505(b)(2) applies to NDAs for a drug for which the investigations relied upon to show that the drug is safe and effective for the intended use "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted."

Section 505(b)(2) authorizes NDAs filed under Section 505(b)(2) may provide an alternate and potentially more expeditious pathway to FDA approval for new or improved formulations or new uses of previously approved products. If the 505(b)(2) applicant can establish that reliance on the FDA's previous approval is scientifically appropriate, the applicant may eliminate the need to conduct certain pre-clinical or clinical studies of the new product. The FDA may also require companies to perform additional studies or measurements to support the change from the approved product. The FDA may then approve the new drug candidate for all or some of the label indications for which the referenced product has been approved, as well as for any new indication sought by the Section 505(b)(2) applicant.

Abbreviated New Drug Applications for Generic Drugs

In 1984, with passage of the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Act, Congress authorized the FDA to approve generic drugs that are the same as drugs previously approved by the FDA under the NDA provisions of the statute. To obtain approval of a generic drug, an applicant must submit an abbreviated new drug application, or ANDA, to the agency. In support of such applications, a generic manufacturer may rely on the pre-clinical and clinical testing previously conducted for a drug product previously approved under an NDA, known as the reference listed drug, or RLD.

Specifically, in order for an ANDA to be approved, the FDA must find that the generic version is identical to the RLD with respect to the active ingredients, the route of administration, the dosage form, and the strength of the drug. At the same time, the FDA must also determine that the generic drug is "bioequivalent" to the innovator drug. Under the statute, a generic drug is bioequivalent to a RLD if "the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug." The Generic Drug User Fee Act (GDUFA), as reauthorized, sets forth performance goals for the FDA to review standard ANDA's within 10 months of their submission, and priority ANDA's within 8 months of their submission if they satisfy certain requirements.

Upon approval of an ANDA, the FDA indicates that the generic product is "therapeutically equivalent" to the RLD and it assigns a therapeutic equivalence rating to the approved generic drug in its publication "Approved Drug Products with Therapeutic Equivalence Evaluations," also referred to as the "Orange Book." Physicians and pharmacists consider an "AB" therapeutic equivalence rating to mean that a generic drug is fully substitutable for the RLD. In addition, by operation of certain state laws and numerous health insurance programs, FDA's designation of an "AB" rating often results in substitution of the generic drug without the knowledge or consent of either the prescribing physician or patient.

Special FDA Expedited Review and Approval Programs

The FDA has various programs, including fast track designation, accelerated approval, priority review and Breakthrough Therapy Designation, that are intended to expedite or simplify the process for the development and FDA review of drugs that are intended for the treatment of serious or life threatening diseases or conditions and demonstrate the potential to address unmet medical needs. The purpose of these programs is to provide important new drugs to patients earlier than under standard FDA review procedures. While these pathways can reduce the time it takes for the FDA to review an NDA, they do not guarantee that a product will receive FDA approval. In addition, the Right to Try Act of 2018 established a new regulatory pathway to increase access to unapproved, investigational treatments for patients diagnosed with life-threatening diseases or conditions who have exhausted approved treatment options and who are unable to participate in a clinical trial.

Fast Track Designation

To be eligible for a fast track designation, the FDA must determine, based on the request of a sponsor, that a drug is intended to treat a serious or life threatening disease or condition for which there is no effective treatment and demonstrates the potential to address an unmet medical need for the disease or condition. Under the fast track program, the sponsor of a drug candidate may request the FDA to designate the product for a specific indication as a fast track product concurrent with or after the filing of the IND for the drug candidate. The FDA must make a fast track designation determination within 60 days after receipt of the sponsor's request.

In addition to other benefits, such as the ability to use surrogate endpoints and have greater interactions with the FDA, the FDA may initiate review of sections of a fast track product's NDA before the application is complete. This rolling review is available if the applicant provides, and the FDA approves, a schedule for the submission of the remaining information and the applicant pays applicable user fees. However, the FDA's time period goal for reviewing a fast track application does not begin until the last section of the NDA is submitted. A fast track drug also may be eligible for accelerated approval and priority review. In addition, the fast track designation may be withdrawn by the FDA if it believes that the designation is no longer supported by data emerging in the clinical trial process.

Priority Review

The FDA may give a priority review designation to drugs that offer major advances in treatment, or provide a treatment where no adequate therapy exists. A priority review means that the goal for the FDA to review an application is six months, rather than the standard review of 10 months under current PDUFA guidelines. These 6- and 10-month review periods are measured from the "filing" date rather than the receipt date for NDAs for new molecular entities, which typically adds approximately two months to the timeline for review and decision from the date of submission. Most products that are eligible for fast track designation are also likely to be considered appropriate to receive a priority review.

Breakthrough Therapy Designation

Under the provisions of the new Food and Drug Administration Safety and Innovation Act, or FDASIA, enacted by Congress in 2012, a sponsor can request designation of a drug candidate as a "breakthrough therapy," typically by the end of the drug's Phase II trials. A breakthrough therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. Drugs designated as breakthrough therapies are also eligible for accelerated approval. For breakthrough therapies, the FDA may take certain actions, such as intensive and early guidance on the drug development program, that are intended to expedite the development and review of an application for approval.

Accelerated Approval

FDASIA also codified and expanded on FDA's accelerated approval regulations, under which FDA may approve a drug for a serious or life-threatening illness that provides meaningful therapeutic benefit over existing treatments based on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on an intermediate clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit. A surrogate endpoint is a marker that does not itself measure clinical benefit but is believed to predict clinical benefit. This determination takes into account the severity, rarity or prevalence of the disease or condition and the availability or lack of alternative treatments. As a condition of approval, the FDA may require a sponsor of a drug receiving accelerated approval to perform Phase IV or post-marketing studies to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical endpoint, and the drug may be subject to accelerated withdrawal procedures. All promotional materials for drug candidates approved under accelerated regulations are subject to prior review by the FDA.

Even if a product qualifies for one or more of these programs, the FDA may later decide that the product no longer meets the conditions for qualification or decide that the time period for the FDA review or approval will not be shortened. Furthermore, fast track designation, priority review, accelerated approval and Breakthrough Therapy Designation, do not change the standards for approval and may not ultimately expedite the development or approval process.

Pediatric Trials

Under PREA, an NDA or supplement thereto must contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. With the enactment of FDASIA, a sponsor who is planning to submit a marketing application for a drug that includes a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration must also submit an initial Pediatric Study Plan, or PSP, within sixty days of an end-of-Phase II meeting or as may be agreed between the sponsor and the FDA. The initial PSP must include an outline of the pediatric study or studies that the sponsor plans to conduct, including study objectives and design, age groups, relevant endpoints and statistical approach, or a justification for not including such detailed information, and any request for a deferral of pediatric assessments or a full or partial waiver of the requirement to provide data from pediatric studies along with supporting information. The FDA and the sponsor must reach agreement on the PSP. A sponsor can submit amendments to an agreed-upon initial PSP at any time if changes to the pediatric plan need to be considered based on data collected from pre-clinical studies, early phase clinical trials, and/or other clinical development programs. The law requires the FDA to send a non-compliance letters to sponsors who do not submit their pediatric assessments as required.

Under the Best Pharmaceuticals for Children Act, or BPCA, certain therapeutic candidates may obtain an additional six months of exclusivity if the sponsor submits information requested by the FDA, relating to the use of the active moiety of the product candidate in children. Although the FDA may issue a written request for studies on either approved or unapproved indications, it may only do so where it determines that information relating to that use of a product candidate in a pediatric population, or part of the pediatric population, may produce health benefits in that population.

FDASIA permanently reauthorized PREA and BPCA, modifying some of the requirements under these laws, and established priority review vouchers for rare pediatric diseases. Pursuant to the Consolidated Appropriations Act of 2021, the FDA's authority to award rare pediatric disease vouchers has been extended until September 30, 2024, and until September 30, 2026 for products that receive rare pediatric disease designation by September 30, 2024.

Orphan Drug Designation and Exclusivity

Under the Orphan Drug Act, the FDA may designate a drug product as an "orphan drug" if it is intended to treat a rare disease or condition (generally meaning that it affects fewer than 200,000 individuals in the United States, or more in cases in which there is no reasonable expectation that the cost of developing and making a drug product available in the United States for treatment of the disease or condition will be recovered from sales of the product). A company must request orphan product designation before submitting an NDA. If the request is granted, the FDA will disclose the identity of the therapeutic agent and its potential use. Orphan product designation does not convey any advantage in or shorten the duration of the regulatory review and approval process, but the product will be entitled to orphan product exclusivity, meaning that the FDA may not approve any other applications for the same product for the same indication for seven years, except in certain limited circumstances. Competitors may receive approval of different products for the indication for which the orphan product has exclusivity and may obtain approval for the same product but for a different indication. If a drug or drug product designated as an orphan product ultimately receives regulatory approval for an indication broader than what was designated in its orphan product application, it may not be entitled to exclusivity. The 21st Century Cures Act, which became law in December 2016, expanded the types of studies that qualify for orphan drug grants. Orphan drug designation also may qualify an applicant for federal and possibly state tax credits relating to research and development costs.

Post-Marketing Requirements

Following approval of a new drug, a pharmaceutical company and the approved drug are subject to continuing regulation by the FDA, including, among other things, monitoring and recordkeeping activities, reporting to the applicable regulatory authorities of adverse experiences with the drug, providing the regulatory authorities with updated safety and efficacy information, drug sampling and distribution requirements, and complying with applicable promotion and advertising requirements.

Prescription drug advertising is subject to federal, state and foreign regulations. In the United States, the FDA regulates prescription drug promotion, including standards for direct-to-consumer advertising, restrictions on promoting drugs for uses or in patient populations that are not described in the drug's approved labeling (known as "off-label use"), limitations on industry-sponsored scientific and educational activities, and requirements for promotional activities involving the internet. Although physicians may legally prescribe drugs for off-label uses, manufacturers may not market or promote such off-label uses. Prescription drug promotional materials must be submitted to the FDA in conjunction with their first use. Modifications or enhancements to the drug or its labeling or changes of the site of manufacture are often subject to the approval of the FDA and other regulators, which may or may not be received or may result in a lengthy review process. Any distribution of prescription drugs and pharmaceutical samples also must comply with the U.S. Prescription Drug Marketing Act, a part of the FDCA.

In the United States, once a drug is approved, its manufacture is subject to comprehensive and continuing regulation by the FDA. The FDA regulations require that drugs be manufactured in specific approved facilities and in accordance with cGMP. Applicants may also rely on third parties for the production of clinical and commercial quantities of drugs, and these third parties must operate in accordance with cGMP regulations. cGMP regulations require among other things, quality control and quality assurance as well as the corresponding maintenance of records and documentation and the obligation to investigate and correct any deviations from cGMP. Drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMP and other laws. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance. These regulations also impose certain organizational, procedural and documentation requirements with respect to manufacturing and quality assurance activities. NDA holders using third-party contract manufacturers, laboratories or packagers are responsible for the selection and monitoring of qualified firms, and, in certain circumstances, qualified suppliers to these firms. These firms and, where applicable, their suppliers are subject to inspections by the FDA at any time, and the discovery of violative conditions, including failure to conform to cGMP, could result in enforcement actions that interrupt the operation of any such facilities or the ability to distribute drugs manufactured, processed or tested by them. Discovery of problems with a drug after approval may result in restrictions on a drug, manufacturer, or holder of an approved NDA, including, among other things, recall or withdrawal of the drug from the market, and may require substantial resources to correct.

The FDA also may require Phase IV testing, risk minimization action plans and post-marketing surveillance to monitor the effects of an approved drug or place conditions on an approval that could restrict the distribution or use of the drug. Discovery of previously unknown problems with a drug or the failure to comply with applicable FDA requirements can have negative consequences, including adverse publicity, judicial or administrative enforcement, warning letters from the FDA, mandated corrective advertising or communications with doctors, and civil or criminal penalties, among others. Newly discovered or developed safety or effectiveness data may require changes to a drug's approved labeling, including the addition of new warnings and contraindications, and also may require the implementation of other risk management measures. Also, new government requirements, including those resulting from new legislation, may be established, or the FDA's policies may change, which could delay or prevent regulatory approval of our drugs under development.

Other U.S. Regulatory Matters

Manufacturing, sales, promotion and other activities following drug approval are also subject to regulation by numerous regulatory authorities in addition to the FDA, including, in the United States, the Department of Justice, Centers for Medicare & Medicaid Services, other divisions of the Department of Health and Human Services, the Drug Enforcement Administration for Controlled Substances, the Consumer Product Safety Commission, the Federal Trade Commission, the Occupational Safety & Health Administration, the Environmental Protection Agency and state and local governments. In the United States, sales, marketing and scientific/educational programs must also comply with state and federal fraud and abuse laws. Pricing and rebate programs must comply with the Medicaid rebate requirements of the U.S. Omnibus Budget Reconciliation Act of 1990 and more recent requirements in the Affordable Care Act. If drugs are made available to authorized users of the Federal Supply Schedule of the General Services Administration, additional laws and requirements apply. The handling of any controlled substances must comply with the U.S. Controlled Substances Act and Controlled Substances Import and Export Act. Drugs must meet applicable child-resistant packaging requirements under the U.S. Poison Prevention Packaging Act. Manufacturing, sales, promotion and other activities are also potentially subject to federal and state consumer protection and unfair competition laws.

The distribution of pharmaceutical drugs is subject to additional requirements and regulations, including extensive record-keeping, licensing, storage and security requirements intended to prevent the unauthorized sale of pharmaceutical drugs.

The failure to comply with regulatory requirements subjects firms to possible legal or regulatory action. Depending on the circumstances, failure to meet applicable regulatory requirements can result in criminal prosecution, fines or other penalties, injunctions, recall or seizure of drugs, total or partial suspension of production, denial or withdrawal of product approvals, or refusal to allow a firm to enter into supply contracts, including government contracts. In addition, even if a firm complies with FDA and other requirements, new information regarding the safety or efficacy of a product could lead the FDA to modify or withdraw product approval. Prohibitions or restrictions on sales or withdrawal of future products marketed by us could materially affect our business in an adverse way.

Changes in regulations, statutes or the interpretation of existing regulations could impact our business in the future by requiring, for example: (i) changes to our manufacturing arrangements; (ii) additions or modifications to product labeling; (iii) the recall or discontinuation of our products; or (iv) additional record-keeping requirements. If any such changes were to be imposed, they could adversely affect the operation of our business.

U.S. Patent Term Restoration and Marketing Exclusivity

Depending upon the timing, duration and specifics of the FDA approval of our drug candidates, some of our U.S. patents may be eligible for limited patent term extension under the Hatch-Waxman Act. The Hatch-Waxman Act permits a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of an NDA plus the time between the submission date of an NDA and the approval of that application. Only one patent applicable to an approved drug is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. The USPTO, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. In 2018, the FDA advanced policies aimed at promoting drug competition and patient access to generic drugs, such as issuing guidance about making complex generic drugs and the circumstances in which approval of a generic product application may be delayed.

Marketing exclusivity provisions under the FDCA can also delay the submission or the approval of certain marketing applications. The FDCA provides a five-year period of non-patent marketing exclusivity within the United States to the first applicant to obtain approval of an NDA for a NCE. A drug is a NCE if the FDA has not previously approved any other new drug containing the same active moiety, which is the molecule or ion responsible for the action of the drug substance. During the exclusivity period, the FDA may not accept for review an ANDA, or a 505(b)(2) NDA submitted by another company for another drug based on the same active moiety, regardless of whether the drug is intended for the same indication as the original innovator drug or for another indication, where the applicant does not own or have a legal right of reference to all the data required for approval. However, an application may be submitted after four years if it contains a certification of patent invalidity or non-infringement to one of the patents listed with the FDA by the innovator NDA holder. Specifically, the applicant must certify with respect to each relevant patent that: the required patent information has not been filed; the listed patent has expired; the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration, or the listed patent is invalid, unenforceable or will not be infringed by the new product. A certification that the new product will not infringe the already approved product's listed patents or that such patents are invalid or unenforceable is called a Paragraph IV certification. If the applicant does not challenge the listed patents or indicate that it is not seeking approval of a patented method of use, the ANDA application will not be approved until all the listed patents claiming the referenced product have expired. If the ANDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of 30 months after the receipt of the Paragraph IV notice, expiration of the patent, or a decision in the infringement case that is favorable to the ANDA applicant. To the extent that the Section 505(b)(2) applicant relies on prior FDA findings of safety and efficacy, the applicant is required to certify to the FDA concerning any patents listed for the previously approved product in the Orange Book to the same extent that an ANDA applicant would.

The FDCA also provides three years of marketing exclusivity for an NDA, or supplement to an existing NDA if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are deemed by the FDA to be essential to the approval of the application, for example new indications, dosages or strengths of an existing drug. This three-year exclusivity covers only the modification for which the drug received approval on the basis of the new clinical investigations and does not prohibit the FDA from approving ANDAs for drugs containing the active agent for the original indication or condition of use. Five-year and three-year exclusivity will not delay the submission or approval of a full NDA. However, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the pre-clinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness. Orphan drug exclusivity, as described above, may offer a seven-year period of marketing exclusivity, except in certain circumstances. Pediatric exclusivity is another type of regulatory market exclusivity in the United States. Pediatric exclusivity, if granted, adds six months to existing exclusivity periods and patent terms. This six-month exclusivity, which runs from the end of other exclusivity protection or patent term, may be granted based on the voluntary completion of a pediatric trial in accordance with an FDA-issued "Written Request" for such a trial.

Rest of the World Regulation of Pharmaceutical Product Development and Approval

For other countries outside of China and the United States, such as countries in Europe, Latin America or other parts of Asia, the requirements governing the conduct of clinical trials, drug licensing, pricing and reimbursement vary from country to country. In all cases the clinical trials must be conducted in accordance with GCP requirements and the applicable regulatory requirements and ethical principles.

If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

Coverage and Reimbursement

PRC Coverage and Reimbursement

Historically, most of Chinese healthcare costs have been borne by patients out-of-pocket, which has limited the growth of more expensive pharmaceutical products. However, in recent years the number of people covered by government and private insurance has increased. According to the PRC National Healthcare Security Administration, as of December 31, 2020, approximately 1.4 billion employees and residents in China were enrolled in the national medical insurance program, with participation rates remaining steadily above 95%. The PRC government has announced a plan to give every person in China access to basic healthcare by year 2020. In 2020, total income of the National Basic Medical Insurance Fund (including maternity insurance) reached RMB2,484.6 billion, an increase of 1.7% over the previous year and accounting for about 2.4% of GDP.

Reimbursement under the National Medical Insurance Program

The National Medical Insurance Program was adopted pursuant to the Decision of the State Council on the Establishment of the Urban Employee Basic Medical Insurance Program issued by the State Council on December 14, 1998, under which all employers in urban cities are required to enroll their employees in the basic medical insurance program and the insurance premium is jointly contributed by the employers and employees. The State Council promulgated Guiding Opinions of the State Council about the Pilot Urban Resident Basic Medical Insurance on July 10, 2007, under which urban residents of the pilot district, rather than urban employees, may voluntarily join Urban Resident Basic Medical Insurance. The State Council expected the Pilot Urban Resident Basic Medical Insurance to cover the whole nation by 2010.

Participants of the National Medical Insurance Program and their employers, if any, are required to contribute to the payment of insurance premiums on a monthly basis. Program participants are eligible for full or partial reimbursement of the cost of medicines included in the NRDL. The Notice Regarding the Tentative Measures for the Administration of the Scope of Medical Insurance Coverage for Pharmaceutical Products for Urban Employees, jointly issued by several authorities including the Ministry of Labor and Social Security and the MOF, among others, on May 12, 1999, provides that a pharmaceutical product listed in the NRDL must be clinically needed, safe, effective, reasonably priced, easy to use, available in sufficient quantity, and must meet the following requirements:

- it is set forth in the Pharmacopoeia of the PRC;
- it meets the standards promulgated by the NMPA; and

- if imported, it is approved by the NMPA for import.

Factors that affect the inclusion of a pharmaceutical product in the NRDL include whether the product is consumed in large volumes and commonly prescribed for clinical use in the PRC and whether it is considered to be important in meeting the basic healthcare needs of the general public.

The PRC Ministry of Labor and Social Security, together with other government authorities, has the power to determine inclusion of medicines in the NRDL (also referred to as the "Drug Catalog"), which is divided into two parts, Category A and Category B. Per the Notice on the "National Basic Medical Insurance, Work Injury Insurance and Maternity Insurance Drug Catalog (2021)" issued by the National Healthcare Security Administration and the Ministry of Labor and Social Security, local authorities are required to strictly implement the Drug Catalog (2021) and must not adjust the defined payment conditions and the classification of drugs in the Drug Catalog.

Patients purchasing medicines included in Category A of the NRDL are entitled to reimbursement of the entire amount of the purchase price. Patients purchasing medicines included in Category B of the NRDL are required to pay a certain percentage of the purchase price and obtain reimbursement for the remainder of the purchase price. The percentage of reimbursement for Category B medicines differs from region to region in the PRC.

The total amount of reimbursement for the cost of medicines, in addition to other medical expenses, for an individual participant under the National Medical Insurance Program in a calendar year is capped at the amounts in such participant's individual account under such program. The amount in a participant's account varies, depending on the amount of contributions from the participant and his or her employer.

National Essential Medicines List

On August 18, 2009, MOH and eight other ministries and commissions in the PRC issued the Provisional Measures on the Administration of the National Essential Medicines List, which was later amended in 2015, and the Guidelines on the Implementation of the Establishment of the National Essential Medicines System, which aim to promote essential medicines sold to consumers at fair prices in the PRC and ensure that the general public in the PRC has equal access to the drugs contained in the National Essential Medicines List. MOH promulgated the National Essential Medicines List (Catalog for the Basic Healthcare Institutions) on August 18, 2009, and promulgated the revised National Essential Medicines List on March 13, 2013 and September 30, 2018. According to these regulations, basic healthcare institutions funded by government, which primarily include county-level hospitals, county-level Chinese medicine hospitals, rural clinics and community clinics, shall store up and use drugs listed in the National Essential Medicines List. Per the Opinions of the General Office of the State Council on Improving the National Essential Medicines System, issued and effective on September 13, 2018, with respect to the qualifying drugs on the National Essential Medicines List, the medical insurance department shall prioritize their inclusion in the NDRL and adjust their classifications as Category A or B, respectively, in accordance with the stipulated procedures.

Price Controls

According to the PRC Drug Administration Law and the Implementing Measures of the PRC Drug Administration Law, pharmaceutical products are subject to a directive pricing system or to be adjusted by the market. Per the Notice of the National Healthcare Security Administration on issuing the "Opinions on Doing a Good Job in the Current Drug Price Management", or the Notice on Current Drug Price Management, effective on November 26, 2019, government guidance prices are to be implemented for narcotic drugs and Class I psychotropic drugs, while prices of other drugs are to be determined by the market. Government guidance prices refer to prices as fixed by business operators according to benchmark prices and ranges of the prices as set by the government department in charge of pricing or other related departments. According to the Pricing Catalogue Initiated by the Central Government (2020 Edition), which was promulgated by the NDRC and effective on May 1, 2020, the National Healthcare Security Administration shall be responsible for setting prices of narcotic drugs and Class I psychotropic drugs.

Further, pursuant to the Notice Regarding Further Improvement of the Order of Market Price of Pharmaceutical Products and Medical Services, or the Market Price Notice, jointly promulgated by the NDRC, the State Council Legislative Affairs Office and the State Council Office for Rectifying, the MOH, the NMPA, the MOFCOM, the MOF and Ministry of Labor and Social Security on May 19, 2006, the PRC government exercises price control over pharmaceutical products included in the NRDL and made an overall adjustment of their prices by reducing the retail price of certain overpriced pharmaceutical products and increasing the retail price of certain underpriced pharmaceutical products in demand for clinical use but that have not been produced in large quantities by manufacturers due to their low retail price level. In particular, the retail price charged by hospitals at the county level or above may not exceed 115% of the procurement cost of the relevant pharmaceutical products or 125% for Chinese herbal pieces. The Market Price Notice has been abolished per the NDRC Decision to Abolish Standardized Pricing Directories, effective May 20, 2021.

On February 9, 2015, the General Office of the State Council issued the Guiding Opinion on Enhancing Consolidated Procurement of Pharmaceutical Products by Public Hospitals, or the Opinion. The Opinion encourages public hospitals to consolidate their demands and to play a more active role in the procurement of pharmaceutical products. Hospitals are encouraged to directly settle the prices of pharmaceutical products with manufacturers. Consolidated procurement of pharmaceutical products should facilitate hospital reform, reduce patient costs, prevent corrupt conducts, promote fair competition and induce the healthy growth of the pharmaceutical industry. According to the Opinion, provincial tendering processes will continue to be used for the pricing of essential drugs and generic drugs with significant demands, and transparent multi-party price negotiation will be used for some patented drugs and exclusive drugs.

On April 26, 2014, the NDRC issued the Notice on Issues concerning Improving the Price Control of Low Price Drugs, or the Low Price Drugs Notice, together with the Low Price Drug List, or LPDL. According to the Low Price Drugs Notice, for drugs with relatively low average daily costs within the current government-guided pricing scope (low price drugs), the maximum retail prices set by the government were cancelled. Within the standards of average daily costs, the specific purchase and sale prices are fixed by the producers and operators based on the drug production costs, market supply and demand and market competition. The standards of average daily costs of low price drugs were determined by the NDRC in consideration of the drug production costs, market supply and demand and other factors and based on the current maximum retail prices set by the government (or the national average bid-winning retail prices where the government does not set the maximum retail prices) and the average daily dose calculated according to the package insert. Under the Low Price Drugs Notice, the standards for the daily cost of low price chemical pharmaceuticals and of low price traditional Chinese medicine pharmaceuticals were less than RMB3.0 ($0.46) per day and RMB5.0 ($0.76) per day respectively. The Low Price Drugs Notice has been abolished per the NDRC Decision to Abolish Standardized Pricing Directories, effective May 20, 2021.

On May 4, 2015, the NDRC, the National Health and Family Planning Commission, the NMPA, MOFCOM and three other departments issued Opinions on Promoting Drug Pricing Reform. Under these opinions, beginning on June 1, 2015, the restrictions on the prices of the drugs that were subject to government pricing were cancelled except for narcotic drugs and Class I psychotropic drugs which remained subject to maximum factory prices and maximum retail prices set by the NDRC, and following the November 2019 Notice on Current Drug Price Management, narcotic drugs and Class I psychotropic drugs prices have transitioned towards government guidance prices. The medical insurance regulatory authority now has the power to prescribe the standards, procedures, basis and methods of the payment for drugs paid by medical insurance funds. The prices of patented drugs are set through transparent and public negotiation among multiple parties. The prices for blood products not listed in the NRDL, immunity and prevention drugs that are purchased by the Chinese government in a centralized manner, and AIDS antiviral drugs and contraceptives provided by the Chinese government for free, are set through a tendering process. Except as otherwise mentioned above, the prices for other drugs may be determined by the manufacturers and the operators on their own on the basis of production or operation costs and market supply and demand.

Centralized Procurement and Tenders

The Guiding Opinions concerning the Urban Medical and Health System Reform, promulgated on February 21, 2000, aim to provide medical services with reasonable price and quality to the public through the establishment of an urban medical and health system. One of the measures used to realize this aim is the regulation of the purchasing process of pharmaceutical products by medical institutions. Accordingly, the MOH and other relevant government authorities have promulgated a series of regulations and releases in order to implement the tender requirements.

According to the Notice on Issuing Certain Regulations on the Trial Implementation of Centralized Tender Procurement of Drugs by Medical Institutions promulgated on July 7, 2000 and the Notice on Further Improvement on the Implementation of Centralized Tender Procurement of Drugs by Medical Institutions promulgated on August 8, 2001, medical institutions established by county or higher level government are required to implement centralized tender procurement of drugs.

The MOH promulgated the Working Regulations of Medical Institutions for Procurement of Drugs by Centralized Tender and Price Negotiations (for Trial Implementation), or the Centralized Procurement Regulations, on March 13, 2002, and promulgated Sample Document for Medical Institutions for Procurement of Drugs by Centralized Tender and Price Negotiations (for Trial Implementation), or the Centralized Tender Sample Document in November 2001, as amended in 2010, to implement the tender process requirements and ensure the requirements are followed uniformly throughout the country. The Centralized Tender Regulations and the Centralized Tender Sample Document provide rules for the tender process and negotiations of the prices of drugs, operational procedures, a code of conduct and standards or measures of evaluating bids and negotiating prices. On January 17, 2009, the MOH, the NMPA and other four national departments jointly promulgated the Opinions on Further Regulating Centralized Procurement of Drugs by Medical Institutions. According to the notice, public medical institutions owned by the government at the county level or higher or owned by state-owned enterprises (including state-controlled enterprises) shall purchase pharmaceutical products through centralized procurement. Each provincial government shall formulate its catalogue of drugs subject to centralized procurement. Specifically, the procurement could be achieved through public tendering, online bidding, centralized price negotiations and online competition platform. Except for drugs in the National Essential Medicines List (the procurement of which shall comply with the relevant rules on the National Essential Medicines List), certain pharmaceutical products which are under the national government's special control and traditional Chinese medicines, in principle, all drugs used by public medical institutions shall be covered by the catalogue of drugs subject to centralized procurement. On July 7, 2010, the MOH and six other ministries and commissions jointly promulgated the Working Regulations of Medical Institutions for Centralized Procurement of Drugs to further regulate the centralized procurement of drugs and clarify the code of conduct of the parties in centralized drug procurement.

The centralized tender process takes the form of public tender operated and organized by provincial or municipal government agencies in principle is conducted once every year in all provinces and cities in China. Drug manufacturing enterprises, in principle, shall bid directly for the centralized tender process. Certain related parties, however, may be engaged to act as bidding agencies. Such intermediaries are not permitted to engage in the distribution of drugs and must have no conflict of interest with the organizing government agencies. The bids are assessed by a committee composed of pharmaceutical experts who will be randomly selected from a database of experts approved by the relevant government authorities. The committee members assess the bids based on a number of factors, including but not limited to, bid price, product quality, clinical effectiveness, qualifications and reputation of the manufacturer, and after-sale services. Only pharmaceuticals that have won in the centralized tender process may be purchased by public medical institutions funded by government in the relevant region.

4+7 Quality Consistency Evaluation

On November 15, 2018, China's Joint Procurement Office published its Paper on Centralized Drug Procurement in "4+7 Cities," known as the 4+7 Quality Consistency Evaluation process, or 4+7 QCE. The 4+7 QCE initiative is aimed at driving consolidation in the fragmented generic drug market in China. The 4+7 QCE initiative began as a pilot program in 11 cities: Beijing, Tianjin, Shanghai, Chongqing, Shenyang, Dalian, Xiamen, Guangzhou, Shenzhen, Chengdu and Xi'an. Under this pilot program, the public medical institutions in these 11 cities bulk-buy certain generic drugs together, forcing companies to bid for contracts and driving down prices. The 4+7 QCE initiative has expanded nationwide and now covers more varieties of drugs. On September 1, 2019, the Joint Procurement Office published its Paper on Centralized Drug Procurement in Alliance Areas (GY-YD2019-1), such areas covering 25 provinces and regions across China. On December 29, 2019, the Joint Procurement Office published its Paper on Nationwide Centralized Drug Procurement (GY-YD2019-2), promoting procurement nationwide, and on January 13, 2020, the National Healthcare Security Administration, the NHC, the NMPA, the Ministry of Industrial and Information Technology and the Logistics Support Department of the Central Military Commission promulgated the Notice on the Commencement of the Second Batch of State Organized Centralized Drug Procurement and Use, which states that the second batch of national organization of centralized procurement and use of drugs would not be carried out in selected areas but nationwide.

U.S. Coverage and Reimbursement

Successful sales of our products or drug candidates in the U.S. market, if approved, will depend, in part, on the extent to which our drugs will be covered by third-party payors, such as government health programs, commercial insurance and managed healthcare organizations. Patients who are provided with prescriptions as part of their medical treatment generally rely on such third-party payors to reimburse all or part of the costs associated with their prescriptions and therefore adequate coverage and reimbursement from such third-party payors are critical to new product success. These third-party payors are increasingly reducing reimbursements for medical drugs and services. Additionally, the containment of healthcare costs has become a priority of federal and state governments, and the prices of drugs have been a focus in this effort. The U.S. government, state legislatures and foreign governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement, requirements for substitution of generic drugs, and pricing transparency requirements. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit our net revenue and results. Decreases in third-party reimbursement for our drug candidates, if approved, or a decision by a third-party payor to not cover our drug candidates could reduce physician usage of such drugs and have a material adverse effect on our sales, results of operations and financial condition.

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the MMA, established the Medicare Part D program to provide a voluntary prescription drug benefit to Medicare beneficiaries. Under Part D, Medicare beneficiaries may enroll in prescription drug plans offered by private entities that provide coverage of outpatient prescription drugs. Unlike Medicare Part A and B, Part D coverage is not standardized. Part D prescription drug plan sponsors are not required to pay for all covered Part D drugs, and each drug plan can develop its own drug formulary that identifies which drugs it will cover and at what tier or level. However, Part D prescription drug formularies must include drugs within each therapeutic category and class of covered Part D drugs, though not necessarily all the drugs in each category or class. Any formulary used by a Part D prescription drug plan must be developed and reviewed by a pharmacy and therapeutic committee. Medicare payment for some of the costs of prescription drugs may increase demand for drugs for which we receive regulatory approval. However, any negotiated prices for our drugs covered by a Part D prescription drug plan will likely be lower than the prices we might otherwise obtain. Moreover, while the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own payment rates. Any reduction in payment that results from the MMA may result in a similar reduction in payments from non-governmental payors.

The American Recovery and Reinvestment Act of 2009 provides funding for the federal government to compare the effectiveness of different treatments for the same illness. The plan for the research was published in 2012 by the U.S. Department of Health and Human Services, the Agency for Healthcare Research and Quality and the National Institutes for Health, and periodic reports on the status of the research and related expenditures are made to Congress. Although the results of the comparative effectiveness studies are not intended to mandate coverage policies for public or private payors, if third-party payors do not consider a drug to be cost-effective compared to other available therapies, they may not cover such drugs as a benefit under their plans or, if they do, the level of payment may not be sufficient.

The Affordable Care Act, enacted in March 2010, has had a significant impact on the health care industry. The Affordable Care Act expanded coverage for the uninsured while at the same time containing overall healthcare costs. With regard to pharmaceutical products, the Affordable Care Act, among other things, addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected, increased the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extended the rebate program to individuals enrolled in Medicaid managed care organizations, established annual fees and taxes on manufacturers of certain branded prescription drugs, and created a new Medicare Part D coverage gap discount program, in which, beginning in 2019, manufacturers must agree to offer 70% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D. The Bipartisan Budget Act of 2018 made certain changes to Medicare Part D coverage, including changing the date when the Medicare Part D coverage gap is eliminated from 2020 to 2019, sunsetting the exclusion of biosimilars from the Medicare Part D coverage gap discount program in 2019 and reallocating responsibility for discounted pricing under the Medicare Part D coverage gap discount program from third-party payors to pharmaceutical companies. In December 2017, Congress also repealed the "individual mandate," which was an Affordable Care Act requirement that individuals obtain healthcare insurance coverage or face a penalty. This repeal could affect the total number of patients who have coverage from third-party payors that reimburse for use of our products. In July 2021, the U.S. Supreme Court dismissed a constitutional challenge to the Affordable Care Act brought by a group of Republican attorneys general seeking to invalidate the law in its entirety because of Congress's repeal of the individual mandate.

On December 14, 2018, a U.S. District Court judge in Texas ruled that the Affordable Care Act is unconstitutional in its entirety because of Congress's repeal of the individual mandate. On December 18, 2019, the U.S. Court of Appeals for the Fifth Circuit affirmed the portion of the district court's ruling declaring the individual mandate unconstitutional and remanded for the district court to conduct analysis in the first instance on which provisions of the statute are severable from it and thus remain intact. The U.S. Supreme Court agreed to hear the case and a decision is expected by the Spring of 2021.

In addition, other legislative and regulatory changes have been proposed and adopted in the United States since the Affordable Care Act was enacted that affect reimbursement for prescription drugs. On August 2, 2011, the Budget Control Act of 2011 among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, started in April 2013. Section 4408 of the CARES Act temporarily suspended Medicare sequestration during the period of May 1, 2020 through December 31, 2021, while extending the Medicare sequestration sunset date through 2030. On January 2, 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which among other things, also reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

Regulations adopted by the Centers for Medicare & Medicaid Services or CMS grant Medicare Part B plans authority to apply new cost control measures to steer patients toward lower-priced drug products prior to covering non-preferred, more expensive products. This could potentially have the result of reducing coverage of our products under Medicare Part B.

In addition, other proposed legislative and regulatory changes could affect reimbursement for prescription drugs. In January 2017, the Medicare Prescription Drug Price Negotiation Act was proposed in Congress, which would require the government to negotiate Medicare prescription drug prices with pharmaceutical companies. In October 2017, a similar bill, the Medicare Drug Price Negotiation Act of 2017 was proposed in Congress. In November 2017, the CMS announced a Final Rule that would adjust the applicable payment rate as necessary for certain separately payable drugs and biologicals acquired under the 340B Program from average sales price plus 6% to average sales price minus 22.5%. Congress and the U.S. administration continue to evaluate other proposals that could affect third-party reimbursement for our drug candidates, if approved.

In October 2020, the U.S. Department of Health and Human Services and the FDA issued a final rule and guidance concerning two new pathways for importing lower-cost drugs into the United States. The final rule allows certain prescription drugs to be imported from Canada, and the guidance describes procedures for drug manufacturers to facilitate the importation of FDA-approved drugs and biologics manufactured abroad and originally intended for sale in a foreign country into the United States.

In November 2020, the Department of Health and Human Services, under the outgoing Trump administration, issued a rule eliminating the safe harbor shielding Medicare Part D rebates to pharmacy benefit managers from the Anti-Kickback Statute. In response to litigation brought by a trade association on behalf of pharmacy benefit managers, the Biden administration agreed to delay the rule's effective date until January 1, 2023. On November 15, 2021, President Biden signed into law the Infrastructure Investment and Jobs Act, which imposed a moratorium until January 1, 2026 at the earliest on the rule removing rebates from safe harbor protection under the Anti-Kickback Statute.

In November 2021, the U.S. House of Representatives passed the Build Back Better Act. Under this Act, the federal government would be permitted to negotiate prices for certain Medicare Part B and Part D drugs, and manufacturers would be required to pay Medicare rebates for some Part B and many Part D drugs if their prices increased faster than inflation. To date, the U.S. Senate has not passed the Act, and it is unclear whether the Act or component parts of the Act will ultimately be enacted. Such legislative and regulatory changes could have the effect of lowering the level of coverage or reimbursement for our products.

Rest of the World Coverage and Reimbursement

In some foreign countries, the proposed pricing for a drug must be approved before it may be lawfully marketed. The requirements governing drug pricing vary widely from country to country. For example, the E.U. provides options for its member states to restrict the range of medicinal drugs for which their national health insurance systems provide reimbursement and to control the prices of medicinal drugs for human use. A member state may approve a specific price for the medicinal drug or it may instead adopt a system of direct or indirect controls on the profitability of our company placing the medicinal drug on the market. Historically, drugs launched in the E.U. do not follow price structures of the United States and generally tend to be significantly lower.

Other Healthcare Laws

Other PRC Healthcare Laws

Advertising of Pharmaceutical Products

In accordance with the Interim Administrative Measures for the Censorship of Advertisements for Drugs, Medical Devices, Health Food and Formula Food for Special Medical Purposes effective from March 1, 2020, the State Administration for Market Regulation is responsible for organizing and guiding the censorship of advertisements for drugs, medical devices, health foods and formula foods for special medical purposes. Any advertisement for drugs, medical devices, health food or formula food for special medical purposes shall indicate the advertisement approval number in a prominent position. The validity period of the advertisement approval number for drugs, medical devices, health food and formula food for special medical purposes shall be consistent with the shortest period of validity of the product registration certificate, record-filing certificate, or production license. Where no period of validity is prescribed in the product registration certificate, record-filing certificate or production license, the period of validity of the advertisement approval number shall be two years.

Packaging of Pharmaceutical Products

According to the Measures for The Administration of Pharmaceutical Packaging, effective on September 1, 1988, pharmaceutical packaging must comply with the provisions of the national standard and professional standard. If there are no standards, the enterprise can formulate its own standard after obtaining the approval of the provincial level drug administration or bureau of standards. The enterprise shall reapply to the relevant authorities if it needs to change the packaging standard. Drugs without packing must not be sold in PRC (except for drugs needed by the army).

Labor Protection

Under the Labor Law of the PRC, effective on January 1, 1995 and subsequently amended on August 27, 2009 and December 29, 2018, the Labor Contract Law of the PRC, effective on January 1, 2008 and subsequently amended on December 28, 2012, and the Implementing Regulations of the Labor Contract Law of the PRC, effective on September 18, 2008, employers must establish a comprehensive management system to protect the rights of their employees, including a system governing occupational health and safety to provide employees with occupational training to prevent occupational injury, and employers are required to truthfully inform prospective employees of the job description, working conditions, location, occupational hazards and status of safe production as well as remuneration and other conditions as requested by the Labor Contract Law of the PRC.

Pursuant to the Law of Manufacturing Safety of the People's Republic of China effective on November 1, 2002 and subsequently amended on December 1, 2014 and September 1, 2021, manufacturers must establish a comprehensive management system to ensure manufacturing safety in accordance with applicable laws and regulations. Manufacturers not meeting relevant legal requirements are not permitted to commence their manufacturing activities.

Pursuant to the Administrative Measures for Production effective on March 1, 2011, manufacturers of pharmaceutical products are required to establish production safety and labor protection measures in connection with the operation of their manufacturing equipment and manufacturing process.

Pursuant to applicable PRC laws, rules and regulations, including the Social Insurance Law which became effective on July 1, 2011 and subsequently amended on December 29, 2018, the Interim Regulations on the Collection and Payment of Social Security Funds which became effective on January 22, 1999 and subsequently amended on March 24, 2019, the Interim Measures concerning the Maternity Insurance which became effective on January 1, 1995 and the Regulations on Work-related Injury Insurance which became effective on January 1, 2004 and were subsequently amended on December 20, 2010, employers are required to contribute, on behalf of their employees, to a number of social security funds, including funds for basic pension insurance, unemployment insurance, basic medical insurance, work-related injury insurance, and maternity insurance. If an employer fails to make social insurance contributions timely and in full, the social insurance collecting authority will order the employer to make up outstanding contributions within the prescribed time period and impose a late payment fee at the rate of 0.05% per day from the date on which the contribution becomes due. If such employer fails to make social insurance registration, the social insurance collecting authority will order the employer to correct within the prescribed time period. The relevant administrative department may impose a fine equivalent to three times the overdue amount and management personnel who are directly responsible can be fined RMB500 ($76.43) to RMB3,000 ($458.02) if the employer fails to correct within the prescribed time period.

Commercial Bribery

Medical production and operation enterprises involved in criminal, investigation or administrative procedure for commercial bribery will be listed in the Adverse Records of Commercial Briberies by provincial health and family planning administrative department. Pursuant to the Provisions on the Establishment of Adverse Records of Commercial Briberies in the Medicine Purchase and Sales Industry enforced on March 1, 2014 by the National Health and Family Planning Commission, if medical production and operation enterprises are listed into the Adverse Records of Commercial Briberies for the first time, their production shall not be purchased by public medical institutions, and medical and health institutions receiving financial subsidies in local provincial regions for a period of two years following the publication of the Adverse Records, and public medical institutions, and medical and health institutions receiving financial subsidies in other provinces shall lower their rating in bidding or purchasing process. If medical production and operation enterprises are listed into the Adverse Records of Commercial Briberies twice or more times in five years, their production may not be purchased by public medical institutions, and medical and health institutions receiving financial subsidies nationwide in two years from public of the record.

As advised by our PRC legal advisor, from a PRC law perspective, a pharmaceutical company will not be penalized by the relevant PRC government authorities merely by virtue of having contractual relationships with distributors or third-party promoters who are engaged in bribery activities, so long as such pharmaceutical company and its employees are not utilizing the distributors or third-party promoters for the implementation of, or acting in conjunction with them in, the prohibited bribery activities. In addition, a pharmaceutical company is under no legal obligation to monitor the operating activities of its distributors and third-party promoters, and will not be subject to penalties or sanctions by relevant PRC government authorities as a result of failure to monitor their operating activities.

Product Liability

In addition to the strict new drug approval process, certain PRC laws have been promulgated to protect the rights of consumers and to strengthen the control of medical products in the PRC. Under current PRC law, manufacturers and vendors of defective products in the PRC may incur liability for loss and injury caused by such products. Pursuant to the Civil Code of the PRC, or the PRC Civil Code, promulgated on May 28, 2020 and effective on January 1, 2021, a defective product which causes property damage or physical injury to any person may subject the manufacturer or vendor of such product to civil liability for such damage or injury.

On February 22, 1993, the Product Quality Law of the PRC, or the Product Quality Law, was promulgated aiming to define responsibilities for product quality, to protect the legitimate rights and interests of the end-users and consumers and to strengthen the supervision and control of the quality of products. The Product Quality Law was amended by the Ninth National People's Congress on July 8, 2000 and was later amended by the Eleventh National People's Congress on August 27, 2009 and the Thirteenth National People's Congress on December 29, 2018. Pursuant to the amended Product Quality Law, manufacturers who produce defective products may be subject to civil or criminal liability and have their business licenses revoked.

The Law of the PRC on the Protection of the Rights and Interests of Consumers was promulgated on October 13, 1993 and was amended on October 25, 2013 to protect consumers' rights when they purchase or use goods and accept services. All business operators must comply with this law when they manufacture or sell goods and/or provide services to customers. Under the amendment on October 25, 2013, all business operators shall pay high attention to protect the customers' privacy which they obtain during the business operation. In addition, in extreme situations, pharmaceutical product manufacturers and operators may be subject to criminal liabilities under applicable laws of the PRC if their goods or services lead to the death or injuries of customers or other third parties.

Pursuant to the PRC Civil Code, if damages to other persons are caused by defective products that are resulted from the fault of a third party such as the parties providing transportation or warehousing, the producers and the sellers of the products have the right to recover their respective losses from such third parties. If defective products are identified after they have been put into circulation, the producers or the sellers shall take remedial measures such as issuance of warning, and recall of products, etc. in a timely manner. The producers or the sellers shall be liable under tort if they cause damages due to their failure to take remedial measures in a timely manner or have not made efforts to take remedial measures, thus causing damages. If the products are produced and sold with known defects, causing deaths or severe damage to the health of others, the infringed party shall have the right to claim respective punitive damages in addition to compensatory damages.

Other PRC National and Provincial-Level Laws and Regulations

We are subject to changing regulations under many other laws and regulations administered by governmental authorities at the national, provincial and municipal levels, some of which are or may become applicable to our business. Our hospital customers are also subject to a wide variety of laws and regulations that could affect the nature and scope of their relationships with us.

For example, regulations control the confidentiality of patients' medical information and the circumstances under which patient medical information may be released for inclusion in our databases, or released by us to third parties. These laws and regulations governing both the disclosure and the use of confidential patient medical information may become more restrictive in the future.

We also comply with numerous additional state and local laws relating to matters such as safe working conditions, manufacturing practices, environmental protection and fire hazard control. We believe that we are currently in compliance with these laws and regulations; however, we may be required to incur significant costs to comply with these laws and regulations in the future. Unanticipated changes in existing regulatory requirements or adoption of new requirements could therefore have a material adverse effect on our business, results of operations and financial condition.

Other U.S. Healthcare Laws

We may also be subject to healthcare regulation and enforcement by the U.S. federal government and the states where we may market our drug candidates, if approved. These laws include, without limitation, state and federal anti-kickback, fraud and abuse, false claims, privacy and security and physician sunshine laws and regulations.

Anti-Kickback Statute

The federal Anti-Kickback Statute prohibits, among other things, any person from knowingly and willfully offering, soliciting, receiving or providing remuneration, directly or indirectly, to induce either the referral of an individual, for an item or service, or the purchase or order of a good or service, for which payment may be made under federal healthcare programs such as the Medicare and Medicaid programs. The majority of states also have anti-kickback laws, which establish similar prohibitions and in some cases may apply to items or services reimbursed by any third-party payor, including commercial insurers. The Anti-Kickback Statute is subject to evolving interpretations. In the past, the government has enforced the Anti-Kickback Statute to reach large settlements with healthcare, pharmaceutical, and biotechnology companies based on a range of financial arrangements with physicians and other healthcare industry entities. A person or entity does not need to have actual knowledge of the Anti-Kickback Statute or specific intent to violate it in order to have committed a violation. Violations of the Anti-Kickback Statute can result in criminal, civil, or administrative liability. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for the purposes of the federal False Claims Act.

False Claims

Additionally, the civil False Claims Act prohibits knowingly presenting or causing the presentation of a false, fictitious or fraudulent claim for payment to the U.S. government. Actions under the False Claims Act may be brought by the U.S. Attorney General or as a qui tam action by a private individual in the name of the government. Analogous state law equivalents may apply and may be broader in scope than the federal requirements. Violations of the False Claims Act can result in very significant monetary penalties and treble damages. The federal government is using the False Claims Act, and the accompanying threat of significant liability, in its investigation and prosecution of pharmaceutical and biotechnology companies throughout the United States, for example, in connection with the violations of the Anti-Kickback Statute, the promotion of products for unapproved uses and other sales and marketing practices. The government has obtained multi-million and multi-billion dollar settlements under the False Claims Act in addition to individual criminal convictions and corporate resolutions under applicable criminal statutes. Given the significant size of actual and potential settlements, it is expected that the government will continue to devote substantial resources to investigating healthcare providers' and manufacturers' compliance with applicable fraud and abuse laws.

The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, also created new federal criminal statutes that prohibit, among other actions, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, including private third-party payors, knowingly and willfully embezzling or stealing from a healthcare benefit program, willfully obstructing a criminal investigation of a healthcare offense, and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. Similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation.

Payments to Physicians

There has also been a recent trend of increased federal and state regulation of payments made to physicians and other healthcare providers. The Affordable Care Act, among other things, imposes new reporting requirements on drug manufacturers for payments made by them to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Failure to submit required information may result in civil monetary penalties of up to an aggregate of $150,000 per year (or up to an aggregate of $1 million per year for "knowing failures"), for all payments, transfers of value or ownership or investment interests that are not timely, accurately and completely reported in an annual submission. Drug manufacturers were required to begin collecting data on August 1, 2013 and submit reports to the government by March 31, 2014 and June 30, 2014, and the 90th day of each subsequent calendar year. Certain states also mandate implementation of compliance programs, impose restrictions on drug manufacturer marketing practices and/or require the tracking and reporting of gifts, compensation and other remuneration to physicians. The federal government has begun to impose penalties on companies that fail to appropriately report required information.

Data Privacy and Security

We may also be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology and Clinical Health Act, or HITECH, and their respective implementing regulations, including the final omnibus rule published on January 25, 2013, imposes specified requirements relating to the privacy, security and transmission of individually identifiable health information. Among other things, HITECH makes HIPAA's privacy and security standards directly applicable to "business associates," defined as independent contractors or agents of covered entities that create, receive, maintain or transmit protected health information in connection with providing a service for or on behalf of a covered entity. HITECH also increased the civil and criminal penalties that may be imposed against covered entities, business associates and possibly other persons, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of personal health information in certain circumstances, many of which differ from each other in significant ways, thus complicating compliance efforts.

PRC Regulation of Foreign Currency Exchange, Offshore Investment and State-Owned Assets

PRC Foreign Currency Exchange

Foreign currency exchange regulation in China is primarily governed by the following rules:

- Foreign Currency Administration Rules (1996), as last amended on August 5, 2008, or the Exchange Rules; and
- Administration Rules of the Settlement, Sale and Payment of Foreign Exchange (1996), or the Administration Rules.

Under the Exchange Rules, the renminbi is convertible for current account items, including the distribution of dividends, interest payments, trade and service-related foreign exchange transactions. Conversion of renminbi for capital account items, such as direct investment, loan, security investment and repatriation of investment, however, is still subject to the SAFE's scrutiny.

Under the Administration Rules, foreign-invested enterprises may only buy, sell and/or remit foreign currencies at those banks authorized to conduct foreign exchange business after providing valid commercial documents and, in the case of capital account item transactions, obtaining approval from the SAFE. Capital investments by foreign-invested enterprises outside of China are also subject to limitations, which include approvals by the MOFCOM, the SAFE and the NDRC.

Pursuant to the Circular on Further Improving and Adjusting the Direct Investment Foreign Exchange Administration Policies, or Circular 59, promulgated by the SAFE on November 19, 2012 and became effective on December 17, 2012, approval is not required for the opening of and payment into foreign exchange accounts under direct investment, for domestic reinvestment with legal income of foreign investors in China. Circular 59 also simplified the capital verification and confirmation formalities for Chinese foreign-invested enterprises and the foreign capital and foreign exchange registration formalities required for the foreign investors to acquire the equities of Chinese party and other items. Circular 59 further improved the administration on exchange settlement of foreign exchange capital of Chinese foreign-invested enterprises.

Foreign Exchange Registration of Offshore Investment by PRC Residents

In July 2014, the SAFE issued the Notice on Relevant Issues Concerning Foreign Exchange Administration for PRC Residents to Engage in Offshore Investment and Financing and Round Trip Investment via Special Purpose Vehicles, or Circular 37, and its implementation guidelines, which abolishes and supersedes the SAFE's Circular on Relevant Issues Concerning Foreign Exchange Administration for PRC Residents to Engage in Financing and Round Trip Investment via Overseas Special Purpose Vehicles, or Circular 75. Pursuant to Circular 37 and its implementation guidelines, PRC residents (including PRC institutions and individuals) must register with local branches of the SAFE in connection with their direct or indirect offshore investment in an overseas special purpose vehicle, or SPV, directly established or indirectly controlled by PRC residents for the purposes of offshore investment and financing with their legally owned assets or interests in domestic enterprises, or their legally owned offshore assets or interests. Such PRC residents are also required to amend their registrations with the SAFE when there is a significant change to the SPV, such as changes of the PRC individual resident's increase or decrease of its capital contribution in the SPV, or any share transfer or exchange, merger, division of the SPV. Failure to comply with the registration procedures set forth in Circular 37 may result in restrictions being imposed on the foreign exchange activities of the relevant onshore company, including the payment of dividends and other distributions to its offshore parent or affiliate, the capital inflow from the offshore entities and settlement of foreign exchange capital, and may also subject relevant onshore company or PRC residents to penalties under PRC foreign exchange administration regulations.

In February 2012, the SAFE promulgated the Notices on Issues Concerning the Foreign Exchange Administration for Domestic Individuals Participating in Stock Incentive Plans of Overseas Publicly Listed Companies. Based on this regulation, directors, supervisors, senior management and other employees of domestic subsidiaries or branches of a company listed on an overseas stock market who are PRC citizens or who are non-PRC citizens residing in China for a continuous period of not less than one year, subject to a few exceptions, are required to register with the SAFE or its local counterparts by following certain procedures if they participate in any stock incentive plan of the company listed on an overseas stock market. Foreign exchange income received from the sale of shares or dividends distributed by the overseas listed company may be remitted into a foreign currency account of such PRC citizen or be exchanged into renminbi. Our PRC citizen employees who have been granted share options have been subject to these rules due to our admission to trading on the AIM market and the listing of our ADSs on Nasdaq.

Regulation on Investment in Foreign-invested Enterprises

Pursuant to PRC law, the registered capital of a limited liability company is the total capital contributions subscribed for by all the shareholders as registered with the company registration authority. A foreign-invested enterprise also has a total investment limit that is approved by or filed with the MOFCOM or its local counterpart by reference to both its registered capital and expected investment scale. The difference between the total investment limit and the registered capital of a foreign-invested enterprise or the cross-border financing risk weighted balance calculated based on a formula by the PBOC represents the foreign debt financing quota to which it is entitled (i.e., the maximum amount of debt which the company may borrow from a foreign lender). A foreign-invested enterprise is required to obtain approval from or file with the MOFCOM or its local counterpart for any increases to its total investment limit. In accordance with these regulations, we and our joint venture partners have contributed financing to our PRC subsidiaries and joint ventures in the form of capital contributions up to the registered capital amount and/or in the form of shareholder loans up to the foreign debt quota. According to the financing needs of our PRC subsidiaries and joint ventures, we and our joint venture partners have requested and received approvals from the government authorities for increases to the total investment limit for certain of our PRC subsidiaries and joint ventures from time to time. As a result, these regulations have not had a material impact to date on our ability to finance such entities.

Regulation on Dividend Distribution

The principal regulations governing distribution of dividends paid by wholly foreign-owned enterprises include:

- Company Law of the PRC (1993), as amended in 1999, 2004, 2005, 2013 and 2018;
- Foreign Investment Law of the PRC; and
- Implementation Rules for the Foreign Investment Law.

- Under these laws and regulations, foreign-invested enterprises in China may pay dividends only out of their accumulated profits, if any, determined in accordance with PRC accounting standards and regulations. In addition, a wholly foreign-owned enterprise in China is required to set aside at least 10.0% of its after-tax profit based on PRC accounting standards each year to its general reserves until the accumulative amount of such reserves reach 50.0% of its registered capital. These reserves are not distributable as cash dividends. The board of directors of a foreign-invested enterprise has the discretion to allocate a portion of its after-tax profits to staff welfare and bonus funds, which may not be distributed to equity owners except in the event of liquidation.

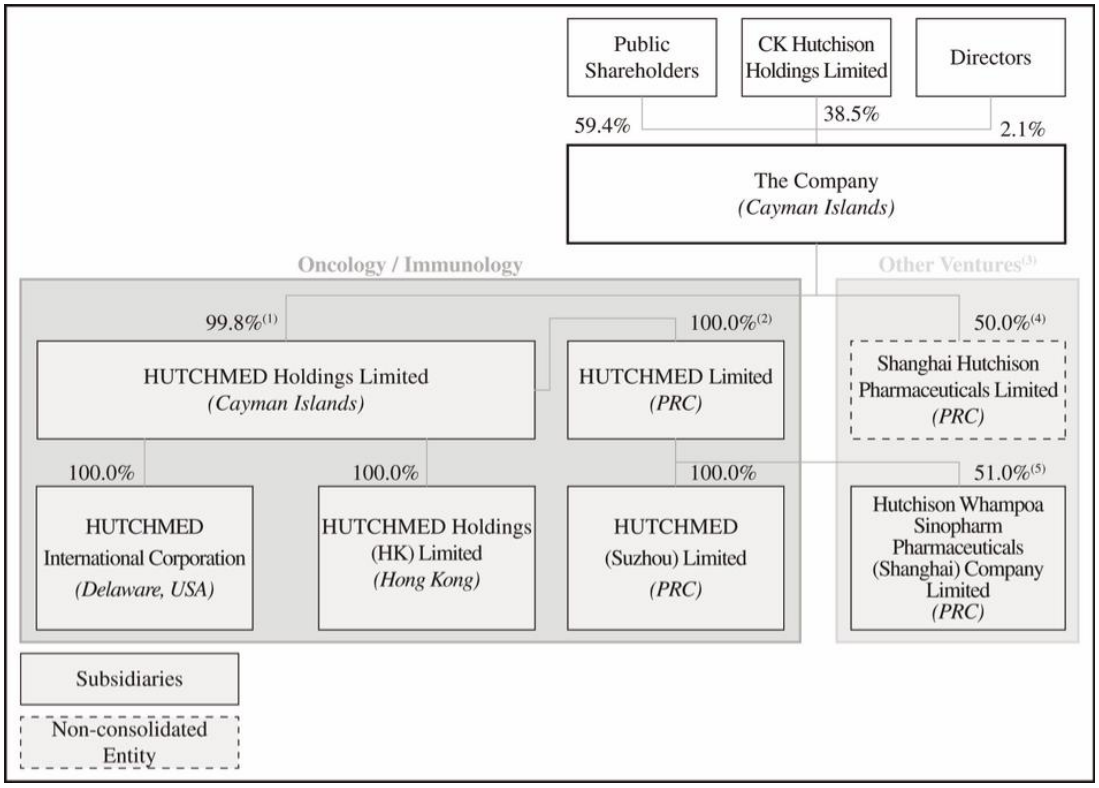
Filings and Approvals Relating to State-Owned Assets

Pursuant to applicable PRC state-owned assets administration laws and regulations, incorporating a joint venture that will have investments of assets that are both state-owned and non-state-owned, investing in an entity that was previously owned by a state-owned enterprise and restructuring an enterprise ultimately owned by the general public require the performance of an assessment of the relevant state-owned assets and the filing of the assessment results with the competent state-owned assets administration, finance authorities or other regulatory authorities and, if applicable, the receipt of approvals from such authorities.

Our joint venture partners were required to perform a state-owned asset assessment when Shanghai Hutchison Pharmaceuticals and Hutchison Baiyunshan were incorporated and our joint venture partners contributed state-owned assets, and when we invested in Hutchison Sinopharm, which was previously wholly-owned by Sinopharm, a state-owned enterprise. In addition, Hutchison Sinopharm was required to perform a state-owned asset assessment when Hutchison Sinopharm restructured from an enterprise ultimately owned by the general public into a limited liability enterprise. In all four instances, our joint venture partners have informed us that they or Hutchison Sinopharm have duly filed the relevant state-owned asset assessment results with, and obtained the requisite approvals from, the relevant governmental authorities as required by the foregoing laws and regulations. Accordingly, we believe that such joint ventures are in full compliance with all applicable laws and regulations governing the administration and restructuring of state-owned assets, although we are currently unable to obtain copies of certain filing and approval documents from our joint venture partners due to their internal confidentiality constraints. We have not received any notice of warning or been subject to any penalty or other disciplinary action from the relevant governmental authorities with respect to the applicable laws and regulations governing the administration and restructuring of state-owned assets.

C. Organizational Structure

The chart below shows our organizational structure, including our principal subsidiaries and joint ventures, as of March 1, 2022.



Notes:

(1) Employees and former employees of HUTCHMED Limited hold the remaining 0.2% shareholding in HUTCHMED Holdings Limited.

(2) Held through HUTCHMED Investment (HK) Limited (formerly Hutchison MediPharma (HK) Investment Limited), a 100.0% subsidiary of HUTCHMED Holdings Limited. HUTCHMED Limited's revenue generated by sales of, and royalties, manufacturing costs and services fees paid in connection with, our current and future internally developed drug candidates are allocated to the Oncology/Immunology operations.

(3) Our Other Ventures also include Hutchison Hain Organic Holdings Limited, a consolidated joint venture with The Hain Celestial Group, Inc., which wholly-owns Hutchison Hain Organic (Hong Kong) Limited and Hutchison Hain Organic (Guangzhou) Limited.

(4) Held through our 100.0% subsidiary Shanghai HUTCHMED Investment (HK) Limited (formerly Shanghai Hutchison Chinese Medicine (HK) Investment Limited). Shanghai Pharmaceuticals Holding Co., Limited is the other 50.0% joint venture partner.

(5) Sinopharm Group Co. Limited is the other 49.0% joint venture partner.

D. Property, Plants and Equipment

We are headquartered in Hong Kong where we have our main administrative offices.

We rent and operate a 4,968 square meter manufacturing facility that complies with applicable GMP standards for fruquintinib and surufatinib in Suzhou, Jiangsu Province in Eastern China, and own a 5,024 square meter facility in Shanghai which houses research and development operations. We lease 9,080 square meters of office and lab space in Shanghai which houses HUTCHMED Limited's management and staff. In 2020, we entered into a 50-year land use rights agreement for a 28,771 square meter site in Shanghai. We have commenced construction of an almost 55,000 square meter large-scale manufacturing facility for innovative drugs on the site. We plan to install small molecule equipment in late 2022, with GMP compliance targeted for late 2023. The Shanghai factory will be our largest manufacturing facility, with a production capacity estimated to be five times that of our facility in Suzhou. The first phase will be primarily for small molecule production, with an expected production capacity of 250 million tablets and capsules per years.

We also lease a 26,989 square foot facility in Florham Park, New Jersey where we house our U.S.-based clinical, regulatory and commercial management and staff.

Our non-consolidated joint venture, Shanghai Hutchison Pharmaceuticals, operates a 78,000 square meter large-scale research and development and manufacturing facility in Shanghai for which it has obtained land use rights and property ownership certificates.

Our and our joint ventures' manufacturing operations consist of bulk manufacturing and formulation, fill, and finishing activities that produce products and drug candidates for both clinical and commercial purposes. Our manufacturing capabilities have a large operation scale for our own-brand products. We and our joint ventures manufacture and sell about 2.5 billion doses of medicines a year, in the aggregate, through our well-established manufacturing base. See "—Other Ventures—Shanghai Hutchison Pharmaceuticals" for more details on our manufacturing operations.

ITEM 4A. UNRESOLVED STAFF COMMENTS

None.

ITEM 5. OPERATING AND FINANCIAL REVIEW AND PROSPECTS

You should read the following discussion and analysis of our financial condition and results of operations together with Item 3.A. "Selected Financial Data," our consolidated financial statements and the related notes and our non-consolidated joint ventures' consolidated financial statements and the related notes appearing elsewhere in this annual report. This report contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Exchange Act, including, without limitation, statements regarding our expectations, beliefs, intentions or future strategies that are signified by the words "expect," "anticipate," "intend," "believe," or similar language. All forward-looking statements included in this annual report are based on information available to us on the date hereof, and we assume no obligation to update any such forward-looking statements. In evaluating our business, you should carefully consider the information provided under Item 3.D. "Risk Factors." Actual results could differ materially from those projected in the forward-looking statements.

A. Operating Results.

Overview

We are a global commercial-stage biopharmaceutical company focused on the discovery, development and commercialization of targeted therapies and immunotherapies for the treatment of patients with cancer and immunological diseases. We conduct our business through our Oncology/Immunology and Other Ventures operations.

Through our Oncology/Immunology operations, our team of over 820 scientists and staff has created, developed and in-licensed a deep portfolio of thirteen drug candidates. We have advanced thirteen oncology drug candidates to clinical trials in China, with seven also in clinical development in the United States and Europe. In China, we have brought three of our internally developed drugs, Elunate (fruquintinib), Sulanda (surufatinib) and Orpathys (savolitinib), to patients. All three drugs are also in late-stage development outside of China, with the most advanced being surufatinib for which the FDA has accepted our NDA in the United States. We have additional drug candidates in earlier stage clinical development (Phase I/Ib and Phase Ib/II proof-of-concept studies) and several advanced pre-clinical drug candidates. These drug candidates are being developed to treat a wide spectrum of diseases, including solid tumors, hematological malignancies and immunological diseases which we believe may address unmet medical needs and represent large commercial opportunities. Our success in research and development has led to partnerships with leading global pharmaceutical companies, including AstraZeneca and Eli Lilly. We and our collaboration partners have invested over $1,260 million in our Oncology/Immunology operations as of December 31, 2021, with almost all of these funds used for research and development expenses for the development of our drug candidates. Net loss attributable to our company from our Oncology/Immunology operations was $127.4 million, $175.5 million and $291.7 million for the years ended December 31, 2019, 2020 and 2021, respectively.

In addition, we have built large-scale and profitable drug marketing and distribution capabilities through subsidiaries and joint ventures in our Other Ventures, which primarily manufacture, market and distribute prescription drugs and consumer health products in China. Net income attributable to our company generated from our Other Ventures operations was $41.5 million, $72.8 million and $142.9 million for the years ended December 31, 2019, 2020 and 2021, respectively. In addition to helping to fund our Oncology/Immunology operations, we utilize the know-how from our Other Ventures to support the launch of our internally developed Oncology/Immunology products in China. Our Other Ventures also include our businesses focused on a range of health-focused consumer products.

Our consolidated revenue was $204.9 million, $228.0 million and $356.1 million for the years ended December 31, 2019, 2020 and 2021, respectively. Net loss attributable to our company was $106.0 million, $125.7 million and $194.6 million for the years ended December 31, 2019, 2020 and 2021, respectively.

Basis of Presentation

Our consolidated statements of operations data presented herein for the years ended December 31, 2021, 2020 and 2019 and our consolidated balance sheet data presented herein as of December 31, 2021 and 2020 have been derived from our audited consolidated financial statements, which were prepared in accordance with U.S. GAAP, and should be read in conjunction with those statements which are included elsewhere in this annual report.

We have two strategic operations, Oncology/Immunology and Other Ventures, that offer different products and services. Our Shanghai Hutchison Pharmaceuticals and Hutchison Baiyunshan (until September 28, 2021 when the disposal of our shareholding interest in Hutchison Baiyunshan was completed) joint ventures under our Other Ventures operations are accounted for under the equity accounting method as non-consolidated entities in our consolidated financial statements, and their consolidated financial statements were prepared in accordance with IFRS as issued by the IASB and audited under auditing standards generally accepted in the United States and included elsewhere in this annual report. The presentation of financial data for our business units excludes certain unallocated costs attributed to expenses incurred by our corporate head office. For more information on our corporate structure, see Item 4.A. “History and Development of the Company.”

Factors Affecting our Results of Operations

Research and Development Expenses

We believe our ability to successfully develop innovative drug candidates through our Oncology/Immunology operations will be the primary factor affecting our long-term competitiveness, as well as our future growth and development. Creating high quality global first-in-class or best-in-class drug candidates requires significant investment of resources over a prolonged period of time, and a core part of our strategy is to continue making sustained investments in this area. As a result of this commitment, our pipeline of drug candidates has been steadily advancing and expanding, with thirteen in China and global clinical development. For more information on the nature of the efforts and steps necessary to develop our drug candidates, see Item 4.B. “Business Overview—Our Clinical Pipeline” and “Business Overview—Regulation.”

The drug candidates of our Oncology/Immunology operations are still in development, and we have incurred and will continue to incur significant research and development costs for pre-clinical studies and clinical trials. We expect that our research and development expenses will significantly increase in future periods in line with the advancement and expansion of the development of our drug candidates.

Research and development expenses include:

- employee compensation related expenses, including salaries, benefits and equity compensation expense;
- expenses incurred for payments to CROs, investigators and clinical trial sites that conduct our clinical studies;
- the cost of acquiring, developing, and manufacturing clinical study materials;
- facilities, depreciation, and other expenses, which include office leases and other overhead expenses; and
- costs associated with pre-clinical activities and regulatory operations.

Research and development expenses incurred by our Oncology/Immunology operations totaled $138.2 million, $174.8 million and $299.1 million for the years ended December 31, 2019, 2020 and 2021, respectively, representing approximately 67.4%, 76.7% and 84.0% of our total consolidated revenue for the respective period. These research and development figures do not include payments made by our collaboration partners directly to third parties to help fund the research and development of our drug candidates.

We have been able to fund the research and development expenses for our Oncology/Immunology operations via a range of sources, including revenue generated from our commercialized drugs, payments received from our collaboration partners, cash flows generated from and dividend payments from our Other Ventures, the proceeds raised from our initial public offering on the AIM, initial public offering and follow-on offerings on Nasdaq, initial public offering on the SEHK, investments from other third parties and bank borrowings.

This diversified approach to funding allows us to not depend on any one method of funding for our research and development activities, thereby reducing the risk that sufficient financing will be unavailable as we continue to accelerate the development of our drug candidates.

For more information on the research and development expenses incurred for the development of our drug candidates, see "—Key Components of Results of Operations—Cost of Revenues and Operating Expenses—Research and Development Expenses."

Our Ability to Commercialize Our Drug Candidates

Our ability to generate revenue from our drug candidates depends on our ability to successfully complete clinical trials for our drug candidates and obtain regulatory approvals for them in the United States, Europe, China and other major markets.

We believe that our globally-facing strategy of focusing on drug development for novel but relatively well-characterized targets and for validated targets, in combination with our development of multiple drug candidates concurrently and testing them for multiple indications and in combinations with other drugs, enhances the likelihood that our research and development efforts will yield successful drug candidates. Nonetheless, we cannot be certain if any of our drug candidates will receive regulatory approvals. Even if such approvals are granted, we will need to thereafter establish manufacturing supply and engage in extensive marketing prior to generating any revenue from such drugs. The effectiveness of our marketing will depend on the efforts of our dedicated oncology team in China and the United States. The ultimate commercial success of our drugs will depend on their acceptance by patients, the medical community and third-party payors and their ability to compete effectively with other therapies on the market.

To date, fruquintinib, surufatinib and savolitinib have been approved for sale in China.

Our manufacturing site in Suzhou produces commercial supplies of fruquintinib and surufatinib. Our commercial supplies of savolitinib are outsourced and manufactured by a third-party manufacturer based in Shanghai, China. Beginning in October 2020, we assumed responsibility for the development and execution of all on-the-ground medical detailing, promotion and local and regional marketing activities in China for Elunate. Sulanda is marketed by us without the support of a collaboration partner. However, we have a limited history of successfully commercializing our internally developed drug candidates, which makes it difficult to evaluate our future prospects.

The competitive environment is also an important factor with the commercial success of our potential global first-in-class products, such as sovleplenib, depending on whether we are able to gain regulatory approvals and quickly bring such products to market ahead of competing drug candidates being developed by other companies.

For our drug candidates where we retain all rights worldwide, which currently include surufatinib, sovleplenib, amdizalisib, HMPL-306, HMPL-760, HMPL-453, HMPL-295, HMPL-653, epitinib and theliatinib, we will be able to retain all the profits if any of them are successfully commercialized if they remain unpartnered, though we will need to bear all the costs associated with such drug candidates. Conversely, as discussed below, for our drug candidates which are subject to collaboration partnerships, our collaboration partners provide funding for development of the drug candidates but are entitled to retain a significant portion of any revenue generated by such drug candidates.

Our Collaboration Partnerships

Our results of operations have been, and we expect them to continue to be, affected by our collaborations with third parties for the development and commercialization of certain of our drug candidates. Currently, these include savolitinib (collaboration with AstraZeneca) and fruquintinib (collaboration with Eli Lilly). In addition to providing us with clinical and regulatory support, the payments received from these collaborations have been critical to our ability to develop and quickly advance the pre-clinical and clinical studies of multiple drug candidates concurrently.

In particular, our partners cover a portion of our research and development costs for drug candidates developed in collaboration with them. For example, under our collaboration agreement with AstraZeneca, it is responsible for a significant portion of the development costs for savolitinib. However, in August 2016 and December 2020, we and AstraZeneca amended our collaboration agreement whereby we agreed to contribute additional funding for the research and development of savolitinib in return for a larger share of the upside if and when savolitinib is approved. In November 2021, we further amended our collaboration revising the sharing between us and AstraZeneca of development costs of savolitinib in China for non-small cell lung cancer, as well as adding potential development milestones. Under our original collaboration agreement with Eli Lilly, it was responsible for a significant portion of all fruquintinib development costs in China. Under the terms of our December 2018 amendment to this agreement, we are responsible for all development costs for fruquintinib in new life cycle indications. In July 2020, we amended our collaboration with Eli Lilly to assume responsibility for all on-the-ground medical detailing, promotion and local and regional marketing activities in China for Elunate, thereby expanding its potential economic value to our company.

In addition, under our licensing, co-development and commercialization agreements with AstraZeneca and Eli Lilly, we received upfront payments upon our entry into such agreements and milestone payments upon the achievement of certain development, regulatory and commercial milestones payments for our provision of research and development services for the relevant drug candidate as well as royalties and revenue from product sales of Orpathys which we source from a third-party manufacturer and sell to AstraZeneca at cost and Elunate which we manufacture and sell to Eli Lilly at cost. Revenue recognized in our consolidated financial statements from such agreements with AstraZeneca and Eli Lilly totaled $26.3 million, $29.7 million and $107.1 million for the years ended December 31, 2019, 2020 and 2021, respectively. AstraZeneca and Eli Lilly are entitled to a significant proportion of any future revenue from commercialization of our drug candidates developed in collaboration with them, as well as a degree of influence over the clinical development process for such drug candidates.

Moreover, we have entered into and may consider entering in the future in-licensing arrangements to expand and complement our existing portfolio of novel oncology assets under which we may be obligated to make upfront, milestone and royalty payments. For example, in August 2021, we entered into an in-licensing agreement with Epizyme to collaborate in research, development, manufacturing and commercialization of tazemetostat in Greater China, the licensed territory. In connection with this collaboration, Epizyme received a $25 million upfront payment and is eligible to receive up to an additional $110 million in development and regulatory milestone payments and up to an additional $175 million in sales milestone payments. Epizyme is also eligible to receive tiered royalties of mid-teen to low-twenties percent based on annual net sales of tazemetostat in the licensed territory.

The achievement of milestones for our and in-licensed drug candidates, which is dependent on the outcome of clinical studies, is subject to a high degree of uncertainty and, as a result, we cannot reasonably estimate when we can expect to receive or incur future milestone payments, revenue from related product sales, or other relevant income or expenses or at all. If we are unable to achieve development milestones for our drug candidates or if our partners were to terminate their collaborative agreements with us, payments for research and development services could also be affected.

For more information regarding our collaboration agreements, see Item 4.B. "Business Overview—Overview of Our Collaborations."

China Government Insurance Reimbursement and Drug Pricing Policies

Our revenue is affected by the sales volume and pricing of our current and future internally developed drug candidates, if approved. Eligible participants in the government-sponsored medical insurance programs in China are entitled to reimbursement for varying percentages of the cost for any medicines that are included in applicable reimbursement lists. Factors that affect the inclusion of medicines in China's NRDL and any other applicable reimbursement list may include whether the medicine is consumed in large volumes and commonly prescribed for clinical use in China and whether it is considered to be important in meeting the basic healthcare needs of the general public. For more information, see Item 4.B. "Business Overview—Coverage and Reimbursement—PRC Coverage and Reimbursement." The inclusion of a medicine in the NRDL or other applicable reimbursement lists can substantially improve the sales volume of the medicine due to the availability of third-party reimbursements. On the other hand, such inclusion may also subject it to centralized procurement processes. The National Healthcare Security Administration has stated that centralized procurement will focus on NRDL-listed and costly-to-procure drugs. Centralized procurement may negatively affect the retail price of our drug candidates. On balance, we believe that, if priced appropriately, the benefit of the inclusion of our drug candidates in the NRDL and other applicable reimbursement lists outweighs the cost of such inclusion. Elunate was added to the NRDL in January 2020 at approximately 60% discount to its initial retail price, and such inclusion was renewed for an additional two-year term starting in January 2022 at a discount of 5% relative to the prior NRDL price. Sulanda was included in the NRDL starting in January 2022 at a 52% discount on its main dosage form, relative to its 2021 initial retail price.

Revenue from our Other Ventures, including the revenue of our non-consolidated joint venture Shanghai Hutchison Pharmaceuticals, is affected by the sales volume and pricing of their own-brand and third-party prescription pharmaceutical products. The sales volume of the products sold by these businesses is driven in part by the level of Chinese government spending on healthcare and the coverage of Chinese government medical insurance schemes, which is correlated with patient reimbursements for drug purchases, all of which have increased significantly in recent years as part of healthcare reforms in China. The sales volume of pharmaceutical products in China is also influenced by their representation on the NRDL, which determines eligibility for drug reimbursement, as well as their representation on the National Essential Medicines List, which mandates distribution of drugs in China. Substantially all pharmaceutical products manufactured and sold by Shanghai Hutchison Pharmaceuticals in 2021 were capable of being reimbursed under the NRDL as of December 31, 2021. There were 17 of its drugs included in the National Essential Medicine List, of which three were in active production as of December 31, 2021. She Xiang Bao Xin pills, Shanghai Hutchison Pharmaceuticals' top-selling drug, is one of the few proprietary drugs included on the National Essential Medicines List.

The NRDL and the National Essential Medicines List are subject to revision by the government from time to time, and our results could be materially and adversely affected if any of our products are removed from the NRDL or the National Essential Medicines List. For more information, see Item 3.D. "Risk Factors—Risks Relating to Sales of our Internally Developed Drugs and other Drugs—Reimbursement may not be available for the products currently sold through our Oncology/Immunology and Other Ventures operations or our drug candidates in China, the U.S. or other countries, which could diminish our sales or affect our profitability."

In addition, the pricing of Shanghai Hutchison Pharmaceuticals' prescription drugs is influenced by the outcomes of periodic provincial and municipal tender processes organized by the various provincial or municipal government agencies in China. For more information, see Item 4.B. "Business Overview—Coverage and Reimbursement—PRC Coverage and Reimbursement."

Ability to Effectively Market Own-Brand and Third-Party Drugs

A key component of our Other Ventures operations is the extensive prescription drugs marketing network operated by our joint ventures Shanghai Hutchison Pharmaceuticals and Hutchison Sinopharm, which includes approximately 2,900 medical sales representatives covering hospitals in about 290 cities and towns in China. Our results of operations are impacted by the effectiveness of this network, including the ability of Shanghai Hutchison Pharmaceuticals to generate sales of She Xiang Bao Xin pills, which represented approximately 88%, 90% and 92% of its total revenue for the years ended December 31, 2019, 2020 and 2021, respectively. In addition, in recent years Hutchison Sinopharm has been increasingly focused on providing distribution and commercialization services for prescription drugs licensed from third parties, and we have established and continue to expand our oncology drug sales team which we utilize for our internally developed drugs for which we have commercialization rights, if approved, throughout China.

If the marketing efforts of these joint ventures to doctors and hospitals are not successful, our revenue and profitability may be negatively affected. Moreover, if we are unsuccessful in marketing any third party drugs, it may adversely affect our ability to enter into commercialization arrangements on acceptable terms, gain rights to market additional third-party drugs or prevent us from expanding the geographic scope of existing arrangements.

Seasonality

The results of operations of our Other Ventures operations are also affected by seasonal factors. Our Other Ventures operations typically experience higher profits in the first half of the year due to the sale cycles of our distributors, whereby they typically increase their inventories at the beginning of each year. In addition, in the second half of each year, our Other Ventures operations typically spend more on marketing activities to help reduce such inventory held by distributors. We do not experience material seasonal variations in the results of our Oncology/Immunology operations.

Critical Accounting Policies and Significant Judgments and Estimates

Our discussion and analysis of operating results and financial condition are based upon our consolidated financial statements. The preparation of consolidated financial statements requires us to estimate the effect of various matters that are inherently uncertain as of the date of the consolidated financial statements. Each of these required estimates varies with regard to the level of judgment involved and its potential impact on our reported financial results. Estimates are deemed critical when a different estimate could have reasonably been used or where changes in the estimates are reasonably likely to occur from period to period, and a different estimate would materially impact our financial position, changes in financial position or results of operations. Our significant accounting policies are discussed under note 3 to our consolidated financial statements included in this annual report. We believe the following critical accounting policies are affected by significant judgments and estimates used in the preparation of our consolidated financial statements and that the judgments and estimates are reasonable.

Revenue recognition— Goods and Services

We generate revenue from (1) sales of goods, which are the manufacture or purchase and distribution of pharmaceutical products and other consumer health products and (2) provision of services, which are the provision of sales, distribution and marketing services to pharmaceutical manufacturers. We evaluate whether we are the principal or agent for these contracts. Where we obtain control of the goods for distribution, we are the principal (i.e. recognizes sales of goods on a gross basis). Where we do not obtain control of the goods for distribution, we are the agent (i.e. recognizes provision of services on a net basis). Control is primarily evidenced by taking physical possession and inventory risk of the goods.

Revenue from sales of goods is recognized when the customer takes possession of the goods. We have determined that this usually occurs upon completed delivery of the goods to the customer site. The amount of revenue recognized is adjusted for expected sales incentives as stipulated in the contract, which are generally issued to customers as direct discounts at the point of sale or indirectly in the form of rebates. Sales incentives are estimated using the expected value method. Additionally, sales are generally made with a limited right of return under certain conditions. Revenues are recorded net of provisions for sales discounts and returns.

Revenue from provision of services is recognized when the benefits of the services transfer to the customer over time, which is based on the proportionate value of services rendered as determined under the terms of the relevant contract. Additionally, when the amounts that can be invoiced correspond directly with the value to the customer for performance completed to date, we recognize revenue from provision of services based on amounts that can be invoiced to the customer.

Revenue recognition— License and Collaboration Contracts

Our Oncology/Immunology reportable segment includes revenue from license and collaboration contracts. The license and collaboration contracts generally contain multiple performance obligations including (1) the license to the commercialization rights of a drug compound and (2) the research and development services for each specified treatment indication, which are accounted for separately if they are distinct, i.e. if a product or service is separately identifiable from other items in the arrangement and if a customer can benefit from it on its own or with other resources that are readily available to the customer.

The transaction price generally includes fixed and variable consideration in the form of upfront payment, research and development cost reimbursements, contingent milestone payments and sales-based royalties. Contingent milestone payments are not included in the transaction price until it becomes probable that a significant reversal of revenue will not occur, which is generally when the specified milestone is achieved. The allocation of the transaction price to each performance obligation is based on the relative standalone selling prices of each performance obligation determined at the inception of the contract. We estimate the standalone selling prices based on the income approach.

Control of the license to the drug compounds transfers at the inception date of the collaboration agreements and consequently, amounts allocated to this performance obligation are generally recognized at a point in time. Conversely, research and development services for each specified indication are performed over time and amounts allocated to these performance obligations are generally recognized over time using cost inputs as a measure of progress. We have determined that research and development expenses provide an appropriate depiction of measure of progress for the research and development services. Changes to estimated cost inputs may result in a cumulative catch-up adjustment. Royalty revenues are recognized as future sales occur as they meet the requirements for the sales-usage based royalty exception.

Deferred revenue is recognized if allocated consideration is received in advance of the rendering of research and development services. Accounts receivable is recognized based on the terms of the contract and when we have an unconditional right to bill the customer, which is generally when research and development services are rendered.

Share-based Compensation

We recognize share-based compensation expense on share options granted to employees and directors based on their estimated grant date fair value using the polynomial model. Determining the fair value of share options requires the use of highly subjective assumptions. This polynomial pricing model uses various inputs to measure fair value, including the market value of our underlying ordinary shares at the grant date, contractual terms, estimated volatility, risk-free interest rates and expected dividend yields. The assumptions in determining the fair value of share options are highly subjective and represent our best estimates, which involve inherent uncertainties and the application of judgment. As a result, if factors change and different assumptions are used, our level of share-based compensation could be materially different in the future.

We recognize share-based compensation expense in the consolidated statements of operations on a graded vesting basis over the requisite service period, and account for forfeitures as they occur.

Impairment of Long-lived Assets

We evaluate the recoverability of long-lived assets in accordance with authoritative guidance on accounting for the impairment or disposal of long-lived assets.

We evaluate long-lived assets for impairment whenever events or changes in circumstances indicate that the carrying value of these assets may not be recoverable. Indicators that we consider in deciding when to perform an impairment review include significant under-performance of a business or product line in relation to expectations, significant negative industry or economic trends, and significant changes or planned changes in our use of the assets.

If indicators of impairment exist, the first step of the impairment test is performed to assess if the carrying value of the net assets exceeds the undiscounted cash flows of the assets. If yes, the second step of the impairment test is performed in order to determine if the carrying value of the net assets exceeds the fair value. If yes, impairment is recognized for the excess.

Impairment of Goodwill

Goodwill is recorded when the purchase price of an acquisition exceeds the fair value of the net tangible and identified intangible assets acquired. Goodwill is allocated to our reporting units based on the relative expected fair value provided by the acquisition. Reporting units may be operating segments as a whole or an operation one level below an operating segment, referred to as a component. Goodwill is attributable to our Other Ventures' operations.

We perform an annual impairment assessment in the fourth quarter of each year, or more frequently if indicators of potential impairment exist, to determine whether it is more likely than not that the fair value of a reporting unit in which goodwill resides is less than its carrying value. For reporting units in which this assessment concludes that it is more likely than not that the fair value is more than its carrying value, goodwill is not considered impaired and we are not required to perform the goodwill impairment test. Qualitative factors considered in this assessment include industry and market considerations, overall financial performance, and other relevant events and factors affecting the reporting unit. Additionally, as part of this assessment, we may perform a quantitative analysis to support the qualitative factors above by applying sensitivities to assumptions and inputs used in measuring a reporting unit's fair value. For reporting units in which the impairment assessment concludes that it is more likely than not that the fair value is less than its carrying value, we perform the goodwill impairment test, which compares the fair value of the reporting unit to its carrying value. If the fair value of the reporting unit exceeds the carrying value of the net assets assigned to that reporting unit, goodwill is not considered impaired. If the carrying value of the net assets assigned to the reporting unit exceeds the fair value of the reporting unit, an impairment loss shall be recognized in an amount equal to that excess, limited to the total amount of goodwill allocated to that reporting unit.

Our goodwill impairment test uses the income method to estimate a reporting unit's fair value. The income method is based on a discounted future cash flow approach that uses the following assumptions and inputs: revenue, based on assumed market segment growth rates; and appropriate discount rates based on a reporting unit's weighted average cost of capital as determined by considering the observable weighted average cost of capital of comparable companies. Our estimate of market segment growth is based on historical data, various internal estimates, and a variety of external sources. This estimate is developed as part of our routine long-range planning process. We test the reasonableness of the inputs and outcomes of our discounted cash flow analysis against available comparable market data. A reporting unit's carrying value represents the assignment of various assets and liabilities, excluding certain corporate assets and liabilities, such as cash, investments, and debt. We performed the goodwill impairment test and determined that the fair values of the reporting units exceeded their carrying values and considered that impairment was not necessary for any reporting unit.

Allowance for Current Expected Credit Losses

Effective from January 1, 2020, we adopted Accounting Standards Update 2016-13 "Financial Instruments – Credit Losses (Topic 326), Measurement of Credit Losses on Financial Instruments." We estimate our allowance for current expected credit losses based on an expected loss model, which requires the consideration of forward-looking economic variables and conditions in the reserve calculation across the portfolio.

We estimate our allowances for expected credit losses for accounts and other receivables (except for prepayments) by considering past events, including any historical default, current economic conditions and certain forward-looking information, including reasonable and supportable forecasts. From January 1, 2020 onwards, the methodologies that the Group uses to estimate the allowance for expected credit losses for accounts and other receivables are as follows:

Individually evaluated—we review all accounts and other receivables considered at risk on a timely basis and perform an analysis based upon current information available about the customers and other debtors, which may include financial statements, news reports, published credit ratings as well as collateral net of repossession cost, prior collection history and current and future expected economic conditions. Using this information, we determine the expected cash flow for the accounts and other receivables and calculate an estimate of the potential loss and the probability of loss. For those accounts for which the loss is probable, we record a specific allowance.

Collectively evaluated—we determine our allowance for credit losses for collectively evaluated accounts and other receivables based on appropriate groupings.

We consider forward-looking macroeconomic variables, which may include gross domestic product, unemployment rates, equity prices and corporate profits when quantifying the impact of economic forecasts on our allowance for expected credit losses. Macroeconomic variables may vary based on historical experiences, portfolio composition and current environment. We also consider the impact of current conditions and economic forecasts relating to specific industries and client-credit ratings, in addition to performing a qualitative review of credit risk factors across the portfolio. Forward-looking estimates require the use of judgment, particularly in times of economic uncertainty.

Recent Accounting Pronouncements

See note 3 to our consolidated financial statements included in this annual report for information regarding recent accounting pronouncements.

Key Components of Results of Operations

The following tables set forth our selected consolidated financial data. We have derived the selected consolidated statements of operations data for the years ended December 31, 2021, 2020 and 2019 and the selected consolidated balance sheet data as of December 31, 2021 and 2020 from our audited consolidated financial statements, which were prepared in accordance with U.S. GAAP and are included elsewhere in this annual report. The following selected consolidated financial data for years ended December 31, 2018 and 2017 and as of December 31, 2019, 2018 and 2017 have been derived from our audited consolidated financial statements for those years, which were prepared in accordance with U.S. GAAP and are not included in this annual report.

	Year Ended December 31,				
	2021	2020	2019	2018	2017
	$'000 (except share and per share data)				
Consolidated statement of operations data:					
Revenues					
Goods—third parties	266,199	203,606	175,990	156,234	194,860
—related parties	4,256	5,484	7,637	8,306	8,486
Services —commercialization—third parties	27,428	3,734	2,584	11,660	1,860
—collaboration research and development —third parties	18,995	9,771	15,532	17,681	16,858
—research and development—related parties	525	491	494	7,832	9,682
Other collaboration revenue —royalties—third parties	15,064	4,890	2,653	261	—
—licensing—third parties	23,661	—	—	12,135	9,457
Total revenues	**356,128**	**227,976**	**204,890**	**214,109**	**241,203**
Operating expenses					
Costs of goods—third parties	(229,448)	(178,828)	(152,729)	(129,346)	(168,331)
Costs of goods—related parties	(3,114)	(3,671)	(5,494)	(5,978)	(6,056)
Costs of services—commercialization —third parties	(25,672)	(6,020)	(1,929)	(8,620)	(1,433)
Research and development expenses	(299,086)	(174,776)	(138,190)	(114,161)	(75,523)
Selling expenses	(37,827)	(11,334)	(13,724)	(17,736)	(19,322)
Administrative expenses	(89,298)	(50,015)	(39,210)	(30,909)	(23,955)
Total operating expenses	**(684,445)**	**(424,644)**	**(351,276)**	**(306,750)**	**(294,620)**
	(328,317)	**(196,668)**	**(146,386)**	**(92,641)**	**(53,417)**
Gain on divestment of an equity investee	121,310	—	—	—	—
Other income/(expense)					
Interest income	2,076	3,236	4,944	5,978	1,220
Other income	2,426	4,600	1,855	1,798	808
Interest expense	(592)	(787)	(1,030)	(1,009)	(1,455)
Other expense	(12,643)	(115)	(488)	(781)	(692)
Total other income/(expense)	**(8,733)**	**6,934**	**5,281**	**5,986**	**(119)**
Loss before income taxes and equity in earnings of equity investees	**(215,740)**	**(189,734)**	**(141,105)**	**(86,655)**	**(53,536)**
Income tax expense	(11,918)	(4,829)	(3,274)	(3,964)	(3,080)
Equity in earnings of equity investees, net of tax	60,617	79,046	40,700	19,333	33,653
Net loss	**(167,041)**	**(115,517)**	**(103,679)**	**(71,286)**	**(22,963)**
Less: Net income attributable to non-controlling interests	(27,607)	(10,213)	(2,345)	(3,519)	(3,774)
Net loss attributable to the Company	**(194,648)**	**(125,730)**	**(106,024)**	**(74,805)**	**(26,737)**
Losses per share attributable to the Company—basic and diluted (US$per share)	(0.25)	(0.18)	(0.16)	(0.11)	(0.04)
Number of shares used in per share calculation—basic and diluted	792,684,524	697,931,437	665,683,145	664,263,820	617,171,710
Net loss	**(167,041)**	**(115,517)**	**(103,679)**	**(71,286)**	**(22,963)**
Other comprehensive income/(loss)					
Foreign currency translation gain/(loss)	2,964	9,530	(4,331)	(6,626)	10,964
Total comprehensive loss	**(164,077)**	**(105,987)**	**(108,010)**	**(77,912)**	**(11,999)**
Less: Comprehensive income attributable to non-controlling interests	(28,029)	(11,413)	(1,620)	(2,566)	(5,033)
Total comprehensive loss attributable to the Company	**(192,106)**	**(117,400)**	**(109,630)**	**(80,478)**	**(17,032)**

	As of December 31,				
	2021	2020	2019	2018	2017
			$'000		
Consolidated balance sheet data:					
Cash and cash equivalents	377,542	235,630	121,157	86,036	85,265
Short-term investments	634,158	199,546	96,011	214,915	273,031
Total assets	1,372,661	724,118	465,122	532,118	597,932
Total current liabilities	311,658	158,397	113,101	85,479	104,600
Total non-current liabilities	21,489	46,772	39,118	34,384	8,366
Total shareholders' equity	1,039,514	518,949	312,903	412,255	484,966

Revenues

We derive our consolidated revenue primarily from (i) the sales of goods and services to Eli Lilly as well as royalties on in-market sales of Elunate by Eli Lilly, (ii) the sales of goods to AstraZeneca as well as royalties on in-market sales of Orpathys by AstraZeneca, (iii) sales of our unpartnered drug Sulanda, (iv) licensing and collaboration projects conducted by our Oncology/Immunology operations, which generate revenue in the form of upfront payments, milestone payments, payments received for providing research and development services for our collaboration projects; and (v) the sales of goods and services by our Other Ventures, which generate revenue from the distribution and marketing of prescription pharmaceutical and consumer health products.

The following table sets forth the components of our consolidated revenue for the years indicated, which does not include the revenue from our non-consolidated joint venture, Shanghai Hutchison Pharmaceuticals. In September 2021, we sold our interest in our non-consolidated joint venture, Hutchison Baiyunshan, and its historical financial results and the gain on its divestment are reflected in our consolidated financial statements. Our revenue from research and development projects for related parties is attributable to income for research and development services that we received from Shanghai Hutchison Pharmaceuticals. Our revenue from sales to related parties is attributable to sales by our Other Ventures to indirect subsidiaries of CK Hutchison.

	Year Ended December 31,					
	2021		2020		2019	
	$'000	%	$'000	%	$'000	%
Revenues						
Oncology/Immunology:						
Goods—third parties	33,937	9.5	11,329	5.0	8,113	4.0
Services:						
Services—Commercialization—third parties	27,428	7.7	3,734	1.7	—	—
Collaboration R&D—third parties	18,995	5.3	9,771	4.3	15,532	7.6
R&D services—related parties	525	0.2	491	0.2	494	0.2
Other collaboration revenue:						
Royalties—third parties	15,064	4.2	4,890	2.1	2,653	1.3
Licensing—third parties	23,661	6.7	—	—	—	—
Subtotal	119,610	33.6	30,215	13.3	26,792	13.1
Other Ventures:						
Goods—third parties	232,262	65.2	192,277	84.3	167,877	81.9
Goods—related parties	4,256	1.2	5,484	2.4	7,637	3.7
Services—third parties	—	—	—	—	2,584	1.3
Subtotal	236,518	66.4	197,761	86.7	178,098	86.9
Total	356,128	100.0	227,976	100.0	204,890	100.0

Revenue from Oncology/Immunology primarily comprises revenue from Elunate, Sulanda and Orpathys in China. The revenue we generate from Elunate is primarily comprised of revenue from the sales of Elunate to Eli Lilly which we manufacture and sell at cost, promotion and marketing services to Eli Lilly and royalty revenue. The revenue we generate from Sulanda, an unpartnered drug, is primarily comprised of revenue from sales of Sulanda to distributors. The revenue we generate from Orpathys is primarily comprised of revenue from the sales of Orpathys to AstraZeneca as well as royalty revenue. Additionally, Oncology/Immunology revenue includes revenue from licensing, co-development and commercialization agreements for upfront, milestone and research and development services payments for our drug candidates developed in collaboration with AstraZeneca and Eli Lilly.

The following table sets forth the components of revenues of our Other Ventures by product type for the years indicated.

	Year Ended December 31,					
	2021		2020		2019	
	$'000	%	$'000	%	$'000	%
Revenues—Other Ventures						
Prescription drug products	204,091	86.3	165,072	83.5	141,124	79.2
Consumer health products	32,427	13.7	32,689	16.5	34,390	19.3
Services	—	—	—	—	2,584	1.5
Total	236,518	100.0	197,761	100.0	178,098	100.0

Revenue from our Other Ventures primarily comprises revenue from prescription drugs including the commercial services, logistics and distribution business of our consolidated Hutchison Sinopharm joint venture with Sinopharm, a leading distributor of pharmaceutical and healthcare products and a leading supply chain service provider in China.

Revenue from our Other Ventures also comprises revenue from sales of organic and natural products by Hutchison Hain Organic, Zhi Ling Tong infant nutrition and other health supplement products manufactured by Hutchison Healthcare and distributed through Hutchison Sinopharm, and certain third-party consumer products distributed and marketed by HUTCHMED Science Nutrition.

The revenue of our non-consolidated joint venture, Shanghai Hutchison Pharmaceuticals, the accounts of which are prepared in accordance with IFRS as issued by the IASB and whose revenue is not included in our consolidated revenue, was $272.1 million, $276.4 million and $332.6 million for the years ended December 31, 2019, 2020 and 2021, respectively. Shanghai Hutchison Pharmaceuticals is a joint venture with Shanghai Pharmaceuticals, a leading pharmaceuticals company in China, and primarily focuses on the manufacture and sale of prescription pharmaceutical products in China. We and Shanghai Pharmaceuticals each own 50% of this joint venture. We have the right to nominate the general manager and other management of this joint venture and run its day-to-day operations. The effect of Shanghai Hutchison Pharmaceuticals on our consolidated financial results is discussed below under "—Equity in Earnings of Equity Investees."

The revenue of our former non-consolidated joint venture, Hutchison Baiyunshan, the accounts of which are prepared in accordance with IFRS as issued by the IASB and whose financial results up to September 28, 2021 are reflected in our consolidated financial statements, was $215.4 million, $232.4 million and $209.5 million for the years ended December 31, 2019 and 2020 and the period ended September 28, 2021, respectively. Hutchison Baiyunshan was a joint venture with Guangzhou Baiyunshan, a leading China-based pharmaceutical company. We sold our interest in this joint venture on September 28, 2021 and recognized a gain on divestment attributable to our Group, net of taxes, of $82.9 million from this transaction. The effect of Hutchison Baiyunshan on our consolidated financial results is discussed under "—Equity in Earnings of Equity Investees."

Cost of Revenues and Operating Expenses

Cost of Revenues

Our cost of revenues is primarily attributable to the cost of revenues of Hutchison Sinopharm and HUTCHMED Limited. Our cost of revenues to related parties is attributable to sales to indirect subsidiaries of CK Hutchison. The following table sets forth the components of our cost of revenues attributable to third parties and related parties for the years indicated.

	Year Ended December 31,					
	2021		2020		2019	
	$'000	%	$'000	%	$'000	%
Cost of Revenues						
Costs of goods—third parties	229,448	88.9	178,828	94.9	152,729	95.4
Costs of goods—related parties	3,114	1.2	3,671	1.9	5,494	3.4
Costs of services—third parties	25,672	9.9	6,020	3.2	1,929	1.2
Total	258,234	100.0	188,519	100.0	160,152	100.0

The following table sets forth the components of cost of revenues of our Other Ventures by product type for the years indicated.

	Year Ended December 31,					
	2021		2020		2019	
	$'000	%	$'000	%	$'000	%
Cost of Revenues—Other Ventures						
Prescription drug products	196,375	92.0	158,910	90.1	133,896	86.2
Consumer health products	17,053	8.0	17,500	9.9	19,447	12.5
Services	—	—	—	—	1,929	1.3
Total	213,428	100.0	176,410	100.0	155,272	100.0

Research and Development Expenses

Our research and development expenses are attributable to our Oncology/Immunology operations. These costs primarily comprise the cost of research and development for our drug candidates, including clinical trial related costs such as payments to third-party CROs, personnel compensation and related costs, and other research and development expenses. The following table sets forth the components of our research and development expenses and the clinical trial related costs incurred for the development of our main drug candidates for the years indicated.

	Year Ended December 31,					
	2021		2020		2019	
	$'000	%	$'000	%	$'000	%
R&D Expenses						
Oncology/Immunology:						
Savolitinib (targeting MET)	26,152	8.7	5,341	3.1	14,630	10.6
Fruquintinib (targeting VEGFR1/2/3)	57,707	19.3	28,254	16.2	19,488	14.1
Surufatinib (targeting VEGFR/FGFR1/CSF-1R)	47,971	16.0	32,106	18.4	23,809	17.2
Sovleplenib (targeting Syk)	8,602	2.9	7,422	4.2	18,338	13.3
Amdizalisib (targeting PI3Kδ)	21,044	7.0	7,383	4.2	5,938	4.3
HMPL-453 (targeting FGFR)	1,708	0.6	1,356	0.8	1,948	1.4
HMPL-306 (targeting IDH 1/2)	10,073	3.4	5,389	3.1	—	—
HMPL-295 (targeting ERK)	692	0.2	—	—	—	—
HMPL-760 (targeting BTK)	5,288	1.8	—	—	—	—
HMPL-653 (targeting CSF-1R)	132	—	—	—	—	—
Tazemetostat (targeting EZH2)	12,139	4.1	—	—	—	—
Epitinib (targeting EGFRm+ with brain metastasis)	—	—	808	0.5	(1,841)	(1.3)
Theliatinib (targeting EGFR wild-type)	—	—	(74)	—	138	0.1
Others and government grant	(1,457)	(0.4)	17,884	10.1	5,329	3.8
Total clinical trial related costs	190,051	63.6	105,869	60.6	87,777	63.5
Personnel compensation and related costs	91,639	30.6	63,542	36.3	46,246	33.5
Other research and development costs	17,396	5.8	5,365	3.1	4,167	3.0
Total	299,086	100.0	174,776	100.0	138,190	100.0

The following table summarizes our research and development expenses by location for the years indicated.

	Year Ended December 31,					
	2021		2020		2019	
	$'000	%	$'000	%	$'000	%
PRC	159,038	53.2	111,473	63.8	116,479	84.3
U.S. and others	140,048	46.8	63,303	36.2	21,711	15.7
Total	299,086	100.0	174,776	100.0	138,190	100.0

We cannot determine with certainty the duration and completion costs of the current or future pre-clinical or clinical studies of our drug candidates or if, when, or to what extent we will generate revenues from the commercialization and sale of any of our drug candidates that obtain regulatory approval. We may never succeed in achieving regulatory approval for any of our drug candidates currently under development. The duration, costs, and timing of clinical studies and development of our drug candidates will depend on a variety of factors, including:

- the scope, rate of progress and expense of our ongoing as well as any additional clinical studies and other research and development activities;
- future clinical study results;
- uncertainties in clinical study enrollment rate;
- significant and changing government regulation; and

- the timing and receipt of any regulatory approvals.

A change in the outcome of any of these variables with respect to the development of a drug candidate could mean a significant change in the costs and timing associated with the development of that drug candidate.

For more information on the risks associated with the development of our drug candidates, see Item 3.D. "Risk Factors—Risks Relating to Our Oncology/Immunology Operations and Development of Our Drug Candidates—All of our drug candidates, other than fruquintinib, surufatinib and savolitinib for approved indications in China, are still in development. If we are unable to obtain regulatory approval and ultimately commercialize our drug candidates, or if we experience significant delays in doing so, our business will be materially harmed."

Selling Expenses

The following table sets forth the components of our selling expenses for the years indicated.

	Year Ended December 31,					
	2021		2020		2019	
	$'000	%	$'000	%	$'000	%
Selling Expenses						
Oncology/Immunology	24,627	65.1	237	2.1	—	—
Other Ventures	13,200	34.9	11,097	97.9	13,724	100.0
Total	37,827	100.0	11,334	100.0	13,724	100.0

Our selling expenses primarily comprise selling expenses incurred by our Oncology/Immunology operations by HUTCHMED Limited for sales and marketing expenses and related personnel expenses for our unpartnered drug Sulanda and sales of Elunate to third parties other than Eli Lilly. It also includes sales and marketing expenses and related personnel expenses incurred by our Other Ventures in their distribution and marketing of pharmaceutical and consumer health products.

Administrative Expenses

The following table sets forth the components of our administrative expenses for the years indicated.

Administrative expenses are also incurred by our corporate head office, which are not allocated to either Oncology/Immunology or Other Ventures.

	Year Ended December 31,					
	2021		2020		2019	
	$'000	%	$'000	%	$'000	%
Administrative Expenses						
Oncology/Immunology	48,359	54.2	19,144	38.3	12,189	31.1
Other Ventures	7,712	8.6	6,129	12.3	5,292	13.5
Corporate Head Office	33,227	37.2	24,742	49.4	21,729	55.4
Total	89,298	100.0	50,015	100.0	39,210	100.0

Oncology/Immunology's administrative expenses are comprised of the salaries and benefits of administrative staff, office leases and other overhead expenses incurred by HUTCHMED Limited. It also includes the preparation costs incurred for the potential launch in the United States of products marketed elsewhere and others.

Our Other Ventures' administrative expenses primarily comprise the salaries and benefits of administrative staff, office leases and other overhead expenses incurred by Hutchison Sinopharm, Hutchison Hain Organic and Hutchison Healthcare.

Our corporate head office administrative expenses primarily comprise the salaries and benefits of our corporate head office employees and directors, office leases and other overhead expenses.

Equity in Earnings of Equity Investees

We have historically derived a significant portion of our net income from our equity in earnings of equity investees, which was primarily attributable to our non-consolidated joint venture, Shanghai Hutchison Pharmaceuticals and former non-consolidated joint venture, Hutchison Baiyunshan. Our equity in earnings of equity investees, net of tax, contributed by Shanghai Hutchison Pharmaceuticals was $30.7 million, $33.5 million and $44.7 million for the years ended December 31, 2019, 2020 and 2021 respectively. Our equity in earnings of equity investees, net of tax, contributed by Hutchison Baiyunshan was $9.9 million, $45.6 million and $15.9 million for the years ended December 31, 2019 and 2020 and 2021 (reflecting the period from January 1, 2021 to September 28, 2021), respectively. Equity in earnings of Hutchison Baiyunshan for year ended December 31, 2020 included a one-time gain of $36.0 million from land compensation for a return of land-use rights to the Guangzhou government and for the period ended September 28, 2021 included a one-time gain of $7.0 million for additional land compensation.

The following table shows the revenue of Shanghai Hutchison Pharmaceuticals and Hutchison Baiyunshan for the periods indicated. The consolidated financial statements of these joint ventures are prepared in accordance with IFRS as issued by the IASB and are presented separately elsewhere in this annual report.

	Year Ended December 31,					
	2021		2020		2019	
	$'000	%	$'000	%	$'000	%
Revenue						
Other Ventures:						
Shanghai Hutchison Pharmaceuticals	332,648	61.4	276,354	54.3	272,082	55.8
Hutchison Baiyunshan [(1)]	209,528	38.6	232,368	45.7	215,403	44.2
Total	542,176	100.0	508,722	100.0	487,485	100.0

(1) On September 28, 2021, we completed the disposal of our equity interest in Hutchison Baiyunshan. Revenue in 2021 reflects the period from January 1, 2021 to September 28, 2021.

The following table shows the amount of equity in earnings of equity investees, net of tax, of our non-consolidated joint ventures for the years indicated.

	Year Ended December 31,					
	2021		2020		2019	
	$'000	%	$'000	%	$'000	%
Equity in earnings of equity investees, net of tax						
Other Ventures:						
Shanghai Hutchison Pharmaceuticals	44,678	73.7	33,502	42.4	30,654	75.3
Hutchison Baiyunshan[(1)]	15,919	26.3	45,641	57.7	9,899	24.3
Oncology/Immunology:						
Others	20	—	(97)	(0.1)	147	0.4
Total	60,617	100.0	79,046	100.0	40,700	100.0

(1) The amount for the year ended December 31, 2020 and for the period ended September 28, 2021 includes a one-time gain of $36.0 million and $7.0 million, respectively, from land compensation for a return of land use rights to the Guangzhou government. On September 28, 2021, we completed the divestment of our shareholding interest in Hutchison Baiyunshan. Equity in earnings of Hutchison Baiyunshan reflects the period from January 1, 2021 to September 28, 2021.

Investments in equity investees mainly consisted of our investment in Shanghai Hutchison Pharmaceuticals and historically, our investment in Hutchison Baiyunshan. The fluctuations in the investments in equity investees was primarily due to recording our equity in earnings of equity investees, net of tax, offset by dividends declared by the equity investees.

The following table shows our investments in our equity investees as of the dates indicated.

	As of December 31,	
	2021	2020
	$'000	
Shanghai Hutchison Pharmaceuticals	75,999	79,408
Hutchison Baiyunshan	—	59,712
Others	480	385
Total	76,479	139,505

The following table shows the financial position of Shanghai Hutchison Pharmaceuticals and Hutchison Baiyunshan as of the dates indicated.

	Shanghai Hutchison Pharmaceuticals		Hutchison Baiyunshan	
	As of December 31,			
	2021	2020	2021[1]	2020
	$'000			
Current assets	190,260	175,965	—	177,888
Non-current assets	91,605	93,361	—	95,731
Current liabilities	(128,993)	(109,873)	—	(137,179)
Non-current liabilities	(7,131)	(6,739)	—	(16,034)
Net assets	145,741	152,714	—	120,406
Non-controlling interests	—	—	—	(982)
	145,741	152,714	—	119,424

(1) On September 28, 2021, we completed the disposal of our shareholding interest in Hutchison Baiyunshan.

Results of Operations

The following table sets forth a summary of our consolidated results of operations for the years indicated, both in absolute amounts and as percentages of our revenues. This information should be read together with our consolidated financial statements and related notes included elsewhere in this annual report. Our operating results in any period are not necessarily indicative of the results that may be expected for any future period.

	Year Ended December 31,					
	2021		2020		2019	
	$'000	%	$'000	%	$'000	%
Revenues	356,128	100.0	227,976	100.0	204,890	100.0
Cost of revenues	(258,234)	(72.5)	(188,519)	(82.7)	(160,152)	(78.2)
Research and development expenses	(299,086)	(84.0)	(174,776)	(76.7)	(138,190)	(67.4)
Selling expenses	(37,827)	(10.6)	(11,334)	(5.0)	(13,724)	(6.7)
Administrative expenses	(89,298)	(25.1)	(50,015)	(21.9)	(39,210)	(19.1)
Gain on divestment of an equity investee	121,310	34.1	—	—	—	—
Other income/(expense)	(8,733)	(2.5)	6,934	3.0	5,281	2.6
Income tax expense	(11,918)	(3.3)	(4,829)	(2.1)	(3,274)	(1.6)
Equity in earnings of equity investees, net of tax	60,617	17.0	79,046	34.7	40,700	19.9
Net loss	(167,041)	(46.9)	(115,517)	(50.7)	(103,679)	(50.6)
Net loss attributable to our company	(194,648)	(54.7)	(125,730)	(55.2)	(106,024)	(51.7)

Taxation

Cayman Islands

HUTCHMED (China) Limited is incorporated in the Cayman Islands. The Cayman Islands currently levies no taxes on profits, income, gains or appreciation earned by individuals or corporations. In addition, our payment of dividends, if any, is not subject to withholding tax in the Cayman Islands. For more information, see Item 10.E. "Taxation—Overview of Tax Implications of Various Other Jurisdictions—Cayman Islands Taxation."

People's Republic of China

Our subsidiaries and a joint venture incorporated in the PRC are governed by the EIT Law and regulations. Under the EIT Law, the standard EIT rate is 25% on taxable profits as reduced by available tax losses. Tax losses may be carried forward to offset any taxable profits for the following five years (extended to ten years for those with HNTE status, with effective from January 1, 2018). HUTCHMED Limited and our non-consolidated joint venture, Shanghai Hutchison Pharmaceuticals, have been successful in their respective applications to renew their HNTE status for three years from January 1, 2020 to December 31, 2022. Accordingly, these entities are eligible to a preferential EIT rate of 15% for the years ended/ending December 31, 2020, 2021 and 2022. HUTCHMED (Suzhou) Limited, a wholly owned subsidiary of HUTCHMED Limited, successful renewed its HNTE status for another three years from January 1, 2021 to December 31, 2023. Accordingly, it is eligible for a preferential EIT rate of 15% for the years ended December 31, 2021, 2022 and 2023.

For more information, see Item 10.E. "Taxation—Taxation in the PRC." Please also see Item. 3 "Key Information—Risk Factors—Other Risks and Risks Relating to Doing Business in China—Our business benefits from certain PRC government tax incentives. The expiration of, changes to, or our PRC subsidiaries/joint venture failing to continuously meet the criteria for these incentives could have a material adverse effect on our operating results by significantly increasing our tax expenses."

According to the EIT Law and its implementation regulations, dividends declared after January 1, 2008 and paid by PRC foreign-invested enterprises to their non-PRC parent companies will be subject to PRC withholding tax at 10% unless there is a tax treaty between the PRC and the jurisdiction in which the overseas parent company is a tax resident and which specifically exempts or reduces such withholding tax, and such tax exemption or reduction is approved by the relevant PRC tax authorities. Pursuant to the tax arrangement between PRC and Hong Kong, if a shareholder of the PRC enterprise is a Hong Kong tax resident and directly holds a 25% or more equity interest in the PRC enterprise and is considered to be the beneficial owner of dividends paid by the PRC enterprise, such withholding tax rate may be lowered to 5%, subject to approval by the relevant PRC tax authorities. For more information, see Item 10.E. "Taxation—Taxation in the PRC" and "Taxation—Overview of Tax Implications of Various Other Jurisdictions— Hong Kong Taxation."

Hong Kong

Our company and certain of its subsidiaries are subject to Hong Kong Profits Tax laws and regulations. Hong Kong has a two-tiered Profits Tax rates regime under which the first HK$2.0 million ($0.3 million) of assessable profits of qualifying corporations will be taxed at 8.25%, with the remaining assessable profits taxed at 16.5%. Hong Kong Profits Tax has been provided for at the relevant rates on the estimated assessable profits less estimated available tax losses, if any, of these entities as applicable.

Period-to-Period Comparison of Results of Operations

Year Ended December 31, 2021 Compared to Year Ended December 31, 2020

Revenues

Our revenue increased by 56.2% from $228.0 million for the year ended December 31, 2020 to $356.1 million for the year ended December 31, 2021, which resulted from increased revenue in both the Oncology/Immunology and Other Ventures operations.

Revenue from Oncology/Immunology increased by 295.9% from $30.2 million for the year ended December 31, 2020 to $119.6 million for the year ended December 31, 2021, primarily due to an increase in revenue related to the sales of Elunate from $20.0 million for the year ended December 31, 2020 (of which $11.3 million was revenue from sales of goods primarily to Eli Lilly, $4.9 million was royalty revenue, and $3.8 million was revenue from promotion and marketing services to Eli Lilly which commenced in October 2020) to $53.5 million for the year ended December 31, 2021 (of which $15.8 million was revenue from sales of goods primarily to Eli Lilly, $10.3 million was royalty revenue and $27.4 million was revenue from promotion and marketing services to Eli Lilly). The increase was also attributable to revenue generated from the commercial launch of Sulanda of $11.6 million and Orpathys of $11.3 million (of which $6.5 million was revenue from sales of goods and $4.8 million was royalty revenue) in January 2021 and July 2021, respectively. In addition, revenue related to collaboration research and development services increased from $9.8 million for the year ended December 31, 2020 to $42.7 million for the year ended December 31, 2021, primarily attributable to the receipt of a $25.0 million milestone payment from AstraZeneca upon the commercial launch of Orpathys.

Revenue from our Other Ventures increased by 19.6% from $197.8 million for the year ended December 31, 2020 to $236.5 million for the year ended December 31, 2021, primarily due to an increase in sales of prescription drug products. Revenue from sales of prescription drugs increased by 23.6% from $165.1 million for the year ended December 31, 2020 to $204.1 million for the year ended December 31, 2021 primarily due to increased sales by our consolidated joint venture Hutchison Sinopharm. Revenue from the sales of our consumer health products remained relatively stable at $32.7 million and $32.4 million for the years ended December 31, 2020 and 2021, respectively.

Cost of Revenues

Our cost of revenues increased by 37.0% from $188.5 million for the year ended December 31, 2020 to $258.2 million for the year ended December 31, 2021. This increase was primarily due to increased sales by both the Oncology/Immunology and Other Ventures operations.

Cost of revenues from Oncology/Immunology increased by 270.0% from $12.1 million for the year ended December 31, 2020 to $44.8 million for the year ended December 31, 2021, primarily due to an increase in sales of Elunate, including the provision of promotion and marketing services to Eli Lilly which commenced in October 2020, and the commencement of sales of Sulanda which launched in January 2021 and Orpathys which launched in July 2021.

Cost of revenues from our Other Ventures increased by 21.0% from $176.4 million for the year ended December 31, 2020 to $213.4 million for the year ended December 31, 2021, which was primarily due to increased sales.

Cost of revenues as a percentage of our revenues decreased from 82.7% to 72.5% across these periods primarily due to the increase in revenue from Oncology/Immunology which has higher margins than Other Ventures.

Research and Development Expenses

Our research and development expenses incurred by Oncology/Immunology increased by 71.1% from $174.8 million for the year ended December 31, 2020 to $299.1 million for the year ended December 31, 2021, which was primarily due to an $84.2 million increase in CROs and other clinical trial related costs and a $40.1 million increase in employee compensation related and other costs. These increased costs were due to a significant expansion of clinical activities in the United States and rapid organizational growth to support such expansion. In particular, this increase was attributable to the expansion of the fruquintinib, savolitinib, surufatinib, amdizalisib, HMPL-306, HMPL-760 development programs and a $10.0 million payment in connection with our in-licensing agreement for tazemetostat. As a result, research and development expenses as a percentage of our revenue increased from 76.7% to 84.0% across these periods.

Selling Expenses

Our selling expenses increased by 233.7% from $11.3 million for the year ended December 31, 2020 to $37.8 million for the year ended December 31, 2021, primarily attributable to the commencement of marketing activities following the commercial launch of Sulanda in January 2021. Selling expenses as a percentage of our revenues increased from 5.0% to 10.6% across these periods.

Administrative Expenses

Our administrative expenses increased by 78.5% from $50.0 million for the year ended December 31, 2020 to $89.3 million for the year ended December 31, 2021. This was primarily due to a $29.2 million increase in administrative expenses incurred by Oncology/Immunology, which was mainly related to increased staff cost to support the expansion of our clinical activities. This increase was also attributable to preparation costs for the potential launch of marketed products in the United States and other countries. Administrative expenses as a percentage of our revenues increased from 21.9% to 25.1% across these periods.

Gain on Divestment of An Equity Investee

We had a gain on divestment of an equity investee of $121.3 million for the year ended December 31, 2021, before applicable capital gain taxes and amounts attributable to non-controlling interests, which is related to the disposal of our shareholding interest in Hutchison Baiyunshan.

Other Income/(Expense)

We had net other income of $6.9 million for the year ended December 31, 2020 compared to net other expense of $8.7 million for the year ended December 31, 2021. The change was primarily due to a $12.5 million fair value loss recorded on a warrant to purchase shares of Epizyme in 2021, a decrease in interest income of $1.2 million due to lower bank deposit rates, and a decrease in foreign currency exchange gains of $1.6 million.

Income Tax Expense

Our income tax expense increased from $4.8 million for the year ended December 31, 2020 to $11.9 million for the year ended December 31, 2021, primarily due to the capital gains taxes related to the disposal of our shareholding interest in Hutchison Baiyunshan.

Equity in Earnings of Equity Investees

Our equity in earnings of equity investees, net of tax, decreased by 23.3% from $79.0 million for the year ended December 31, 2020 to $60.6 million for the year ended December 31, 2021. This change was primarily due to the disposal of our shareholding interest in Hutchison Baiyunshan in September 2021.

Shanghai Hutchison Pharmaceuticals

The following table shows a summary of the results of operations of Shanghai Hutchison Pharmaceuticals for the years indicated. The consolidated financial statements of Shanghai Hutchison Pharmaceuticals are prepared in accordance with IFRS as issued by the IASB and are presented separately elsewhere in this annual report.

	Year Ended December 31,			
	2021		2020	
	($'000)	%	($'000)	%
Revenue	332,648	100.0	276,354	100.0
Cost of sales	(77,559)	(23.3)	(72,163)	(26.1)
Selling expenses	(131,821)	(39.6)	(111,892)	(40.5)
Administrative expenses	(22,627)	(6.8)	(17,907)	(6.5)
Other net operating income	4,759	1.4	3,473	1.3
Taxation charge	(15,896)	(4.8)	(10,833)	(3.9)
Profit for the year	89,388	26.9	67,020	24.3
Equity in earnings of equity investee attributable to our company	44,678	13.4	33,502	12.1

Shanghai Hutchison Pharmaceuticals' revenue increased by 20.4% from $276.4 million for the year ended December 31, 2020 to $332.6 million for the year ended December 31, 2021, primarily due to an increase in sales of She Xiang Bao Xin pills, a vasodilator used in the treatment of heart conditions. Sales of She Xiang Bao Xin pills increased by 22.8% from $250.0 million for the year ended December 31, 2020 to $ 307.1 million for the year ended December 31, 2021.

Cost of sales increased by 7.5% from $72.2 million for the year ended December 31, 2020 to $77.6 million for the year December 31, 2021, primarily due to higher sales of She Xiang Bao Xin pills. Shanghai Hutchison Pharmaceuticals' revenue increased at a higher rate than cost of sales due to an increased proportion of sales of higher margin She Xiang Bao Xin pills.

Selling expenses increased by 17.8% from $111.9 million for the year ended December 31, 2020 to $131.8 million for the year ended December 31, 2021, as a result of increased spending on marketing and promotional activities to support the increase in sales.

Administrative expenses increased by 26.4% from $17.9 million for the year ended December 31, 2020 to $22.6 million for the year ended December 31, 2021, primarily due to an increase in research and development expenses for new products.

Other net operating income increased by 37.0% from $3.5 million for the year ended December 31, 2020 to $4.8 million for the year ended December 31, 2021, primarily due to an increase in government grants and interest income.

Taxation charge increased by 46.7% from $10.8 million for the year ended December 31, 2020 to $15.9 million for the year ended December 31, 2021, primarily due to an increase in taxable profit.

As a result of the foregoing, profit increased by 33.4% from $67.0 million for the year ended December 31, 2020 to $89.4 million for the year ended December 31, 2021. Our equity in earnings of equity investees contributed by this joint venture was $33.5 million and $44.7 million for the years ended December 31, 2020 and 2021, respectively.

Hutchison Baiyunshan

The following table shows a summary of the results of operations of Hutchison Baiyunshan for the periods indicated. The consolidated financial statements of Hutchison Baiyunshan are prepared in accordance with IFRS as issued by the IASB and are presented separately elsewhere in this annual report.

	Period Ended September 28, 2021		Year Ended December 31, 2020	
	($'000)	%	($'000)	%
Revenue	209,528	100.0	232,368	100.0
Cost of sales	(98,462)	(47.0)	(115,564)	(49.7)
Selling expenses	(74,425)	(35.5)	(74,066)	(31.9)
Administrative expenses	(21,659)	(10.3)	(25,664)	(11.0)
Gain on return of land	16,433	7.8	84,667	36.4
Other net operating income	5,306	2.5	6,071	2.6
Taxation charge	(4,840)	(2.3)	(16,494)	(7.1)
Profit attributable to equity holders of Hutchison Baiyunshan	31,850	15.2	91,276	39.3
Equity in earnings of equity investee attributable to our company	15,919	7.6	45,641	19.6

Fluctuations in revenue, cost of sales, administrative expenses and other net operating income between the periods presented is primarily due to the disposal of Hutchison Baiyunshan on September 28, 2021.

Selling expenses as a percentage of revenue increased by 3.6% from 31.9% for the year ended December 31, 2020 to 35.5% for the period ended September 28, 2021, primarily due to an increase in advertising expenses for brand building activities.

Gain on return of land was related to a one-time gain from land compensation for a return of land use rights to the Guangzhou government, and the majority of the compensation amount was received and recognized in 2020.

Taxation charge decreased by 70.7% from $16.5 million for the year ended December 31, 2020 to $4.8 million for the period ended September 28, 2021, primarily due to a decrease in gain on return of land between these periods.

As a result of the foregoing, profit attributable to equity holders of Hutchison Baiyunshan decreased by 65.1% from $91.3 million for the year ended December 31, 2020 to $31.9 million for the period ended September 28, 2021. Our equity in earnings of equity investees contributed by this joint venture was $45.6 million and $15.9 million for the year ended December 31, 2020 and the period ended September 28, 2021, respectively.

For more information on the financial results of our non-consolidated joint ventures, see "—Key Components of Results of Operations— Equity in Earnings of Equity Investees."

Net Loss

As a result of the foregoing, our net loss increased from $115.5 million for the year ended December 31, 2020 to $167.0 million for the year ended December 31, 2021. Net loss attributable to our company increased from $125.7 million for the year ended December 31, 2020 to $194.6 million for the year ended December 31, 2021.

Year Ended December 31, 2020 Compared to Year Ended December 31, 2019

Revenues

Our revenue increased by 11.3% from $204.9 million for the year ended December 31, 2019 to $228.0 million for the year ended December 31, 2020, which was caused by increased revenue from both Oncology/Immunology and Other Ventures operations.

Revenue from Oncology/Immunology increased by 12.8% from $26.8 million for the year ended December 31, 2019 to $30.2 million for the year ended December 31, 2020, primarily due to an increase in revenue related to the sale of Elunate from $10.8 million for the year ended December 31, 2019 (of which $2.7 million was royalty revenue and $8.1 million was revenue from sales to Eli Lilly) to $20.0 million for the year ended December 31, 2020 (of which $4.9 million was royalty revenue, $11.3 million was revenue from sales of goods primarily to Eli Lilly and $3.8 million was revenue from promotion and marketing services to Eli Lilly which commenced in October 2020) as a result of the inclusion of Elunate in the 2020 China NRDL. Elunate was included on China's NRDL at an approximately 60% discount to its initial retail price. The inclusion of Elunate resulted in a substantial improvement in sales volume due to the availability of third-party reimbursements. This increase was offset in part by a decrease in revenue related to collaboration research and development services from $15.5 million for the year ended December 31, 2019 to $9.8 million for the year ended December 31, 2020 as there was less clinical activity subject to reimbursement from our collaboration partners.

Revenue from our Other Ventures increased by 11.0% from $178.1 million for the year ended December 31, 2019 to $197.8 million for the year ended December 31, 2020, primarily due to an increase in sales of prescription drug products. Revenue from sales of prescription drugs increased by 17.0% from $141.1 million for the year ended December 31, 2019 to $165.1 million for the year ended December 31, 2020 primarily due to increased sales by our consolidated joint venture Hutchison Sinopharm. The increase was offset in part by lower provision of services which decreased from $2.6 million for the year ended December 31, 2019 to nil for the year ended December 31, 2020 after the discontinuation of our distribution of Seroquel in May 2019. This increase was also offset in part by a decrease in sales of consumer health products which decreased by 4.9% from $34.4 million for the year ended December 31, 2019 to $32.7 million for the year ended December 31, 2020. This decrease was primarily attributable to decreased sales of infant nutrition products.

Our Other Ventures' results of operations are affected by seasonality. For more information, see "—Factors Affecting our Results of Operations—Other Ventures—Seasonality."

Cost of Revenues

Our cost of revenues increased by 17.7% from $160.2 million for the year ended December 31, 2019 to $188.5 million for the year ended December 31, 2020. This increase was primarily due to increased sales by our Other Ventures. Our cost of revenues increased at a higher rate than revenue due to an increased proportion of sales of lower margin products by Hutchison Sinopharm. As a result, cost of revenues as a percentage of our revenues increased from 78.2% to 82.7% across these periods.

Research and Development Expenses

Our research and development expenses incurred by Oncology/Immunology increased by 26.5% from $138.2 million for the year ended December 31, 2019 to $174.8 million for the year ended December 31, 2020, which was primarily attributable to a $18.1 million increase in payments to CROs and other clinical trial related costs and a $18.5 million increase in employee compensation related and other costs. These increased costs were due to a significant expansion of clinical activities in the United States and rapid organizational growth to support such expansion. In particular, this increase was attributable to the expansion of the fruquintinib, surufatinib, HMPL-306 and amdizalisib development programs. As a result, research and development expenses as a percentage of our revenue increased from 67.4% to 76.7% across these periods.

Selling Expenses

Our selling expenses decreased by 17.4% from $13.7 million for the year ended December 31, 2019 to $11.3 million for the year ended December 31, 2020, primarily due to decreased marketing activities after the COVID-19 outbreak. Selling expenses as a percentage of our revenues from our Other Ventures decreased from 7.7% to 5.6% across these periods.

Administrative Expenses

Our administrative expenses increased by 27.6% from $39.2 million for the year ended December 31, 2019 to $50.0 million for the year ended December 31, 2020. This was primarily due to $7.0 million increase in administrative expenses incurred by Oncology/Immunology, which was mainly related to increased staff cost to support the expansion of our clinical activities. There was also an increase of $3.0 million in administrative expenses incurred by our corporate head office for organizational expansion. Administrative expenses as a percentage of our revenues increased from 19.1% to 21.9% across these periods.

Other Income/(Expense)

We had net other income of $5.3 million for the year ended December 31, 2019, compared to net other income of $6.9 million for the year ended December 31, 2020. The increase was primarily due to foreign currency exchange gains of $3.0 million, offset in part by a decline in interest income of $1.7 million due to lower bank deposit rates.

Income Tax Expense

Our income tax expense increased from $3.3 million for the year ended December 31, 2019 to $4.8 million for the year ended December 31, 2020 primarily due to the accrual of withholding tax on the undistributed earnings in relation to the gain on return of land by Hutchison Baiyunshan.

Equity in Earnings of Equity Investees

Our equity in earnings of equity investees, net of tax, increased by 94.2% from $40.7 million for the year ended December 31, 2019 to $79.0 million for the year ended December 31, 2020. This change was primarily due to the one-time gain on return of land recorded by our former non-consolidated joint venture, Hutchison Baiyunshan, of which our attributable portion recorded to equity in earnings of equity investees, net of tax, was $36.0 million for the year ended December 31, 2020.

Shanghai Hutchison Pharmaceuticals

The following table shows a summary of the results of operations of Shanghai Hutchison Pharmaceuticals for the years indicated. The consolidated financial statements of Shanghai Hutchison Pharmaceuticals are prepared in accordance with IFRS as issued by the IASB and are presented separately elsewhere in this annual report.

	Year Ended December 31,			
	2020		2019	
	($'000)	%	($'000)	%
Revenue	276,354	100.0	272,082	100.0
Cost of sales	(72,163)	(26.1)	(77,313)	(28.4)
Selling expenses	(111,892)	(40.5)	(110,591)	(40.6)
Administrative expenses	(17,907)	(6.5)	(14,761)	(5.4)
Other net operating income	3,473	1.3	2,941	1.1
Taxation charge	(10,833)	(3.9)	(11,015)	(4.0)
Profit for the year	67,020	24.3	61,301	22.5
Equity in earnings of equity investee attributable to our company	33,502	12.1	30,654	11.3

Shanghai Hutchison Pharmaceuticals' revenue increased by 1.6% from $272.1 million for the year ended December 31, 2019 to $276.4 million for the year ended December 31, 2020, primarily due to an increase in sales of She Xiang Bao Xin pills, a vasodilator used in the treatment of heart conditions. Sales of She Xiang Bao Xin pills increased by 4.4% from $239.5 million for the year ended December 31, 2019 to $250.0 million for the year ended December 31, 2020. Additionally, revenue from Shanghai Hutchison Pharmaceuticals' distribution business decreased from $11.1 million for the year ended December 31, 2019 to $5.4 million for the year ended December 31, 2020, primarily due to lower provision of services after the discontinuation of our distribution of Seroquel.

Cost of sales decreased by 6.7% from $77.3 million for the year ended December 31, 2019 to $72.2 million for the year ended December 31, 2020, primarily due to the discontinuation of our distribution of Seroquel. Additionally, Shanghai Hutchison Pharmaceuticals' revenue increased at a higher rate than cost of sales due to an increased proportion of sales of higher margin She Xiang Bao Xin pills.

Selling expenses increased by 1.2% from $110.6 million for the year ended December 31, 2019 to $111.9 million for the year ended December 31, 2020, in line with the increase in revenues.

Administrative expenses increased by 21.3% from $14.8 million for the year ended December 31, 2019 to $17.9 million for the year ended December 31, 2020, primarily due to an increase in research and development expenses for new products.

Other net operating income is primarily comprised of government grants and interest income. Other net operating income increased by 18.1% from $2.9 million for the year ended December 31, 2019 to $3.5 million for the year ended December 31, 2020, primarily due to higher interest income of $0.4 million.

Taxation charge decreased by 1.7% from $11.0 million for the year ended December 31, 2019 to $10.8 million for the year ended December 31, 2020, primarily due to more tax concessions received in the year ended December 31, 2020.

As a result of the foregoing, profit increased by 9.3% from $61.3 million for the year ended December 31, 2019 to $67.0 million for the year ended December 31, 2020. Our equity in earnings of equity investees contributed by this joint venture was $30.7 million and $33.5 million for the years ended December 31, 2019 and 2020, respectively.

Hutchison Baiyunshan

The following table shows a summary of the results of operations of our former non-consolidated joint venture, Hutchison Baiyunshan, for the years indicated. The consolidated financial statements of Hutchison Baiyunshan are prepared in accordance with IFRS as issued by the IASB and are presented separately elsewhere in this annual report.

	Year Ended December 31,			
	2020		2019	
	($'000)	%	($'000)	%
Revenue	232,368	100.0	215,403	100.0
Cost of sales	(115,564)	(49.7)	(100,279)	(46.6)
Selling expenses	(74,066)	(31.9)	(74,013)	(34.4)
Administrative expenses	(25,664)	(11.0)	(23,817)	(11.1)
Gain on return of land	84,667	36.4	—	—
Other net operating income	6,071	2.6	5,626	2.6
Taxation charge	(16,494)	(7.1)	(3,634)	(1.7)
Profit attributable to equity holders of Hutchison Baiyunshan	91,276	39.3	19,792	9.2
Equity in earnings of equity investee attributable to our company	45,641	19.6	9,899	4.6

Hutchison Baiyunshan's revenue increased by 7.9% from $215.4 million for the year ended December 31, 2019 to $232.4 million for the year ended December 31, 2020, primarily due to an increase in sales of Banlangen, an anti-viral product, after the COVID-19 outbreak.

Cost of sales increased by 15.2% from $100.3 million for the year ended December 31, 2019 to $115.6 million for the year ended December 31, 2020, primarily due to an increase in raw material costs for Banlangen.

Selling expenses remained stable at $74.0 million and $74.1 million for the years ended December 31, 2019 and 2020, respectively.

Administrative expenses increased by 7.8% from $23.8 million for the year ended December 31, 2019 to $25.7 million for the year ended December 31, 2020, primarily due to an increase in general overhead costs incurred.

Other net operating income is primarily comprised of government grants, interest income, brand-licensing income and rental income. Other net operating income increased by 7.9% from $5.6 million for the year ended December 31, 2019 to $6.1 million for the year ended December 31, 2020, primarily due to higher government grants of $0.3 million and higher brand-licensing income of $0.2 million.

Taxation charge increased by 354% from $3.6 million for the year ended December 31, 2019 to $16.5 million for the year ended December 31, 2020, primarily due to a tax of $12.7 million on a one-time gain on return of land for the year ended December 31, 2020.

As a result of the foregoing and the one-time gain on return of land of $84.7 million related to land compensation received from the Guangzhou government, profit attributable to equity holders of Hutchison Baiyunshan increased by 361% from $19.8 million for the year ended December 31, 2019 to $91.3 million for the year ended December 31, 2020. Our equity in earnings of equity investees contributed by this joint venture was $9.9 million and $45.6 million for the years ended December 31, 2019 and 2020, respectively.

For more information on the financial results of our non-consolidated joint ventures, see "—Key Components of Results of Operations— Equity in Earnings of Equity Investees."

Net Loss

As a result of the foregoing, our net loss increased from $103.7 million for the year ended December 31, 2019 to $115.5 million for the year ended December 31, 2020. Net loss attributable to our company increased from $106.0 million for the year ended December 31, 2019 to $125.7 million for the year ended December 31, 2020.

B. Liquidity and Capital Resources

To date, we have taken a multi-source approach to fund our operations, including through cash flows generated and dividend payments from our Oncology/Immunology and Other Ventures operations, service and milestone and upfront payments from our collaboration partners, bank borrowings, investments from other third parties, proceeds from our listings on various stock exchanges and follow-on offerings.

Our Oncology/Immunology operations have historically not generated significant profits or have operated at a net loss, as creating potential global first-in-class or best-in-class drug candidates requires a significant investment of resources over a prolonged period of time. As a result, we anticipate that we may need additional financing for our Oncology/Immunology operations in future periods. See Item 3.D. "Risk Factors—Risks Relating to Our Oncology/Immunology Operations and Development of Our Drug Candidates—Historically, our in house research and development division, which is included in our Oncology/Immunology operations, has not generated significant profits or has operated at a net loss. Our future profitability is dependent on the successful commercialization of our drug candidates."

As of December 31, 2021, we had cash and cash equivalents of $377.5 million and short-term investments of $634.2 million and unutilized bank facilities of $157.4 million. Substantially all of our bank deposits are at major financial institutions, which we believe are of high credit quality. As of December 31, 2021, we had $26.9 million in bank loans, all of which was related to a term loan from HSBC. The total weighted average cost of bank borrowings for the year ended December 31, 2021 was 1.08% per annum. For additional information, see "—Loan Facilities."

Certain of our subsidiaries and joint ventures, including those registered as wholly foreign-owned enterprises in China, are required to set aside at least 10.0% of their after-tax profits to their general reserves until such reserves reach 50.0% of their registered capital. In addition, certain of our joint ventures are required to allocate certain of their after-tax profits as determined in accordance with related regulations and their respective articles of association to the reserve funds upon their board approval. Profit appropriated to the reserve funds for our subsidiaries and joint ventures incorporated in the PRC was approximately $51,000, $44,000 and $89,000 for the years ended December 31, 2019, 2020 and 2021, respectively.

In addition, as a result of PRC regulations restricting dividend distributions from such reserve funds and from a company's registered capital, our PRC subsidiaries are restricted in their ability to transfer a certain amount of their net assets to us as cash dividends, loans or advances. This restricted portion amounted to $0.1 million as of December 31, 2021. Although we do not currently require any such dividends, loans or advances from our PRC subsidiaries to fund our operations, should we require additional sources of liquidity in the future, such restrictions may have a material adverse effect on our liquidity and capital resources. For more information, see Item 4.B. "Business Overview—Regulation—PRC Regulation of Foreign Currency Exchange, Offshore Investment and State-Owned Assets—Regulation on Investment in Foreign invested Enterprises—Regulation on Dividend Distribution."

In addition, our non-consolidated joint venture Shanghai Hutchison Pharmaceuticals held $50.0 million in cash and cash equivalents and no bank borrowings as of December 31, 2021. Such cash and cash equivalents are only accessible by us through dividend payments from the joint venture. The level of dividends declared by the joint venture is subject to agreement each year between us and our joint venture partner based on the profitability and working capital needs of the joint venture. As a result, we cannot guarantee that the joint venture will continue to pay dividends to us in the future at the same rate we have enjoyed in the past, or at all, which may have a material adverse effect on our liquidity and capital resources. For more information, see Item 3.D. "Risk Factors—Risks Relating to Sales of our Internally Developed Drugs and Other Drugs—As a significant portion of the operations of our Other Ventures is conducted through joint venture, we are largely dependent on the success of our joint venture and our receipt of dividends or other payments from our joint venture for cash to fund our operations and our investment in joint venture subject to liquidity risk."

We believe that our current levels of cash and cash equivalents, short-term investments, along with cash flows from operations, dividend payments and unutilized bank borrowings, will be sufficient to meet our anticipated cash needs for at least the next 12 months. In the long term, we believe that we can meet our need for cash through revenues generated from marketed products, public and private sales of our securities and the potential disposals of our remaining non-core businesses. However, we may require additional financing in order to fund all of the clinical development efforts that we plan to undertake to accelerate the development of our clinical-stage drug candidates. For more information, see Item 3.D. "Risk Factors—Risks Relating to Our Financial Position and Need for Capital."

	Year Ended December 31,		
	2021	2020	2019
		($'000)	
Cash Flow Data:			
Net cash used in operating activities	(204,223)	(62,066)	(80,912)
Net cash (used in)/generated from investing activities	(306,320)	(125,441)	119,028
Net cash generated from/(used in) financing activities	650,028	296,434	(1,493)
Net increase in cash and cash equivalents	139,485	108,927	36,623
Effect of exchange rate changes	2,427	5,546	(1,502)
Cash and cash equivalents at beginning of the year	235,630	121,157	86,036
Cash and cash equivalents at end of the year	377,542	235,630	121,157

Net Cash used in Operating Activities

Net cash used in operating activities was $62.1 million for the year ended December 31, 2020, compared to net cash used in operating activities of $204.2 million for the year ended December 31, 2021. The net change of $142.1 million was primarily attributable to higher operating expenses of $259.8 million from $424.6 million for the year ended December 31, 2020 to $684.4 million for the year ended December 31, 2021, offset in part by an increase in revenues of approximately $128.1 million from $228.0 million for the year ended December 31, 2020 to $356.1 million for the year ended December 31, 2021.

Net cash used in operating activities was $80.9 million for the year ended December 31, 2019, compared to net cash used in operating activities of $62.1 million for the year ended December 31, 2020. The net change of $18.8 million was primarily attributable to an increase in dividends received from Shanghai Hutchison Pharmaceuticals and Hutchison Baiyunshan of $58.6 million from $28.1 million for the year ended December 31, 2019 to $86.7 million for the year ended December 31, 2020. The net change was partially offset by higher net losses, primarily due to an increase in research and development expenses of $36.6 million from $138.2 million for the year ended December 31, 2019 to $174.8 million for the year ended December 31, 2020.

Net Cash (used in)/generated from Investing Activities

Net cash used in investing activities was $125.4 million for the year ended December 31, 2020, compared to net cash used in investing activities of $306.3 million for the year ended December 31, 2021. The net change of $180.9 million was primarily attributable to an increase in net deposits in short-term investment of $331.1 million from $103.5 million for the year ended December 31, 2020 to $434.6 million for the year ended December 31, 2021. The net change was also attributable to the payment of $15.0 million during the year ended December 31, 2021 to acquire a warrant to purchase Epizyme shares. The net change was partially offset by the proceeds received from the divestment of Hutchison Baiyunshan of $159.1 million during the year ended December 31, 2021.

Net cash generated from investing activities was $119.0 million for the year ended December 31, 2019, compared to net cash used in investing activities of $125.4 million for the year ended December 31, 2020. The net change of $244.4 million was primarily attributable to a net withdrawal of deposits in short-term investments of $118.9 million for the year ended December 31, 2019 compared to a net deposit in short-term investments of $103.5 million for the year ended December 31, 2020. The net change was also attributable to a purchase of leasehold land of $11.6 million in Shanghai.

Net Cash generated from/(used in) Financing Activities

Net cash generated from financing activities was $296.4 million for the year ended December 31, 2020, compared to net cash generated from financing activities of $650.0 million for the year ended December 31, 2021. The net change of $353.6 million was primarily attributable to the net proceeds of $685.4 million from a private placement in April 2021 and from our public offering on the SEHK in June and exercise of the over-allotment option in July 2021, as compared to net proceeds of $310.0 million from our follow-on offering in the United States and private placements in 2020. This net change was partially offset by an increase in purchases of ADSs by the trustee of our LTIP for the settlement of certain equity awards which totaled $12.9 million for the year ended December 31, 2020 as compared to $27.3 million for the year ended December 31, 2021, as well as an increase in dividends paid to non-controlling shareholders of subsidiaries which totaled $1.5 million for the year ended December 31, 2020 as compared to $9.9 million for the year end December 31, 2021.

Net cash used in financing activities was $1.5 million for the year ended December 31, 2019, compared to net cash generated from financing activities of $296.4 million for the year ended December 31, 2020. The net change of $297.9 million was primarily attributable to net proceeds of $310.0 million from our follow-on offering in the United States in January and February 2020 and private placements in July 2020 and November 2020.

Contractual Obligations

The following table sets forth our contractual obligations as of December 31, 2021. For more information on bank borrowings and interest on bank borrowings, please see "—Loan Facilities." Our purchase obligations relate to property, plant and equipment that are contracted for but not yet paid. Our lease obligations primarily comprise future aggregate minimum lease payments in respect of various factories, warehouse, offices and other assets under non-cancellable lease agreements. For more information on purchase obligations and lease obligations, please see "—Capital Expenditures."

	Payment Due by Period				
	Total	Less Than 1 Year	1-2 Years	2-5 Years	More Than 5 Years
			($'000)		
Bank borrowings	26,923	26,923	—	—	—
Interest on bank borrowings	104	104	—	—	—
Purchase obligations	44,204	42,519	125	1,560	—
Lease obligations	12,818	5,348	3,434	3,241	795
Total	84,049	74,894	3,559	4,801	795

Shanghai Hutchison Pharmaceuticals

The following table sets forth the contractual obligations of our non-consolidated joint venture Shanghai Hutchison Pharmaceuticals as of December 31, 2021. Shanghai Hutchison Pharmaceuticals' purchase obligations comprise capital commitments for property, plant and equipment contracted for but not yet paid. Shanghai Hutchison Pharmaceuticals' lease obligations primarily comprise future aggregate minimum lease payments in respect of various offices under non-cancellable lease agreements.

	Payment Due by Period				
	Total	Less Than 1 Year	1-2 Years	2-5 Years	More Than 5 Years
			($'000)		
Purchase obligations	155	155	—	—	—
Lease obligations	3,149	859	784	1,506	—
Total	3,304	1,014	784	1,506	—

Loan Facilities

In November 2018, our subsidiary HUTCHMED Group (HK) Limited (formerly Hutchison China MediTech (HK) Limited), renewed a three-year revolving loan facility with HSBC. The facility amount of this loan was HK$234.0 million ($30.0 million) with an interest rate at the Hong Kong Inter-bank Offered Rate, or HIBOR, plus 0.85% per annum. This credit facility was guaranteed by us and included certain financial covenant requirements. The revolving loan facility expired in November 2021.

In May 2019, HUTCHMED Group (HK) Limited entered into additional credit facility arrangements with HSBC for the provision of unsecured credit facilities in the aggregate amount of HK$400.0 million ($51.3 million). The 3-year credit facilities include (i) a HK$210.0 million ($26.9 million) term loan facility and (ii) a HK$190.0 million ($24.4 million) revolving loan facility, both with an interest rate at HIBOR plus 0.85% per annum. These credit facilities are guaranteed by us and include certain financial covenant requirements. In October 2019, we drew down HK$210.0 million ($26.9 million) from the term loan facility and as of December 31, 2021, no amount was drawn from the revolving loan facility.

In August 2020, HUTCHMED Group (HK) Limited entered into a 24-month revolving credit facility with Deutsche Bank AG in the amount of HK$117.0 million ($15.0 million) with an interest rate at HIBOR plus 4.5% per annum. This revolving facility is guaranteed by us and includes certain financial covenant requirements. As of December 31, 2021, no amount was drawn from the revolving loan facility.

In October 2021, our subsidiary HUTCHMED Limited entered into a 10-year fixed asset loan facility agreement with Bank of China Limited for the provision of a secured credit facility of RMB754.9 million ($118.1 million) with an annual interest rate at the 5-year China Loan Prime Rate less 0.65%. This credit facility is guaranteed by HUTCHMED Limited's immediate holding company, HUTCHMED Investment (HK) Limited (formerly Hutchison MediPharma (HK) Investment Limited), and secured by the underlying leasehold land and buildings, and includes certain financial covenant requirements. As of December 31, 2021, no amount was drawn from the fixed asset loan facility.

Our non-consolidated joint venture Shanghai Hutchison Pharmaceuticals had no bank borrowings outstanding as of December 31, 2021.

Gearing Ratio

The gearing ratio of our group, which was calculated by dividing total interest-bearing loans by total equity, was 2.6% as of December 31, 2021, a decrease from 5.2% as of December 31, 2020. The decrease was primarily attributable to the increase in equity due to our primary offering of shares on the SEHK.

Capital Expenditures

We had capital expenditures of $8.6 million, $19.6 million and $16.8 million for the years ended December 31, 2019, 2020 and 2021, respectively. Our capital expenditures during these periods were primarily used for the purchases of leasehold land and property, plant and equipment for a new large-scale manufacturing facility for innovative drugs in Shanghai, China and to expand the HUTCHMED Limited research facilities and the manufacturing facility in Suzhou, China. Our capital expenditures have been primarily funded by cash flows from operations and proceeds from our initial public and follow-on offerings in Hong Kong and the United States and other equity offerings.

As of December 31, 2021, we had commitments for capital expenditures of approximately $44.2 million, primarily for the construction of the new manufacturing facility in Shanghai. We expect to fund these capital expenditures through cash flows from operations, bank borrowings and existing cash resources.

Our non-consolidated joint venture Shanghai Hutchison Pharmaceuticals had capital expenditures of $4.6 million, $2.4 million and $3.4 million for the years ended December 31, 2019, 2020 and 2021, respectively. These capital expenditures were primarily related to the renovation of new office and improvements to its production facilities in Shanghai. These capital expenditures were primarily funded through cash flows from operations of Shanghai Hutchison Pharmaceuticals.

C. Research and Development, Patents and Licenses, etc.

Full details of our research and development activities and expenditures are given in the "Business" and "Operating and Financial Review and Prospects" sections of this annual report above.

D. Trend Information.

Other than as described elsewhere in this annual report, we are not aware of any trends, uncertainties, demands, commitments or events that are reasonably likely to have a material adverse effect on our revenue, income, profitability, liquidity or capital resources, or that would cause our reported financial information not necessarily to be indicative of future operation results or financial condition.

E. Critical Accounting Estimates.

For information on our critical accounting estimates, please see "—Operating Resulting—Critical Accounting Policies and Significant Judgments and Estimates" section of this annual report above.

ITEM 6. DIRECTORS, SENIOR MANAGEMENT AND EMPLOYEES

A. Directors and Senior Management.

Business Experience and Qualifications of our Directors

Below is a list of the names and ages of our directors and officers as of March 1, 2022, and a brief account of the business experience of each of them. The business address for our directors and officers is c/o HUTCHMED (China) Limited, Level 18, The Metropolis Tower, 10 Metropolis Drive, Hunghom, Kowloon, Hong Kong.

Name	Age	Position
Chi Keung To, Simon	70	Executive Director and Chairman
Christian Lawrence Hogg	56	Executive Director and Chief Executive Officer
Chig Fung Cheng, Johnny	55	Executive Director and Chief Financial Officer
Weiguo Su	64	Executive Director and Chief Scientific Officer
Dan Eldar	68	Non-executive Director
Edith Shih	70	Non-executive Director and Company Secretary
Paul Rutherford Carter	61	Senior Independent Non-executive Director
Karen Jean Ferrante	64	Independent Non-executive Director
Graeme Allan Jack	71	Independent Non-executive Director
Shu Kam Mok, Tony	61	Independent Non-executive Director
Marek Krzysztof Kania	59	Executive President, Managing Director and Chief Medical Officer
Karen Jane Atkin	56	Executive Vice President and Chief Operating Officer
Zhenping Wu	62	Senior Vice President, Pharmaceutical Sciences
Kin Hung Lee, Mark	44	Senior Vice President, Corporate Finance and Development
Qingmei Wang, May	58	Senior Vice President, Business Development & Strategic Alliances
Hong Chen	51	Senior Vice President and Chief Commercial Officer (China)
Thomas R.Held	61	Senior Vice President, Commercial (U.S.)
Charles George Rupert Nixon	52	Group General Counsel

Chi Keung To, Simon has been a director since 2000 and an executive director and chairman of our board of directors since 2006. He is also a member of our nomination committee, remuneration committee and technical committee. He is the managing director of Hutchison Whampoa (China) Limited and has been with Hutchison Whampoa (China) Limited for over 40 years, building its business from a small trading company to a multi-billion dollar investment group. He has negotiated major transactions with multinational corporations such as Procter & Gamble, or P&G, Lockheed, Pirelli, Beiersdorf, United Airlines and British Airways. He is currently chairman of the board of directors of Gama Aviation Plc, which is admitted to trading on AIM, and formerly served as independent non-executive director on the boards of China Southern Airlines Company Limited and Air China Limited. Mr. To's career in China spans more than 45 years. He is the original founder of the China healthcare business of Hutchison Whampoa Limited (currently a subsidiary of CK Hutchison) and has been instrumental in its acquisitions made to date. He received a bachelor's degree in mechanical engineering from Imperial College, London and a master in business administration from Stanford University's Graduate School of Business.

Christian Lawrence Hogg has been an executive director and our chief executive officer since 2006. He is also a member of our technical committee and sustainability committee. He joined the business in 2000, as its first employee, and has since led all aspects of the creation, implementation and management of our strategy, business and listings. This includes the establishment of our Oncology/Immunology operations which now have an organization of about 1,500 scientific and commercial personnel involved in the launch of its first three oncology drugs, Elunate, Sulanda and Orpathys in China, as well as the management of global clinical development activities on our portfolio of twelve in-house discovered novel oncology drug candidates. Furthermore, Mr. Hogg oversaw the acquisition and operational integration of assets that led to the formation of our Other Ventures operations, which today employs about 3,100 personnel involved in manufacture, market and distribute prescription drugs and consumer health products, covering an extensive network of hospitals across China. Prior to joining us, he spent ten years with P&G, starting in the United States in Finance and then Brand Management in the Laundry and Cleaning Products Division. He then moved to China to manage P&G's detergent business, followed by a move to Brussels to run P&G's global bleach business. Mr. Hogg received a bachelor's degree in civil engineering from the University of Edinburgh in and a master in business administration from the University of Tennessee.

Chig Fung Cheng, Johnny has been an executive director since 2011 and our chief financial officer since 2008. He is a member of our sustainability committee. Prior to joining our company, Mr. Cheng was vice president, finance of Bristol Myers Squibb in China and was a director of Sino-American Shanghai Squibb Pharmaceuticals Ltd. and Bristol-Myers Squibb (China) Investment Co. Ltd. in Shanghai between 2006 and 2008. Mr. Cheng started his career as an auditor with Price Waterhouse (currently PricewaterhouseCoopers) in Australia and then joined KPMG in Beijing before spending eight years with Nestlé China where he was in charge of a number of finance and control functions in various operations. Mr. Cheng received a bachelor of economics from the University of Adelaide and is a member of the Chartered Accountants Australia and New Zealand.

Weiguo Su has been an executive director since 2017 and has been our executive vice president and chief scientific officer since 2012. He is also a member of our technical committee. Dr. Su has headed all drug discovery and research since he joined our company, including master-minding our scientific strategy, being a key leader of our Oncology/Immunology operations, and responsible for the discovery of each and every small molecule drug candidate in our pipeline. Prior to joining our company in 2005, Dr. Su worked with the U.S. research and development department of Pfizer, Inc. In 2017, he was granted the prestigious award by the China Pharmaceutical Innovation and Research Development Association (PhIRDA) as one of the Most Influential Drug R&D Leaders in China. Dr. Su received a bachelor of science degree in chemistry from Fudan University in Shanghai. He completed a Ph.D. and post-doctoral fellowship in chemistry at Harvard University under the guidance of Nobel Laureate Professor E. J. Corey.

Dan Eldar has been a non-executive director since 2016. He has more than 30 years of experience as a senior executive, leading global operations in telecommunications, water, biotech and healthcare. He is an executive director of Hutchison Water Israel Ltd (an associated company of CK Hutchison) which focuses on large scale projects including desalination, wastewater treatment and water reuse. He was formerly an independent non-executive director of Leumi Card Ltd., a subsidiary of Bank Leumi Le-Israel B.M., one of Israel's leading credit card companies. Dr. Eldar received a Ph.D. degree in government from Harvard University, master of arts degree in government from Harvard University, master of arts degree in political science and public administration from the Hebrew University of Jerusalem and a bachelor of arts degree in political science from the Hebrew University of Jerusalem.

Edith Shih has been a non-executive director and company secretary of our company since 2006 and the company secretary of Group companies since 2000. She is also chairman of our sustainability committee. She has over 35 years of experience in legal, regulatory, corporate finance, compliance and corporate governance fields. She is also an executive director and company secretary of CK Hutchison. She has been with the Cheung Kong (Holdings) Limited group, or CKH, since 1989 and with Hutchison Whampoa Limited, or HWL, from 1991 to 2015. Both CKH and HWL became wholly-owned subsidiaries of CK Hutchison in 2015. She has acted in various capacities within the HWL group, including head group general counsel and company secretary of HWL as well as director and company secretary of HWL subsidiaries and associated companies. Ms. Shih is in addition a non-executive director of Hutchison Telecommunications Hong Kong Holdings Limited, Hutchison Port Holdings Management Pte. Limited as the trustee-manager of Hutchison Port Holdings Trust and a member of board of commissioners of PT Duta Intidaya Tbk. In addition, Ms. Shih is a director of certain substantial shareholders (within the meaning of the Securities and Futures Ordinance of Hong Kong) of our company and certain companies controlled by substantial shareholders of our company. The aforementioned companies are either subsidiaries or associated companies of CK Hutchison of which Ms. Shih has oversight as director of CK Hutchison. She is the immediate past international president and current member of the executive committee of The Chartered Governance Institute, or CGI, as well as a past president and current chairperson of the nomination committee of The Hong Kong Charted Governance Institute, or HKCGI, formerly known as The Hong Kong Institute of Chartered Secretaries. She is also chairman of the process review panel for the Financial Reporting Council, a panel member of the Securities and Futures Appeals Tribunal and a member of the Hong Kong-Europe Business Council. Ms. Shih is a solicitor qualified in England and Wales and Hong Kong and Victoria, Australia. She is a fellow of both the CGI and HKCGI, holding chartered secretary and chartered governance professional dual designations. Ms. Shih received a bachelor of science degree and a master of arts degree from the University of the Philippines as well as a master of arts degree and a master of education degree from Columbia University, New York.

Paul Rutherford Carter has been a senior independent non-executive director since 2017. He is also chairman of our remuneration committee and a member of our audit committee and technical committee. He has more than 26 years of experience in the pharmaceutical industry. From 2006 to 2016, Mr. Carter served in various senior executive roles at Gilead Sciences, Inc., or Gilead, a research-based biopharmaceutical company, with the last position as executive vice president, commercial operations. In this role, Mr. Carter headed the worldwide commercial organization responsible for the launch and commercialization of all of Gilead's products. He also worked as a senior executive at GlaxoSmithKline Plc. He is currently a director of Mallinckrodt plc. He is also a director of Immatics N.V. and VectivBio Holding AG. He is chairman of Evox Therapeutics and a retained advisor to several firms active in the life sciences sector. He was formerly a director of Alder Biopharmaceuticals, Inc. Mr. Carter received a degree in business studies from the Ealing School of Business and Management (now merged into University of West London) and is a fellow of the Chartered Institute of Management Accountants in the United Kingdom.

Karen Jean Ferrante has been an independent non-executive director since 2017. She is also chairman of our technical committee and a member of our audit committee. She has more than 26 years of experience in the pharmaceutical industry. She was the former chief medical officer and head of research and development of Tokai Pharmaceuticals, Inc., a biopharmaceutical company focused on developing and commercializing innovative therapies for prostate cancer and other hormonally driven diseases. Dr. Ferrante previously held senior positions at Millennium Pharmaceuticals, Inc. and its parent company, Takeda Pharmaceutical Company Limited, including chief medical officer and most recently as oncology therapeutic area and Cambridge USA site head. She also held positions of increasing responsibility at Pfizer Inc., or Pfizer, with the last position as vice president, oncology development. Dr. Ferrante is currently a member of the board of directors of MacroGenics, Inc. and Cogent Biosciences, Inc. (formerly Unum Therapeutics Inc.). She is also a member of the scientific advisory board of Kazia Therapeutics Limited. Dr. Ferrante was previously a director of Baxalta Incorporated until it was acquired by Shire plc in 2016 and a director of Progenics Pharmaceuticals, Inc., until it was acquired by Lantheus Holdings, Inc. in 2020. She was also previously a member of the scientific advisory board of Trillium Therapeutics Inc. until it was acquired by Pfizer in November 2021. She is an author of a number of papers in the field of oncology, an active participant in academic and professional associations and symposia and holder of several patents. Dr. Ferrante received a bachelor of science degree in chemistry and biology from Providence College and a doctor of medicine from Georgetown University.

Graeme Allan Jack has been an independent non-executive director since 2017. He is also chairman of our audit committee and a member of our nomination committee and remuneration committee. He has more than 40 years of experience in finance and audit. He retired as partner of PricewaterhouseCoopers in 2006 after a distinguished career with the firm for over 33 years. He is currently an independent non-executive director of The Greenbrier Companies, Inc. (an international supplier of equipment and services to the freight rail transportation markets) and Hutchison Port Holdings Management Pte. Limited, and also serves as the trustee-manager of Hutchison Port Holdings Trust (a developer and operator of deep water container terminals). He was formerly a director of COSCO SHIPPING Development Co., Ltd. (formerly China Shipping Container Lines Company Limited, an integrated financial services platform principally engaged in vessel and container leasing). He received a bachelor of commerce degree from the University of New South Wales, Australia and is a Fellow of the Hong Kong Institute of Certified Public Accountants and an Associate of Chartered Accountants Australia and New Zealand.

Shu Kam Mok, Tony has been an independent non-executive director since 2017. He is chairman of our nomination committee and a member of our sustainability committee and technical committee. Professor Mok has more than 31 years of experience in clinical oncology with his main research interest focusing on biomarker and molecular targeted therapy in lung cancer. He is currently Li Shu Fan Medical Foundation named professor and chairman of department of clinical oncology at The Chinese University of Hong Kong. Professor Mok has contributed to over 250 articles in international peer-reviewed journals, as well as multiple editorials and textbooks. In October 2018, Professor Mok was the first Chinese to be bestowed with the European Society for Medical Oncology (ESMO) Lifetime Achievement Award, one of the most prestigious international honors and recognitions given to cancer researchers, for his contribution to and leadership in lung cancer research worldwide. He is a non-executive director of AstraZeneca PLC, a board director of the American Society of Clinical Oncology ("ASCO") and a steering committee member of the Chinese Society of Clinical Oncology ("CSCO"). He is also currently chairman of the board of ACT Genomics Holdings Ltd. ("ACT Genomics") and a non-executive independent director of Lunit USA Inc. He is past president of the International Association for the Study of Lung Cancer, and co-founder of Sanomics Limited (acquired by ACT Genomics in November 2021) and Aurora Tele-Oncology Limited. Professor Mok is also closely affiliated with the oncology community in China and has been awarded an Honorary Professorship at Guangdong Province People's Hospital, Guest Professorship at Peking Union Medical College Hospital and Visiting Professorship at Shanghai Jiao Tong University. He received his bachelor of medical science degree and a doctor of medicine from University of Alberta, Canada. He is also a fellow of the Royal College of Physicians and Surgeons of Canada, Hong Kong College of Physicians, Hong Kong Academy of Medicine, Royal College of Physicians of Edinburgh and ASCO.

Marek Krzysztof Kania is our executive president, managing director and chief medical officer. Prior to joining our company in 2018, Dr. Kania spent 25 years with Eli Lilly where he led teams on multiple oncology products around the world. While at Eli Lilly, Dr. Kania was involved in clinical research and development, global medical affairs including product launches and medical policy and strategy. Prior to joining Eli Lilly, Dr. Kania practiced as an anesthesiologist and critical care physician. Dr. Kania is a member of the American Society of Clinical Oncology and the American Association for Cancer Research. He received his medical training at the Silesian School of Medicine in Katowice, Poland, and subsequently completed an anesthesiology and critical-care residency, with board certification from Jagiellonian University School of Medicine in Krakow. Dr. Kania also holds an MBA degree from The University of Chicago Booth Graduate School of Business.

Karen Jane Atkin is our executive vice president and chief operating officer. Prior to joining our company in 2021, Dr. Atkin spent 24 years at AstraZeneca in senior medical, regulatory, pharmacovigilance, R&D and commercial leadership roles, including as senior vice president of medical for biopharmaceuticals, vice president of the global infection, neuroscience and autoimmunity therapy area and the established branch business, country president of Indonesia and led China R&D for over four years. Dr. Atkin is also a registered physician with advanced level qualifications in internal medicine and pharmaceutical medicine. Dr. Atkin holds three bachelor's degrees in physiology, medicine and surgery, respectively, from University College London. She graduated with a first class honors degree in medicine, holds an MBA from the Open University, is a Member of the Royal College of Physicians and a fellow of the Faculty of Pharmaceutical Medicine in the UK.

Zhenping Wu joined our company in 2008 and has been our senior vice president of pharmaceutical sciences since 2012. Dr. Wu has over 28 years of experience in drug discovery and development. His past positions include senior director of pharmaceutical sciences at Phenomix Corporation, a U.S.-based biotechnology company, director of pharmaceutical development at Pfizer Global Research & Development in California (formerly Agouron Pharmaceuticals) and a group leader at Roche at its Palo Alto site. He is a past chairman and president of the board of the Sino-American Biotechnology and Pharmaceutical Association. Dr. Wu received a Ph.D. from the University of Hong Kong and a master in business administration from the University of California at Irvine.

Kin Hung Lee, Mark is our senior vice president of corporate finance and development and joined our company in 2009. He began working in healthcare investment banking in the United States and Europe in 1998. Based in the New York and London offices of Credit Suisse, Mr. Lee was involved in the execution and origination of mergers, acquisitions, public and private financings and corporate strategy for life science companies such as AstraZeneca, Bristol-Myers Squibb and Genzyme, as well as other medical product and service companies. Mr. Lee received his bachelor's degree in biochemical engineering with first class honors from University College London, where he was awarded a Dean's Commendation. He also received a master of business administration from the Massachusetts Institute of Technology's Sloan School of Management.

Qingmei Wang, May is our senior vice president of business development & strategic alliances. Prior to joining our company in 2010, Dr. Wang spent 16 years with Eli Lilly where she was the head of Eli Lilly's Asian Biology Research and responsible for establishing and managing research collaborations in China and across Asia. Dr. Wang holds numerous patents, has published more than 50 peer-reviewed articles and has given dozens of seminars and plenary lectures. Dr. Wang received a Ph.D. in biochemistry from Purdue University.

Hong Chen is our senior vice president and chief commercial officer (China). Prior to joining our company in 2011, Mr. Chen spent 12 years with Bristol-Myers Squibb and was last serving as its national sales & marketing director in China. Mr. Chen received a bachelor's degree in medicine from Nanjing Medical University and an EMBA from Cheung Kong Graduate School of Business.

Thomas R.Held has been our senior vice president, commercial (U.S.) since 2020. He is responsible for establishing and leading our commercial presence in the United States and building the commercial infrastructure for our international operations, including launch strategy, marketing sales, market access and operational planning. Mr. Held has more than 30 years of experience in the pharmaceutical industry with a majority of time spent in the oncology commercial space. In his most recent position, he served as vice president of Daiichi Sankyo's emergent Antibody Drug Conjugate strategic platform. Prior to Daiichi Sankyo, he held commercial roles of increasing responsibility at Novartis Oncology, where he worked from 1997 to 2017, gaining invaluable experience in the solid tumor arena, including importantly neuroendocrine tumors. Mr. Held received a bachelor's degree in economics from Allegheny College and an MBA from Ashland University.

Charles George Rupert Nixon has been our group general counsel since 2015 and has worked with us since 2006. Prior to joining us, Mr. Nixon was group senior legal counsel for Hutchison Whampoa Limited (previously a listed company in Hong Kong and after a restructuring, a subsidiary of CK Hutchison Holdings Limited) in both Hong Kong and London and prior to that senior legal counsel for Three UK, a mobile phone operator. Mr. Nixon has been with the CK Hutchison Group since 2001. Mr. Nixon received an LL.B (Hons) from Middlesex University and is a qualified solicitor in England & Wales with 30 years of experience.

Board Diversity

On August 6, 2021, the SEC approved the Nasdaq Stock Market's proposal to amend its listing standards to encourage greater board diversity and to require board diversity disclosures for Nasdaq-listed companies. Pursuant to the amended listing standards, HUTCHMED, as a foreign private issuer, is required to have at least two diverse board members or explain the reasons for not meeting this objective by 2025. Furthermore, a board diversity matrix is required to be included in the annual report on Form 20-F, containing certain demographic and other information regarding members of our board of directors. HUTCHMED currently complies with the diversity requirement, as we currently have two female and eight male members on our board of directors. The board diversity matrix is set out below.

Board Diversity Matrix (As of March 1, 2022)

Place of Principal Executive Offices	Hong Kong
Foreign Private Issuer	Yes
Disclosure Prohibited under Home Country Law	No
Total Number of Directors	10

	Female	Male	Non-Binary	Did Not Disclose Gender
Part I: Gender Identity				
Directors	2	8	—	—
Part II: Demographic Background				
Underrepresented Individual in Place of Principal Executive Offices	—	—	—	—
LGBTQ+	—	—	—	—
Did Not Disclosure Demographic Background	—	—	—	—

B. Compensation.

Executive Officer Compensation

Summary Compensation Table

The following table sets forth the non-equity compensation paid or accrued during the year ended December 31, 2021 to our chief executive officer, chief financial officer, chief scientific officer and other executive officers on an aggregate basis.

Name and Principal Position	Salary and fees ($)	Bonus[5] ($)	Taxable benefits ($)	Non-taxable benefits ($)	Pension contributions ($)	Total ($)
Christian Lawrence Hogg	469,038 [1][2]	1,000,000	18,365	9,936	30,250	1,527,589
Chig Fung Cheng, Johnny	390,412 [3]	410,256	—	9,936	27,903	838,507
Weiguo Su	470,065 [4]	834,621	10,000	6,790	34,946	1,356,422
Other Executive Officers in the Aggregate	2,438,670	2,440,073	39,805	58,279	129,843	5,106,670

Notes:

(1) Director's fees received from the subsidiaries of our company during the period he served as director that were paid to a subsidiary or an intermediate holding company of our company are not included in the amounts above.

(2) Amount includes director's fees of $77,151.

(3) Amount includes director's fees of $72,151.

(4) Amount includes director's fees of $75,000.

(5) In December 2013 and March 2014, we awarded cash retention bonuses to certain of our executive officers in the aggregate amount of $2,977,751. Each such executive officer receives portions of his or her retention bonus upon certain dates in the future depending on when the bonus was granted and, in each case, assuming he or she remains employed by our company on such future dates. No amounts in relation to such cash retention bonuses were paid in 2021.

Employment Arrangements with our Executive Officers

Offer Letters for Executive Officers at HUTCHMED (China) Limited and HUTCHMED Holdings (HK) Limited (formerly Hutchison MediPharma (Hong Kong) Limited)

We have entered into employment offer letters with each of our executive officers who is employed by our Hong Kong subsidiaries, HUTCHMED Group (HK) Limited or HUTCHMED Holdings (HK) Limited, namely Mr. Christian Lawrence Hogg, Mr. Chig Fung Cheng, Johnny, Ms. Karen Jane Atkin, Mr. Kin Hung Lee, Mark and Mr. Charles George Rupert Nixon. Under these our executives receive compensation in the form of salaries, discretionary bonuses, participation in the Hutchison Provident Fund retirement scheme, medical coverage under the CK Hutchison Group Medical Scheme, personal accident insurance and annual leave. None of the employment arrangements provide benefits to our executive officers upon termination. We may terminate employment by giving the executive three months' prior written notice. The executive officer may also voluntarily terminate his/her employment with us upon not less than three months' prior written notice to us.

Each executive officer has agreed, for the term of employment with us and thereafter, not to disclose or use for his/her own purposes any of our and our associated companies' confidential information that the executive officer may develop or learn in the course of employment with us. Moreover, each of our executive officers has agreed, for the term of employment with us and for a period of twelve months thereafter, (i) not to undertake or be employed or interested directly or indirectly anywhere in Hong Kong in any activity which is similar to and competitive with our company or associated companies in which the executive officer had been involved in the period of 12 months prior to such termination and (ii) not to solicit for any employees of our company or our joint ventures or orders from any person, firm or company which was at any time during the 12 months prior to termination of such employment a customer or supplier of our company or associated companies.

Employment Agreements with Executive Officers at HUTCHMED Limited

We have entered into employment agreements with each of our executive officers who are employed directly by HUTCHMED Limited, namely Dr. Weiguo Su, Dr. Qingmei Wang, May and Dr. Zhenping Wu. Under these employment agreements, we engage the executive officer on either an open-ended or a fixed term. Our executive officers receive compensation in the form of salaries, discretionary bonuses, annual leave, statutory maternity leave and nursing leave.

Under the terms of these agreements, we provide labor protection and work conditions that comply with the safety and sanitation requirements stipulated by the relevant PRC laws. The employment agreements prohibit the executive officers from engaging in any conduct and business activities which may compete with the business or interests of HUTCHMED Limited during the term of the executive officer's employment. These executive officers also enjoy the Hutchison Provident Fund retirement scheme, medical coverage under the CK Hutchison Group Medical Scheme and personal accident insurance.

We may terminate an executive officer's employment for cause at any time without notice. Termination for cause may include a serious breach of our internal rules and policies, serious negligence in the executive officer's performance of his or her duties, an accusation or conviction of a criminal offence, acquisition of another job which materially affects the executive officer's ability to perform his or her duties for our company and other circumstances stipulated by applicable PRC laws. We may terminate an executive officer's employment with three months' prior notice if the executive officer is unable to perform his or her duties (after the expiration of the prescribed medical treatment period) because of an illness or non-work-related injury or the executive officer is incompetent and remains incompetent after training or adjustment of his or her position.

The executive officer may voluntarily terminate his or her contract without cause with three months' prior notice. The executive officer may also terminate the employment agreement immediately for cause, which includes a failure by us to provide labor protection and the work conditions as specified under the employment agreement. In case of termination for any reason, we agree to make any mandatory severance payments required by the relevant PRC labor laws.

Offer Letters for Executive Officers at HUTCHMED International Corporation (formerly Hutchison MediPharma (US), Inc. and Hutchison MediPharma International Inc.

We have entered into employment offer letters with each of our executive officers who is employed by one of our U.S. subsidiaries, HUTCHMED International Corporation, namely Mr. Marek Krzysztof Kania and Mr. Thomas R.Held. Under these offer letters, such executives receive compensation in the form of salaries, discretionary bonuses, group medical, dental and other insurance 401(k) plan and annual leave. We may terminate employment by giving the executive three months' prior written notice. The executive officer may also voluntarily terminate his employment with us upon not less than three months' prior written notice to us. In the event that the employment is terminated by us without cause or by the executive with good reason and the executive has completed at least 12 months of service, the executive may be entitled to up to six months of salary and prorated annual target bonus. Mr. Marek Krzysztof Kania has also agreed, for the term of employment with us and thereafter, not to disclose or use for his own purposes any of our and our associated companies' trade secrets or confidential information that he may develop or learn in the course of employment with us.

Employment Agreement with Executive Officer at Hutchison Sinopharm

We have entered into an employment agreement with Mr. Hong Chen, one of our executive officers, who is employed by Hutchison Sinopharm. Under this employment agreement, Mr. Chen's employment is for a fixed term, and he receives compensation in the form of salaries, discretionary bonuses, annual leave, statutory maternity leave and nursing leave.

Under the terms of this agreement, we provide labor protection and work conditions that comply with the safety and sanitation requirements stipulated by the relevant PRC laws. The employment agreement prohibits any conduct directly or indirectly which is harmful to Hutchison Sinopharm during the term of the employment.

We may terminate Mr. Chen's employment for cause at any time without notice. We may also terminate the employment with prior notice and termination compensation if Mr. Chen is unable to perform his duties because of an illness or non-work-related injury or he is incompetent and remains incompetent after training or adjustment of his position. Mr. Chen may voluntarily terminate his employment agreement without cause with one month's prior notice and immediately for cause.

Share Options

The following table sets forth information concerning the outstanding equity awards held by our chief executive officer, chief financial officer, chief scientific officer and other executive officers on an aggregate basis as of December 31, 2021.

Name and Principal Position	Date of grant of share options	Number of unexercised shares which are exercisable (#)	Number of unexercised shares which are unexercisable (#)	Exercise price	Number of shares issued upon exercise in 2021	Number of options lapsed/ cancelled in 2021	Option expiration date
Christian Lawrence Hogg	Apr 28, 2020	322,925 (=64,585 ADSs)	968,775 (=193,755 ADSs)	$ 22.090	—	—	Apr 27, 2030
Christian Lawrence Hogg	Dec 14, 2020	9,900 (=1,980 ADSs)	29,710 (=5,942 ADSs)	$ 29.000	—	—	Dec 13, 2030
Christian Lawrence Hogg	Mar 26, 2021	—	868,900 (=173,780 ADSs)	$ 27.940	—	—	Mar 25, 2031
Chig Fung Cheng, Johnny	Apr 28, 2020	100,475 (=20,095 ADSs)	301,425 (=60,285 ADSs)	$ 22.090	—	—	Apr 27, 2030
Chig Fung Cheng, Johnny	Mar 26, 2021	—	240,500 (=48,100 ADSs)	$ 27.940	—	—	Mar 25, 2031
Weiguo Su	Jun 15, 2016	3,000,000	—	£ 1.970	—	—	Jun 14, 2026
Weiguo Su	Mar 27, 2017	1,000,000	—	£ 3.105	—	—	Mar 26, 2027
Weiguo Su	Mar 19, 2018	750,000	250,000	£ 4.974	—	—	Mar 18, 2028
Weiguo Su	Apr 28, 2020	197,425 (=39,485 ADSs)	592,275 (=118,455 ADSs)	$ 22.090	—	—	Apr 27, 1930
Weiguo Su	Dec 14, 2020	4,740 (=948 ADSs)	14,220 (=2,844 ADSs)	$ 29.000	—	—	Dec 13, 2030
Weiguo Su	Mar 26, 2021	—	282,400 (=56,480 ADSs)	$ 27.940	—	—	Mar 25, 2031
Weiguo Su	Dec 14, 2021	—	24,930 (=4,986 ADSs)	$ 35.210	—	—	Dec 13, 2031
Other Executive Officers in the Aggregate	Jun 15, 2016	2,936,860	—	£ 1.970	—	—	Dec 19, 2023
Other Executive Officers in the Aggregate	Apr 20, 2018	525,810	175,290	£ 4.645	—	—	Apr 19, 2028
Other Executive Officers in the Aggregate	Aug 6, 2018	281,250	93,750	£ 4.860	—	—	Aug 5, 2028
Other Executive Officers in the Aggregate	Dec 11, 2019	200,000	200,000	£ 3.592	—	—	Dec 10, 2029
Other Executive Officers in the Aggregate	Apr 28, 2020	439,600 (=87,920 ADSs)	1,318,800 (=263,760 ADSs)	$ 22.090	—	—	Apr 27, 2030
Other Executive Officers in the Aggregate	Dec 14, 2020	77,465 (=15,493 ADSs)	232,425 (=46,485 ADSs)	$ 29.000	—	—	Dec 13, 2030
Other Executive Officers in the Aggregate	Mar 26, 2021	—	1,031,100 (=206,220 ADSs)	$ 27.940	—	—	Mar 25, 2031
Other Executive Officers in the Aggregate	Dec 14, 2021	—	356,955 (=71,391 ADSs)	$ 35.210	—	—	Dec 13, 2031

Note: The share options granted on or after April 28, 2020 were in the form of ADSs and the relevant exercise prices were stated in U.S. dollars per ADS. For purposes of this table, these share options are presented in the form of ordinary shares (with the corresponding number of ADSs where appropriate). Each ADS represents five ordinary shares.

Long-Term Incentive Compensation

The following table sets forth information regarding performance based LTIP awards granted to our chief executive officer, chief financial officer, chief scientific officer and other executive officers on an aggregate basis in the year ended December 31, 2021.

Name and Principal Position	Maximum Aggregate Value of LTIP awards[1] [2]
Christian Lawrence Hogg	$ 1,616,538
Chig Fung Cheng, Johnny	$ 657,211
Weiguo Su	$ 1,622,123
Other Executive Officers in the Aggregate	$ 2,738,802

Notes:

(1) The amounts reflected in the table above represent the maximum aggregate value of all LTIP awards outstanding as of December 31, 2021. The LTIP awards are conditional upon the achievement of annual performance targets for the fiscal year 2021. The amounts reflected in the table above assume the maximum amount that may be paid under these contingent LTIP awards. The LTIP awards will be settled in a variable number of shares based on a fixed monetary amount awarded upon achievement of performance targets. An independent third-party trustee who administers the LTIP purchased shares of our company on either the AIM or Nasdaq market which will be used to settle the LTIP awards. See "Outstanding Awards" for more details.

(2) Vesting will occur two business days after the date of the announcement of our annual results for the financial year 2023.

Director Compensation

The following table sets forth a summary of the compensation we paid to our directors other than Christian Lawrence Hogg, Chig Fung Cheng, Johnny and Weiguo Su during 2021.

Name of Director	Fees Earned or Paid in Cash	Maximum Value of Non-Performance Based LTIP Awards Granted[1]
Chi Keung To, Simon	$ 85,000 [2]	$ 250,000 [4]
Dan Eldar	$ 70,000	$ 250,000
Edith Shih	$ 74,301 [3]	$ 250,000 [5]
Paul Rutherford Carter	$ 117,000	$ 250,000
Karen Jean Ferrante	$ 102,500	$ 250,000
Graeme Allan Jack	$ 111,000	$ 250,000
Shu Kam Mok, Tony	$ 99,011	$ 250,000

Notes:

(1) Such awards vest in equal installments of 25% over four years and are not subject to performance based criteria.

(2) Such director's fees were paid to Hutchison Whampoa (China) Limited, a wholly owned subsidiary of CK Hutchison. Director's fees received from our subsidiaries during the period he served as director that were paid to a subsidiary or an intermediate holding company of our company are not included in the amounts above.

(3) Such director's fees were paid to Hutchison International Limited, a wholly owned subsidiary of CK Hutchison. Director's fees received from our subsidiaries during the period she served as director that were paid to a subsidiary or an intermediate holding company of our company are not included in the amounts above.

(4) Such LTIP awards were not received by Mr. Chi Keung To, Simon but were received by or for the account of his employer, Hutchison Whampoa (China) Limited.

(5) Such LTIP awards were not received by Ms. Edith Shih but were received by or for the account of her employer, Hutchison International Limited.

Equity Compensation Schemes and Other Benefit Plans

We have two share option schemes. We refer to these collectively as the Option Schemes. Our shareholder adopted the first option scheme, or the 2005 Option Scheme, in June 2005, and it was subsequently approved by the shareholders of Hutchison Whampoa Limited, our then majority shareholder, in May 2006 and later amended by our board of directors in March 2007. This share option scheme expired in 2016. In April 2015, our shareholders adopted the second option scheme, or the 2015 Option Scheme, which was later approved by the shareholders of CK Hutchison, the ultimate parent of our then majority shareholder, in May 2016. The 2015 Option Scheme was subsequently amended in April 2020.

We also have a long-term incentive scheme which was adopted by our shareholders in April 2015. We refer to this as our LTIP.

Our Option Schemes and LTIP each terminates on the tenth anniversary of their adoption. Each may also be terminated by its board of directors at any time. Any termination of a scheme is without prejudice to the awards outstanding at such time. Options are no longer being granted under the 2005 Option Scheme, but outstanding awards under the 2005 Option Scheme continue to be governed by the terms thereof.

The following describes the material terms of our Option Schemes and LTIP, or collectively the Schemes.

Awards and Eligible Grantees. The Option Schemes provide for the award of share options exercisable for ordinary shares or ADSs of our company to Eligible Employees (as defined in the Option Schemes) or non-executive directors (excluding any independent non-executive directors under the Option Schemes).

Under our LTIP, awards in the form of contingent rights to receive either shares purchased from the market by the scheme trustee or cash payments may be granted to the directors of our company, directors of our subsidiaries and employees of our company, subsidiaries, affiliates or such other companies as determined by our board of directors in its absolute discretion.

Scheme Administration. Our board of directors has delegated its authority for administering our Option Schemes and our LTIP to our remuneration committee. Each such plan administrator has the authority to, among other things, select participants and determine the amount and terms and conditions of the awards under the applicable Schemes as it deems necessary and proper, subject to the restrictions described in "—Restrictions on Grants" below.

Restrictions on Grants. Under the Option Schemes, grants may not be made to independent non-executive directors. Furthermore, those grants may not be made to any of our employees or directors if such person is also a director, chief executive or substantial shareholder of any of our direct or indirect parent companies which is listed on a stock exchange or any of its associates without approval by the independent non-executive directors of such parent company (excluding any independent non-executive director who is a proposed grantee). In addition, approval by our shareholders and the shareholders of such listed parent company is required if an option grant under our Option Schemes is to be made to a substantial shareholder or independent non-executive director of a listed parent company or any of its associates and, upon exercise of such grant and any other grants made during the prior 12-month period to that shareholder, that individual would receive an amount of our ordinary shares equal or greater than 0.1% of our total outstanding shares or with an aggregate value in excess of HK$5 million (equivalent to $0.6 million as of December 31, 2021).

In addition, options under our Option Schemes may not be granted to any individual if, upon the exercise of such options, the individual would receive an amount of shares when aggregated with all other options granted to such individual under the applicable Scheme in the 12-month period up to and including the grant date, that exceeds 1% of the total shares outstanding of the company granting the award on such date. There are no individual limits under our LTIP.

Under our LTIP, no grant to any director, chief executive or substantial shareholder of our company may be made without the prior approval of our independent non-executive directors (excluding an independent non-executive director who is a proposed grantee).

Vesting. Vesting conditions of options granted under the Schemes are determined by the respective board of directors at the time of grant.

Under our Option Schemes, if a participant has committed any misconduct or any conduct making such participant's service terminable for cause, all options (whether vested or unvested) lapse unless the respective board of directors otherwise determines in its absolute discretion. Options may be exercised to the extent vested where a participant's service ceases due to the participant's death, serious illness, injury, disability, retirement at the applicable retirement age, or earlier if determined by the participant's employer, or if a participant's service ceases for any other reason other than for cause.

Under our LTIP, if a participant's employment or service with our company or its subsidiaries is terminated for cause or if the participant breaches certain provisions in our LTIP restricting the transfer of awards by grantees and imposing non-competition obligations on grantees, all unvested awards are automatically cancelled. Where a participant's employment or service ceases for any reason other than the reasons listed above (including due to the participant's resignation, retirement, death or disability or upon the non-renewal of such participant's employment or service agreement other than for cause), our board of directors may determine at its discretion whether unvested awards shall be deemed vested.

Exercise Price. The exercise price for each share pursuant to the initial options granted under the 2005 Option Scheme was a price determined by our board of directors at the date of grant, and for grants made thereafter, the exercise price was the Market Value of a share at the date of grant (as defined in our Option Schemes).

The exercise price for each share pursuant to the options granted under the 2015 Option Scheme must be the Market Value of a share at the date of grant (as defined in our Option Schemes).

Non-transferability of Awards. Awards may not be transferred except in the case of a participant's death by the terms of each Scheme.

Takeover or Scheme of Arrangement. In the event of a general or partial offer for the shares of our company under our Option Schemes, whether by way of takeover, offer, share repurchase offer, or scheme of arrangement, the affected company is required to use all reasonable endeavors to procure that such offer is extended to all holders of options granted by such company on the same terms as those applying to shareholders. Both vested and unvested options may be exercised up until (i) the closing date of any such offer and (ii) the record date for entitlements under a scheme of arrangement, and will lapse thereafter. Certain options may also be exercised on a voluntary winding up of our company.

Under our LTIP, in the event of a general offer for all the shares of our company, whether by way of takeover or scheme of arrangement, or if our company is to be voluntarily wound up, our board of directors shall determine in its discretion whether outstanding unvested awards will vest and the period within which such awards will vest.

Amendment. Our Option Schemes require that amendments of a material nature only be made with the approval of our shareholders.

Our board of directors may alter the terms of our LTIP, but amendments which are of a material nature cannot take effect without shareholders' approval, unless the changes take effect automatically under the terms of our LTIP.

Authorized Shares. Under our 2015 Option Scheme, our board of directors may "refresh" the scheme limit from time to time provided that the total number of shares which may be issued upon exercise of all options to be granted under our Option Schemes shall not exceed 10% of our total shares outstanding on such date. In addition, the limit on the number of shares which may be issued upon exercise of all outstanding options granted and not yet exercised under the 2015 Option Scheme and any options granted and not yet exercised under any other schemes must not exceed 10% of the outstanding shares of the company in issue from time to time. In April 2020, our shareholders approved a refresh of the 2015 Option Scheme.

Following the 2015 Option Scheme refresh discussed above, subject to certain adjustments for share splits, share consolidations and other changes in capitalization, the maximum number of shares that may be issued upon exercise of all options granted may not in the aggregate exceed 5% of our shares outstanding on April 27, 2020. Share awards under our LTIP may not exceed 5% of our shares outstanding on the adoption date of our LTIP.

Outstanding Awards and Grants of Awards

Share options outstanding under the 2005 Option Scheme

The 2005 Option Scheme expired in 2016, and no further share options can be granted under it. As of December 31, 2021, options to purchase an aggregate of 705,060 ordinary shares, representing approximately 0.1% of our outstanding share capital, with an exercise price of £0.61 ($0.81) per ordinary share and an expiration date of December 19, 2023 remained outstanding under the 2005 Option Scheme.

Share options outstanding and grants made in 2021 under the 2015 Option Scheme

As of December 31, 2021, options to purchase an aggregate of 36,485,530 ordinary shares, representing approximately 4.2% of our outstanding share capital, at a weighted average exercise price of £3.72 ($4.95) per ordinary share and an expiration date of 10 years from the respective date of grant remained outstanding under the 2015 Option Scheme. In the year ended December 31, 2021, we granted options to purchase an aggregate of 10,174,840 ordinary shares, representing approximately 1.2% of our outstanding share capital, at a weighted average exercise price of £4.47 ($5.96) per share under the 2015 Option Scheme. Such options vest in equal instalments of 25% over a four-year period.

Grants and vesting of LTIPs

In the year ended December 31, 2021, we granted performance based awards under our LTIP to three of our executive officers and 704 employees, giving them a conditional right to receive ordinary shares to be purchased by the third-party trustee up to an aggregate maximum cash amount of $64,590,505. These awards are related to the achievement of performance targets and will vest two business days after the date of the announcement of our annual results for the financial year 2023. For additional information on LTIP awards held by our executive officers, please see "B. Compensation—Executive Officer Compensation—Long-Term Incentive Compensation."

In the year ended December 31, 2021, we also granted non-performance based awards under our LTIP to each of our seven directors and five employees, giving them a conditional right to receive ordinary shares to be purchased by the third-party trustee up to an aggregate maximum cash amount of $2,453,077. The LTIP awards to our directors vest in equal installments of 25% over four years, $603,077 of the LTIP awards to employees vest over a four-year period and $100,000 of the LTIP awards to an employee vest one year after grant. For additional information on LTIP awards to our directors, please see "B. Compensation—Director Compensation."

Vesting of our LTIP awards will also depend upon the award holder's continued employment or continued service on our board, as the case may be.

In the year ended December 31, 2021, an aggregate of 143,510 ordinary shares and 5,995 ADSs were given to award holders upon the vesting of performance based LTIP awards, and 16,015 ordinary shares and 17,809 ADSs were given to award holders upon the vesting of non-performance based LTIP awards.

C. Board Practices.

Our board of directors consists of ten directors including four executive directors, two non-executive directors and four independent non-executive directors. Pursuant to a relationship agreement dated April 21, 2006, and amended and restated on June 13, 2019, by and between our company and Hutchison Whampoa (China) Limited, a parent company of Hutchison Healthcare Holdings Limited, or the Relationship Agreement, our board of directors must consist of at least one director who is independent of the CK Hutchison group if Hutchison Whampoa (China) Limited is entitled to cast at least 50% votes eligible to be cast on a poll vote at a general meeting of our company. The Relationship Agreement will continue in effect until our ordinary shares cease to be traded on the AIM market or the CK Hutchison group individually or collectively ceases to hold at least 30% of our shares.

Our directors are subject to a three-year term of office and hold office until such time as they wish to retire and not offer themselves up for re-election, are not re-elected by the shareholders, or are removed from office by ordinary resolution at an annual general meeting of the shareholders. Under our Articles of Association, a director will be vacated if, among other things, the director (i) becomes bankrupt or has a receiving order made against him or suspends payment or compounds with his creditors; or (ii) becomes of unsound mind. For information regarding the period during which our officers and directors have served in their respective positions, please see Item 6.A. "Directors and Senior Management."

Board Committees

Our board of directors has established an audit committee, remuneration committee, technical committee, nomination committee and sustainability committee.

Audit Committee

Our audit committee consists of Graeme Allan Jack, Paul Rutherford Carter and Karen Jean Ferrante, with Graeme Allan Jack serving as chairman of the committee. Graeme Allan Jack, Paul Rutherford Carter and Karen Jean Ferrante each meets the independence requirements under the rules of the Nasdaq Stock Market and under Rule 10A-3 under the Exchange Act. We have determined that Graeme Allan Jack is an "audit committee financial expert" within the meaning of Item 407 of Regulation S-K. All members of our audit committee meet the requirements for financial literacy under the applicable rules and regulations of the SEC and the Nasdaq Stock Market.

Although we are a foreign private issuer, we are required to comply with Rule 10A-3 of the Exchange Act, relating to audit committee composition and responsibilities. Rule 10A-3 provides that the audit committee must have direct responsibility for the nomination, compensation and choice of our auditor, as well as control over the performance of their duties, management of complaints made, and selection of consultants. Under Rule 10A-3, if the governing law or documents of a listed issuer require that any such matter be approved by the board of directors or the shareholders of the company, the audit committee's responsibilities or powers with respect to such matter may instead be advisory. Our Articles of Association provide that the appointment of our auditor must be decided by our shareholders at our annual general meeting or at a subsequent extraordinary general meeting in each year.

The audit committee formally meets at least twice a year and otherwise as required. The audit committee's purpose is to oversee our accounting and financial reporting process and the audit of our financial statements. Our audit committee's primary duties and responsibilities are to:

- monitor the integrity of our financial statements, our annual and half-year reports and accounts and our announcements of interim or final results;
- provide advice, where requested by the board of directors, on whether the annual report and accounts, taken as a whole, are fair, balanced and understandable, and provide the information necessary for shareholders to assess our company's position and performance, business model and strategy;
- review significant financial reporting issues and the judgments which they contain;
- review, whenever practicable without being inconsistent with any requirement for prompt reporting under applicable listing rules, other statements containing financial information such as significant financial returns to regulators and release of price sensitive information first where board of director approval is required; and
- review and challenge where necessary:
    - the consistency of, and any changes to, accounting policies both on a year-on-year basis and across our company;
    - the methods used to account for significant or unusual transactions where different approaches are possible;
    - whether our company has followed appropriate accounting standards and made appropriate estimates and judgments, taking into account the views of the external auditor;
    - the clarity of the disclosure in our financial reports and the context in which statements are made; and
    - all material information presented with the financial statements, such as any operations and financial review and any corporate governance statements (insofar as it relates to the audit and risk management).

In relation to our internal controls and risk management systems, our audit committee, among other things:

- reviews the effectiveness of our internal control and risk management systems;
- reviews the policies and procedures for the identification, assessment and reporting of financial and non-financial risks and our management of those risks in accordance with the requirements of the Sarbanes-Oxley Act and other applicable laws, rules and regulations and the applicable requirements of any stock exchange;
- approves the appointment and removal of the head of the internal audit function;
- ensures our internal audit function has adequate standing and resources and is free from management or other restrictions;
- reviews and monitors our executive management's responsiveness to the findings and recommendations of the internal audit function; and
- reviews with management and our independent auditors the adequacy and effectiveness of our internal control over financial reporting and disclosure controls and procedures.

In relation to our external auditor, our audit committee, among other things:

- recommends the appointment, reappointment or removal of the external auditor and considers any issues relating to their resignation, dismissal, remuneration or terms of engagement, subject to approval by the shareholders;
- considers and monitors the external auditor's independence, objectivity and effectiveness;
- reviews and monitors the effectiveness of the audit process, considering relevant ethical or professional requirements;
- develops and implements policy on the engagement of the external auditor to provide non-audit services, taking into any relevant ethical guidance; and
- pre-approves the external auditors' annual audit fees and the nature and scope of proposed audit coverage, subject to approval by our shareholders.

The audit committee is authorized to obtain, at our company's expense, reasonable outside legal or other professional advice on any matters within the scope of its responsibilities.

Remuneration Committee

Our remuneration committee consists of Paul Rutherford Carter, Graeme Allan Jack and Chi Keung To, Simon, with Paul Rutherford Carter serving as chairman of the committee. The remuneration committee is responsible for considering all material elements of remuneration policy and remuneration and incentives of our executive directors and key employees with reference to independent remuneration research and professional advice. The remuneration committee meets formally at least once each year and otherwise as required and make recommendations to our board of directors on the framework for executive remuneration and on proposals for the granting of share options and other equity incentives. Our board of directors is responsible for implementing these recommendations and agreeing the remuneration packages of individual directors. No director is permitted to participate in discussions or decisions concerning his or her own remuneration.

Technical Committee

Our technical committee consists of Karen Jean Ferrante, Paul Rutherford Carter, Chi Keung To, Simon, Christian Lawrence Hogg, Weiguo Su and Shu Kam Mok, Tony, with Karen Jean Ferrante serving as chairman of the committee. The technical committee's responsibility is to consider, from time to time, matters relating to the technical aspects of the research and development activities of our Oncology/Immunology operations. It invites such executives as it deems appropriate to participate in meetings from time to time.

Nomination Committee

Our nomination committee consists of Shu Kam Mok, Tony, Graeme Allan Jack and Chi Keung To, Simon, with Shu Kam Mok, Tony serving as chairman of the committee. Our nomination committee reviews the structure, size, diversity profile and skills set of the board against its needs and makes recommendations on the composition of the board to achieve our corporate strategy as well as promote shareholder value. It facilitates the board in the conduct of the selection and nomination of directors, makes recommendations to the board on the appointment or reappointment of directors and succession planning for directors. It also assesses director independence having regard to the criteria under the applicable corporate governance code, SEC or stock exchange rules.

Sustainability Committee

Our sustainability committee consists of Edith Shih, Christian Lawrence Hogg, Chig Fung Cheng, Johnny and Shu Kam Mok, Tony, with Edith Shih serving as chairman of the committee. The sustainability committee is responsible for strengthening our corporate governance and reporting framework. It advises our board of directors and management on and oversees the development and implementation of our corporate social responsibility and sustainability initiatives, including reviewing related policies and practices as well as assessing and making recommendations on matters pertaining to our sustainability governance, strategies, planning and risk management.

U.K. Corporate Governance Code

The U.K. Corporate Governance Code 2018 published by the U.K. Financial Reporting Council, or the 2018 Code, is the primary source of corporate governance standards for all companies with a premium listing on the Official List of the U.K. Financial Conduct Authority, whether incorporated in the United Kingdom or elsewhere, and it is recognized as a best practice for the largest companies by market capitalization on the AIM market. The 2018 Code is comprised of main and supporting principles of good governance addressing the following areas: (i) board leadership and company purpose; (ii) division of responsibilities; (iii) board composition, succession and evaluation; (iv) audit, risk and internal control; and (v) remuneration. Together with the U.K. Financial Reporting Council's Guidance on Board Effectiveness (published in July 2018), it also includes detailed recommendations derived from these principles, such as the roles of board chairman and chief executive officer should not be exercised by the same individual and the chairman of the board should ensure that new directors receive a full, formal and tailored induction on joining the board. The 2018 Code applies to accounting periods beginning on or after January 1, 2019. We adopted the principles of the UK Corporate Governance Code applicable to companies listed on the premium segment of the London Stock Exchange main market, despite its shares being traded on the AIM market and hence not required to comply with the UK Corporate Governance Code until our listing on the SEHK on June 30, 2021.

Hong Kong Corporate Governance Code

Following the listing on the SEHK on June 30, 2021, our board of directors has adopted the Corporate Governance Code ("Hong Kong Corporate Governance Code") contained in Appendix 14 of the Rules Governing the Listing of Securities on SEHK in replacement of the U.K. Corporate Governance Code 2018 and is in compliance with all code provisions of the Hong Kong Corporate Governance Code.

Code of Ethics

Our board of directors has adopted a code of ethics to set standards for our directors, officers and employees as are reasonably necessary to promote (i) honest and ethical conduct, including the ethical handling of actual or apparent conflicts of interest between personal and professional relationships; (ii) full, fair, accurate, timely and understandable disclosure in the reports and documents that we file or submit to the applicable stock exchanges, and in any other public communications; (iii) compliance with applicable governmental and regulatory laws, rules, codes and regulations; (iv) prompt internal reporting of any violations of the code of ethics; and (v) accountability for adherence to the code of ethics.

Code of Ethics for Business Partners

Our board of directors has adopted a code of ethics for our business partners, including our suppliers, vendors, customers, agents, contractors, joint venture partners and representatives. This code of ethics contains general guidelines to promote the standards outlined in our internal code of ethics as described above.

Complaints Procedures

Our board of directors has adopted procedures for the confidential receipt, retention, and treatment of complaints from, or concerns raised by, employees regarding accounting, internal accounting controls and auditing matters as well as illegal or unethical matters. The complaint procedures are reviewed by the audit committee from time to time as warranted to ensure their continuing compliance with applicable laws and listing standards as well as their effectiveness.

Information Security Policy

Our board of directors has adopted an information security policy to define and help communicate the common policies for information confidentiality, integrity and availability to be applied to us and our joint ventures. The purpose of the information security policy is to ensure business continuity by preventing and minimizing the impact of security risks within our company and our joint ventures. Our information security policy applies to all of our and our joint ventures' business entities across all countries. It applies to the creation, communication, storage, transmission and destruction of all different types of information. It applies to all forms of information, including but not limited to electronic copies, hardcopy, and verbal disclosures whether in person, over the telephone, or by other means.

Code on Dealings in Shares

Our board of directors has adopted a policy on the handling of material inside information, consisting of information which is either "inside information" under the EU Market Abuse Regulation (Regulation (EU) 596/2014), or MAR, or "material non-public information" under U.S. law. This policy, among other things, prohibits any employees, directors, other persons discharging managerial responsibilities or their connected persons dealing in our securities or their derivatives, or those of our collaborators, business partners, suppliers and customers, while in possession of material inside information. Certain members of our senior management or staff, including persons discharging managerial responsibilities, and their connected persons are subject to additional compliance requirements which are outlined in the code (including but not limited to obtaining written pre-clearance from designated members of management prior to any dealing in any such securities is allowed).

Board Diversity Policy

Our board of directors has established a board diversity policy as our board of directors recognizes the benefits of a board of directors that possesses a balance of skills, experience, expertise, independence and knowledge and diversity of perspectives appropriate to the requirements of our businesses.

We maintain that appointment to our board of directors should be based on merit that complements and expands the skills, experience, expertise, independence and knowledge of the board of directors as a whole, taking into account gender, age, professional experience and qualifications, cultural and educational background, and any other factors that our board of directors might consider relevant and applicable from time to time towards achieving a diverse board of directors. See also"—Directors and Senior Management—Board Diversity."

D. Employees.

As of December 31, 2019, 2020 and 2021, we had 853, 1,280 and 1,759 full-time employees, respectively. None of our employees are represented by labor unions or covered by collective bargaining agreements. The number of employees by function as of the end of the period for our fiscal years ended December 31, 2019, 2020 and 2021 was as follows:

	2021	2020	2019
By Function:			
Oncology/Immunology	891	643	500
Other Ventures	820	594	315
Corporate Head Office	48	43	38
Total	1,759	1,280	853

As of December 31, 2021, a total of 139 employees on our Oncology/Immunology research and development team have M.D. or Ph.D. degrees. Additionally, our Other Ventures joint venture Shanghai Hutchison Pharmaceuticals employed a total of 2,883 full time employees as of December 31, 2021, and such employees are represented by labor unions and covered by collective bargaining agreements. To date, Shanghai Hutchison Pharmaceuticals has not experienced any strikes, labor disputes or industrial actions which had a material effect on their business, and consider their relations with the union and our employees to be good.

We recognize the importance of high-quality human resources in sustaining market leadership. Salary and benefits are kept at competitive levels, while individual performance is rewarded within the general framework of the salary, bonus and incentive system of our company, which is reviewed annually. Employees are provided with a wide range of benefits that include medical coverage, provident funds and retirement plans and long service awards. We stress the importance of staff development and provides training programs on an ongoing basis. Employees are also encouraged to play an active role in community care activities.

E. Share Ownership.

See Item 6.B. “Compensation” and Item 7 “Major Shareholders and Related Party Transactions.”

ITEM 7. MAJOR SHAREHOLDERS AND RELATED PARTY TRANSACTIONS

A. Major Shareholders.

We had 864,530,850 ordinary shares outstanding as of March 1, 2022. The following table and accompanying footnotes set forth information relating to the beneficial ownership of our ordinary shares as of December 31, 2021 by:

- each person, or group of affiliated persons, known by us to beneficially own more than 5% of our outstanding ordinary shares;
- each of our directors; and
- each of our named executive officers.

Our major shareholders do not have voting rights that are different from our shareholders in general. Beneficial ownership is determined in accordance with the rules and regulations of the SEC.

Name of beneficial owner	Number of Ordinary Share held	Number of American Depositary Share held	Appropriate percent of Issued Share Capital**
Executive Officers and Directors:**			
Christian Lawrence Hogg	10,938,020	253,364 (1)	1.4 %
Chig Fung Cheng, Johnny	2,561,460	70,814 (1)	*
Chi Keung To, Simon	1,800,000	133,237	*
Edith Shih	700,000	100,000	*
Weiguo Su	5,000,000 (2)	187,125 (1)	*
Dan Eldar	19,000	13,787	*
Shu Kam Mok, Tony	—	14,796	*
Paul Rutherford Carter	35,240	4,074	*
Karen Jean Ferrante	—	10,579	*
Graeme Allan Jack	—	7,794	*
Marek Krzysztof Kania	* (2)	* (1)	*
Karen Jane Atkin	—	—	—
Zhenping Wu	* (2)	* (1)	*
Kin Hung Lee, Mark	* (2)	* (1)	*
Qingmei Wang, May	* (2)	* (1)	*
Hong Chen	* (2)	* (1)	*
Thomas R.Held	—	* (1)	*
Charles George Rupert Nixon	* (2)	* (1)	*
All Executive Officers and Directors as a Group	25,354,284 (3)	1,124,923 (4)	3.6 %
Principal Shareholders:			
Hutchison Healthcare Holdings Limited(5)	332,478,770	—	38.46 %
Capital International Investors(6)	10,524,720	13,957,242	9.3 %

* Less than 1% of our total outstanding ordinary shares.

** Percentage of beneficial ownership of each listed person or group is based on 864,530,850 ordinary shares outstanding as of March 1, 2022.

(1) Amount includes ADSs to be vested under the LTIP and ADSs issuable upon vesting of options within 60 days of March 1, 2022.

(2) Amount includes ordinary shares issuable upon vesting of options within 60 days of March 1, 2022.

(3) Amount includes ordinary shares and ordinary shares issuable upon vesting of options within 60 days of March 1, 2022 held by our executive officers and directors as a group.

(4) Amount includes ADSs and ADSs issuable upon vesting of options within 60 days of March 1, 2022 held by our executive officers and directors as a group.

(5) Hutchison Healthcare Holdings Limited, a British Virgin Islands company, is an indirect wholly owned subsidiary of CK Hutchison, a company incorporated in the Cayman Islands and listed on The Hong Kong Stock Exchange. The registered address of Hutchison Healthcare Holdings Limited is Vistra Corporate Services Centre, Wickhams Cay II, Road Town, Tortola VG1110, British Virgin Islands.

(6) Based on information included in the Schedule 13G filed by Capital International Investors on February 11, 2022.

As of March 1, 2022, based on public filings with the SEC, AIM and SEHK, there are no other major shareholders holding 5% or more of our ordinary shares or ADSs representing ordinary shares except as described above. As of March 1, 2022, there were three ordinary shareholders of record with an address in the United States. Deutsche Bank Trust Company America, as depositary of our ADS program, held 274,907,485 ordinary shares as of that date in the name of DB London (Investors Services) Nominees Limited.

To our knowledge, except as disclosed above, we are not owned or controlled, directly or indirectly, by another corporation, by any foreign government or by any other natural or legal person or persons, severally or jointly. To our knowledge, there are no arrangements the operation of which may at a subsequent date result in us undergoing a change in control. Our major shareholders do not have different voting rights than any of our other shareholders.

B. Related Party Transactions.

Relationship with CK Hutchison

Letters of awareness with respect to loans

CK Hutchison has provided letters of awareness to certain of our lenders stating that it is aware that loan facilities have been provided to us and that its current intention is that for so long as amounts are outstanding under such loan facilities, it will not reduce its direct or indirect shareholding as to result in it ceasing to be the single largest indirect shareholder of our company.

Relationship Agreement with the CK Hutchison group

We entered into a relationship agreement dated April 21, 2006, which was amended and restated on June 13, 2019 with effect from June 3, 2015, with Hutchison Whampoa (China) Limited, which is an indirect wholly owned subsidiary of CK Hutchison, with a view to ensuring that our company is capable of carrying on its business independent of the CK Hutchison group. We refer to this agreement as the Relationship Agreement. The Relationship Agreement provides, among other things, that all transactions between any of us or our joint ventures, on the one hand, and the CK Hutchison group, on the other, will be on an arm's length basis, on normal commercial terms and in a manner consistent with the AIM Rules. The Relationship Agreement further provides that the approval of our board of directors shall be required for any transaction between any of us or our joint ventures, on one hand, and the CK Hutchison group, on the other hand and that in approving any such transaction, our board of directors must consist of at least one director who is independent of CK Hutchison. Our board of directors must consist of at least one director who is independent of the CK Hutchison group if Hutchison Whampoa (China) Limited is entitled to cast at least 50% votes eligible to be cast on a poll vote at a general meeting of our company, see Item 6.C. "Directors, Senior Management and Employees—Board Practices." Hutchison Whampoa (China) Limited has also agreed to procure that each member of the Hutchison Whampoa (China) Limited group will not exercise its voting rights and powers so as to amend our Memorandum or Articles of Association in a manner which is inconsistent with the Relationship Agreement. The Relationship Agreement will continue to be effective until the first to occur of: (i) our shares ceasing to be traded on the AIM market or; (ii) the CK Hutchison group individually or collectively cease to hold or control the exercise of at least 30% or more of the rights to vote at our general meetings.

Products sold to group companies of CK Hutchison

We have entered into agreements with members of the CK Hutchison group, including the retail grocery and pharmacy chains PARKnSHOP and Watsons which are owned and operated by the A.S. Watson Group, an indirect subsidiary of CK Hutchison, in respect of the distribution of certain of our consumer health products. For the year ended December 31, 2021, sales of our products to members of the CK Hutchison group amounted to $4.3 million. In addition, for the year ended December 31, 2021, we paid approximately $0.4 million to members of the CK Hutchison group for the provision of marketing services associated with these products. Our sales to CK Hutchison group companies are made pursuant to purchase orders issued by each purchaser periodically, the terms of which are on an arm's length basis on normal commercial terms.

See Item 3.D. "Risk Factors—Risks Relating to Our Dependence on Third Parties—There is no assurance that the benefits currently enjoyed by virtue of our association with CK Hutchison will continue to be available" for more information on the risks associated with our relationship with CK Hutchison's group companies.

Intellectual property licensed by the CK Hutchison group

We conduct our business using trademarks with various forms of the "Hutchison," "Chi-Med", "Hutchison China MediTech", "HUTCHMED", "Elunate" and "Sulanda" brands, the logos used by HUTCHMED Limited, as well as domain names incorporating some or all of these trademarks. We have entered into a brand license agreement dated April 21, 2006 (as amended and restated on June 13, 2019 with effect from June 3, 2015 and as further amended and restated on June 15, 2021 with effect from March 4, 2021) with Hutchison Whampoa Enterprises Limited, which is an indirect wholly owned subsidiary of CK Hutchison, pursuant to which we have been granted a non-exclusive, non-transferrable, royalty-free right to use the "Hutchison," "Hutchison China MediTech", "Chi-Med", "HUTCHMED" trademarks, domain names and other intellectual property rights owned by the CK Hutchison group in connection with the operation of our business worldwide. We refer to this amended and restated agreement as the Brand License Agreement. We are also permitted to sub-license such intellectual property rights to our affiliates.

The Brand License Agreement contains provisions on quality control pursuant to which we are obliged to use the brands and related materials in compliance with the brand guidelines, industry best practice and other quality directives issued by Hutchison Whampoa Enterprises Limited from time to time. Under this agreement, we assign all intellectual property rights, including future copyrights in any works incorporating brand-related material or translations thereof, to Hutchison Whampoa Enterprises Limited (subject to any third-party rights).

Hutchison Whampoa Enterprises Limited may terminate the Brand License Agreement (or any sub-license) if, among other things, we commit a material breach of the agreement, or within any twelve-month period aggregate direct or indirect shareholding in our company held by CK Hutchison , our indirect shareholder, is reduced to less than 35%, 30% or 20%. On termination of the Brand License Agreement, we (and any sub-licensees) must immediately cease using the brands and are obliged to withdraw from the sale of any products bearing the brands; provided that if the agreement is terminated following a change in CK Hutchison's aggregate direct or indirect shareholding in our company, we will have a six-month transitional period during which we can continue to use the licensed rights.

On June 15, 2021, we entered into a brand license royalty agreement with Hutchison Whampoa Enterprises Limited, pursuant to which we will pay an annual fee of HK$12 million (up to an aggregate royalty payable of no more than HK$120 million) in consideration of the grant of the royalty-free right to use the trademarks owned by Hutchison Whampoa Enterprises Limited to Hutchison Baiyunshan and HBYS JV companies upon the completion of the disposal of shareholding interest in Hutchison Baiyunshan.

Sharing of services with the CK Hutchison group

Pursuant to an amended and restated services agreement dated January 1, 2016 between us and Hutchison Whampoa (China) Limited, an indirect wholly owned subsidiary of CK Hutchison, we share certain services with and receive operational support from the CK Hutchison group including, among others, legal and regulatory services, company secretarial support services, tax and internal audit services, shared use of accounting software system and related services, participation in the CK Hutchison group's pension, medical and insurance plans, participation in the CK Hutchison group's procurement projects with third-party vendors/suppliers, other staff benefits and staff training services, company functions and activities and operation advisory and support services. We refer to this amended and restated agreement as the Services Agreement. The Services Agreement replaces our prior services agreement with Hutchison Whampoa (China) Limited, dated April 21, 2006, which had substantially similar terms. We pay a management fee to Hutchison Whampoa (China) Limited for the provision of such services. In addition, we make payments under the Services Agreement to Hutchison Whampoa (China) Limited for our executive offices in Hong Kong. Furthermore, pursuant to the terms of the Services Agreement, Hutchison Whampoa (China) Limited charges us management fees and other costs through Hutchison Healthcare Holdings Limited, its wholly owned subsidiary.

The Services Agreement may be terminated by either party by giving three months' written notice. Hutchison Whampoa (China) Limited may also immediately terminate if its shareholding in our company falls below 30%. The services provided under the Services Agreement are provided on an arm's length basis, on normal commercial terms.

Any amount unpaid after 30 days accrues interest at the rate of 1.5% per annum. In the year ended December 31, 2021, we paid a management fee of approximately $1.0 million under the Services Agreement. As of December 31, 2021, we had $0.4 million in unpaid fees outstanding to Hutchison Whampoa (China) Limited.

Agreements with Our Directors and Executive Officers

Director and Executive Officer Compensation

See Item 6.B. "Compensation—Executive Officer Compensation" and "Compensation—Director Compensation" for a discussion of our compensation of directors and executive officers.

Equity Compensation

See Item 6.B. "Compensation—Equity Compensation Schemes and Other Benefit Plans."

Employment Agreements

We have entered into employment agreements with our executive officers. For more information regarding these agreements, see Item 6.B. "Compensation—Executive Officer Compensation—Employment Arrangements with our Executive Officers." No director has a service contract with us not terminable by us within one year without payment of compensation (other than statutory compensation).

Indemnification Agreements

We have entered into indemnification agreements with each of our directors and executive officers. We also maintain a general liability insurance policy which covers certain liabilities of our directors and executive officers arising out of claims based on acts or omissions in their capabilities as directors or officers.

C. Interests of Experts and Counsel.

Not applicable.

ITEM 8. FINANCIAL INFORMATION

A. Consolidated Financial Statements and Other Financial Information.

See Item 18 "Financial Statements."

A.7 Legal Proceedings.

There are no material legal proceedings pending or, to our knowledge, threatened against us. We are also not aware of any incidents of non-compliance with laws and regulations that may have a significant impact on us which would have a material adverse effect on our financial condition or results of operations. From time to time we become subject to legal proceedings and claims in the ordinary course of our business, including claims of alleged infringement of patents and other intellectual property rights. Such legal proceedings or claims, even if not meritorious, could result in the expenditure of significant financial and management resources.

A.8 Dividend Policy.

We have never declared or paid dividends on our ordinary shares. We currently expect to retain all future earnings for use in the operation and expansion of our business and do not have any present plan to pay any dividends. The declaration and payment of any dividends in the future will be determined by our board of directors in its discretion, and will depend on a number of factors, including our earnings, capital requirements, overall financial condition, and contractual restrictions.

B. Significant Changes.

We have not experienced any significant changes since the date of our audited consolidated financial statements included in this annual report.

ITEM 9. THE OFFER AND LISTING

Not applicable except for Item 9.A.4 and Item 9.C.

Our ADSs are listed on the Nasdaq Global Select and our ordinary shares are admitted to trading on the AIM market under the symbol "HCM." In addition, our ordinary shares are listed on the SEHK under stock code "0013."

ITEM 10. ADDITIONAL INFORMATION

A. Share Capital.

Not applicable.

B. Memorandum and Articles of Association.

On May 29, 2019, we conditionally adopted an amended and restated memorandum and articles of association by special resolution and effective on the date on which our shares are listed on the SEHK (the "Amended and Restated Articles"). On June 30, 2021, the listing date of our shares on the SEHK, the Amended and Restated Articles replaced the then existing articles of association of our company adopted by at the annual general meeting held on April 27, 2020.

C. Material Contracts.

Except as otherwise disclosed in this annual report (including the exhibits hereto), we are not currently, and have not been in the last two years, party to any material contract, other than contracts entered into in the ordinary course of our business.

D. Exchange Controls.

Foreign currency exchange in the PRC is primarily governed by the Foreign Exchange Administration Rules issued by the State Council on January 29, 1996 and effective as of April 1, 1996 (and amended on January 14, 1997 and August 5, 2008) and the Regulations of Settlement, Sale and Payment of Foreign Exchange which came into effect on July 1, 1996.

Under the Foreign Exchange Administration Rules, renminbi is freely convertible for current account items, including the distribution of dividends payments, interest payments, and trade and service-related foreign exchange transactions. Conversion of renminbi for capital account items, such as direct investment, loans, securities investment and repatriation of investment, however, is still generally subject to the approval or verification of the SAFE.

Under the Regulations of Settlement, Sale and Payment of Foreign Exchange, foreign invested enterprises including wholly foreign owned enterprises, may buy, sell or remit foreign currencies only at those banks that are authorized to conduct foreign exchange business after providing such banks with valid commercial supporting documents and, in the case of capital account item transactions, after obtaining approvals from the SAFE. Capital investments by foreign invested enterprises outside the PRC are also subject to limitations, which include approvals by the MOFCOM, the SAFE and the NDRC.

In March 2015, the SAFE released the Circular on Reforming the Management Approach regarding the Foreign Exchange Capital Settlement of Foreign-invested Enterprises, or FIEs, or the Foreign Exchange Capital Settlement Circular, which became effective from June 1, 2015. This circular replaced the SAFE's previous related circulars, including the Circular on Issues Relating to the Improvement of Business Operation with Respect to the Administration of Foreign Exchange Capital Payment and Settlement of Foreign Invested Enterprises. The Foreign Exchange Capital Settlement Circular clarifies that FIEs may settle a specified proportion of their foreign exchange capital in banks at their discretion, and may choose the timing for such settlement. The proportion of foreign exchange capital to be settled at FIEs' discretion for the time being is 100% and the SAFE may adjust the proportion in due time based on the situation of international balance of payments. The circular also stipulates that FIEs' usage of capital and settled foreign exchange capital shall comply with relevant provisions concerning foreign exchange control and be subject to the management of a negative list. The Notice of the SAFE on Policies for Reforming and Regulating Control over Foreign Exchange Settlement under the Capital Account, which became effective from June 9, 2016 and supplements the Foreign Exchange Capital Settlement Circular, stipulates that the FIEs' capital and Renminbi capital gained from the settlement of foreign exchange capital may not be directly or indirectly used for expenditure beyond the business scope of the FIEs or as prohibited by laws and regulations of the PRC. Such capital also may not be directly or indirectly used for granting loans to non-affiliated enterprises except as permitted by the business scope of the FIE or for construction or purchase of real estate other than self-use (exceptions only apply for real estate enterprises).

In addition, the payment of dividends by entities established in the PRC is subject to limitations. Regulations in the PRC currently permit payment of dividends only out of accumulated profits as determined in accordance with accounting standards and regulations in the PRC. Each of our PRC subsidiaries that is a domestic company is also required to set aside at least 10.0% of its after-tax profit based on PRC accounting standards each year to its general reserves or statutory capital reserve fund until the accumulative amount of such reserves reach 50.0% of its respective registered capital. These restricted reserves are not distributable as cash dividends. In addition, if any of our PRC subsidiaries or joint ventures incurs debt on its own behalf in the future, the instruments governing the debt may restrict its ability to pay dividends or make other distributions to us.

For more information about foreign exchange control, see Item 3.D. "Risk Factors—Other Risks and Risks Relating to Doing Business in China—Restrictions on currency exchange may limit our ability to receive and use our revenue effectively."

E. Taxation.

The following is a general summary of certain PRC, Hong Kong, Cayman Islands and U.S. federal income tax consequences relevant to the acquisition, ownership and disposition of our ADSs. The discussion is not intended to be, nor should it be construed as, legal or tax advice to any particular individual. The discussion is based on laws and relevant interpretations thereof in effect as of March 1, 2022, all of which are subject to change or different interpretations, possibly with retroactive effect. The discussion does not address U.S. state or local tax laws, or tax laws of jurisdictions other than the PRC, Hong Kong, the Cayman Islands and the United States. You should consult your own tax advisors with respect to the consequences of acquisition, ownership and disposition of our ADSs and ordinary shares.

Taxation in the PRC

PRC Enterprise Income Tax

Under the EIT Law, which was promulgated on March 16, 2007 and subsequently amended on February 24, 2017 and December 29, 2018, and its implementation rules which became effective on January 1, 2008 and subsequently amended on April 23, 2019, the standard tax rate of 25% applies to all enterprises (including FIEs) with exceptions in special situations if relevant criteria are met and subject to the approval of the PRC tax authorities.

An enterprise incorporated outside of the PRC whose "de facto management bodies" are located in the PRC is considered a "resident enterprise" and will be subject to a uniform EIT rate of 25% on its global income. In April 2009, the SAT, in Circular 82, specified certain criteria for the determination of what constitutes "de facto management bodies." If all of these criteria are met, the relevant foreign enterprise will be deemed to have its "de facto management bodies" located in the PRC and therefore be considered a resident enterprise in the PRC. These criteria include: (a) the enterprise's day-to-day operational management is primarily exercised in the PRC; (b) decisions relating to the enterprise's financial and human resource matters are made or subject to approval by organizations or personnel in the PRC; (c) the enterprise's primary assets, accounting books and records, company seals, and board and shareholders' meeting minutes are located or maintained in the PRC; and (d) 50% or more of voting board members or senior executives of the enterprise habitually reside in the PRC. Although Circular 82 only applies to foreign enterprises that are majority-owned and controlled by PRC enterprises, not those owned and controlled by foreign enterprises or individuals, the determining criteria set forth in Circular 82 may be adopted by the PRC tax authorities as the test for determining whether the enterprises are PRC tax residents, regardless of whether they are majority-owned and controlled by PRC enterprises. However, it is not entirely clear how the PRC tax authorities will determine whether a non-PRC entity (that has not already been notified of its status for EIT purposes) will be classified as a "resident enterprise" in practice.

Except for our PRC subsidiaries and joint ventures incorporated in China, we believe that none of our entities incorporated outside of China is a PRC resident enterprise for PRC tax purposes. However, the tax resident status of an enterprise is subject to determination by the PRC tax authorities, and uncertainties remain with respect to the interpretation of the term "de facto management body."

If a non-PRC enterprise is classified as a "resident enterprise" for EIT purposes, any dividends to be distributed by that enterprise to non-PRC resident shareholders or ADS holders or any gains realized by such investors from the transfer of shares or ADSs may be subject to PRC tax. If the PRC tax authorities determine that we should be considered a PRC resident enterprise for EIT purposes, any dividends payable by us to our non-PRC resident enterprise shareholders or ADS holders, as well as gains realized by such investors from the transfer of our shares or ADSs may be subject to a 10% withholding tax, unless a reduced rate is available under an applicable tax treaty. Furthermore, if we are considered a PRC resident enterprise for EIT purposes, it is unclear whether our non-PRC individual shareholders (including our ADS holders) would be subject to any PRC tax on dividends or gains obtained by such non-PRC individual shareholders. If any PRC tax were to apply to dividends realized by non-PRC individuals, it would generally apply at a rate of up to 20% unless a reduced rate is available under an applicable tax treaty.

According to the EIT Law, dividends declared after January 1, 2008 and paid by PRC FIEs to their non-PRC parent companies will be subject to PRC withholding tax at 10% unless there is a tax treaty between the PRC and the jurisdiction in which the overseas parent company is a tax resident and which specifically exempts or reduces such withholding tax, and such tax exemption or reduction is approved by the relevant PRC tax authorities. Pursuant to the Arrangement, if the non-PRC immediate holding company is a Hong Kong tax resident and directly holds a 25% or more equity interest in the PRC enterprise and is considered to be the beneficial owner of dividends paid by the PRC enterprise, such withholding tax rate may be lowered to 5%, subject to approval by the relevant PRC tax authorities in accordance with relevant tax regulations upon the assessment of beneficial ownership.

Overview of Tax Implications of Various Other Jurisdictions

Cayman Islands Taxation

According to our Cayman Islands counsel, Conyers Dill & Pearman, the Cayman Islands currently levies no taxes on individuals or corporations based upon profits, income, gains or appreciation and there is no taxation in the nature of inheritance tax or estate duty. There are no other taxes likely to be material to us levied by the government of the Cayman Islands except for stamp duties which may be applicable on instruments executed in, or brought within the jurisdiction of the Cayman Islands. The Cayman Islands is a party to a double tax treaty entered into with the United Kingdom in 2010 but it is otherwise not a party to any double tax treaties that are applicable to any payments made to or by our company. There are no exchange control regulations or currency restrictions in the Cayman Islands.

Pursuant to the Tax Concessions Act of the Cayman Islands, HUTCHMED (China) Limited has obtained an undertaking: (a) that no law which is enacted in the Cayman Islands imposing any tax to be levied on profits or income or gains or appreciations shall apply to us or our operations; and (b) that the aforesaid tax or any tax in the nature of estate duty or inheritance tax shall not be payable (i) on its shares, debentures or other obligations or (ii) by way of the withholding in whole or in part of any relevant payment as defined in the Tax Concessions Act.

The undertaking is for a period of twenty years from December 31, 2020.

Hong Kong Taxation

Profits Tax

HUTCHMED (China) Limited is a Hong Kong tax resident. Hong Kong tax residents are subject to Hong Kong Profits Tax in respect of profits arising in or derived from Hong Kong at the current rate of 16.5% (except portions eligible for the two-tiered profits tax as discussed above). Dividend income earned by a Hong Kong tax resident is generally not subject to Hong Kong Profits Tax.

Hong Kong tax on shareholders and ADS holders

No tax is payable in Hong Kong in respect of dividends paid by a Hong Kong tax resident to their shareholders, including our ADS holders.

Hong Kong Profits Tax will not be payable by our shareholders, including our ADS holders (other than shareholders / ADS holders carrying on a trade, profession or business in Hong Kong and holding the shares / ADSs for trading purposes), on any capital gains made on the sale or other disposal of the shares or ADSs. Shareholders, including our ADS holders, should take advice from their own professional advisors as to their particular tax position.

U.S. Taxation

Corporate Tax

Our subsidiaries in the United States, HUTCHMED International Corporation (formerly Hutchison MediPharma International Inc. and Hutchison MediPharma (US), Inc) and HUTCHMED US Corporation, are subject to a federal corporate tax of 21%.

Material U.S. Federal Income Tax Considerations with Respect to Ordinary Shares and ADSs

The following summary, subject to the limitations set forth below, describes the material U.S. federal income tax consequences for a U.S. Holder (as defined below) of the acquisition, ownership and disposition of ordinary shares and ADSs. It is not a comprehensive description of all tax considerations that may be relevant to a particular person's decision to acquire securities. This discussion is limited to U.S. Holders who hold such ordinary shares or ADSs as capital assets within the meaning of Section 1221 of the Internal Revenue Code of 1986, as amended, or the Code, for tax purposes (generally, property held for investment). For the purposes of this summary, a "U.S. Holder" is a beneficial owner of an ordinary share or ADS that is for U.S. federal income tax purposes:

- a citizen or individual resident of the United States;

- a corporation (or any other entity treated as a corporation for U.S. federal income tax purposes) organized in or under the laws of the United States or any state thereof, or the District of Columbia;
- an estate the income of which is subject to U.S. federal income taxation regardless of its source; or
- a trust if (i) it has a valid election in effect to be treated as a U.S. person for U.S. federal income tax purposes or (ii) a U.S. court can exercise primary supervision over its administration and one or more U.S. persons have the authority to control all of its substantial decisions.

Except as explicitly set forth below, this summary does not address aspects of U.S. federal income taxation that may be applicable to U.S. Holders subject to special rules, including:

- banks or other financial institutions;
- insurance companies;
- real estate investment trusts;
- regulated investment companies;
- grantor trusts;
- tax-exempt organizations;
- persons holding our ordinary shares or ADSs through a partnership (including an entity or arrangement treated as a partnership for U.S. federal income tax purposes) or S corporation;
- dealers or traders in securities, commodities or currencies;
- persons whose functional currency is not the U.S. dollar;
- U.S. expatriates and certain former citizens or former long-term residents of the United States;
- persons required under Section 451(b) of the Code to conform to the timing of income accruals with respect to our ADSs or the ordinary shares represented by such ADSs;
- persons holding our ordinary shares or ADSs as part of a position in a straddle or as part of a hedging, conversion or integrated transaction for U.S. federal income tax purposes; or
- direct, indirect or constructive owners of 10% or more of our equity (by vote or value).

In addition, this summary does not address the U.S. federal estate and gift tax or the alternative minimum tax consequences of the acquisition, ownership, and disposition of our ordinary shares or ADSs. We have not received nor do we expect to seek a ruling from the U.S. Internal Revenue Service, or the IRS, regarding any matter discussed herein. No assurance can be given that the IRS would not assert, or that a court would not sustain, a position contrary to any of those set forth below. Each prospective investor should consult its own tax advisors with respect to the U.S. federal, state, local and non-U.S. tax consequences of acquiring, owning and disposing of our ordinary shares and ADSs.

This discussion is based on the Code, U.S. Treasury Regulations promulgated thereunder and administrative and judicial interpretations thereof, and the income tax treaty between the PRC and the United States, or the U.S.- PRC Tax Treaty, each as available and in effect on the date hereof, all of which are subject to change or differing interpretations, possibly with retroactive effect, which could affect the tax consequences described herein. In addition, this summary assumes representations made by the depositary to us in the deposit agreement are true and assumes that the deposit agreement, and all other related agreements, will be performed in accordance with their terms.

If an entity or arrangement treated as a partnership for U.S. federal income tax purposes holds our ordinary shares or ADSs, the tax treatment of the partnership and a partner in such partnership generally will depend on the status of the partner and the activities of the partnership. Such partner or partnership should consult its own tax advisors as to the U.S. federal income tax consequences of acquiring, owning and disposing of our ordinary shares or ADSs.

PROSPECTIVE INVESTORS SHOULD CONSULT THEIR OWN TAX ADVISORS WITH REGARD TO THE PARTICULAR TAX CONSEQUENCES APPLICABLE TO THEIR SITUATIONS AS WELL AS THE APPLICATION OF ANY U.S. FEDERAL, STATE, LOCAL, NON-U.S. OR OTHER TAX LAWS, INCLUDING GIFT AND ESTATE TAX LAWS.

ADSs

A U.S. Holder of ADSs will generally be treated, for U.S. federal income tax purposes, as the owner of the underlying ordinary shares that such ADSs represent. Accordingly, no gain or loss will be recognized if a U.S. Holder exchanges ADSs for the underlying shares represented by those ADSs.

The U.S. Treasury has expressed concern that parties to whom ADSs are released before shares are delivered to the depositary or intermediaries in the chain of ownership between holders and the issuer of the security underlying the ADSs, may be taking actions that are inconsistent with the claiming of foreign tax credits by U.S. Holders of ADSs. These actions would also be inconsistent with the claiming of the reduced rate of tax, described below, applicable to dividends received by certain non-corporate U.S. Holders. Accordingly, the creditability of non-U.S. withholding taxes (if any), and the availability of the reduced tax rate for dividends received by certain non-corporate U.S. Holders, each described below, could be affected by actions taken by such parties or intermediaries. For the purposes of the discussion below, we assume that intermediaries in the chain of ownership between the holder of an ADS and us are acting consistently with the claim of U.S. foreign tax credits by U.S. Holders.

Taxation of Dividends

As described in "Dividend Policy" above, we do not currently anticipate paying any distributions on our ordinary shares or ADSs in the foreseeable future. However, to the extent there are any distributions made with respect to our ordinary shares or ADSs, and subject to the discussion under "—Passive Foreign Investment Company Considerations" below, the gross amount of any such distribution (including withheld taxes, if any) made out of our current or accumulated earnings and profits (as determined for U.S. federal income tax purposes) will generally be taxable to a U.S. Holder as ordinary dividend income on the date such distribution is actually or constructively received. Distributions in excess of our current and accumulated earnings and profits will be treated as a non-taxable return of capital to the extent of the U.S. Holder's adjusted tax basis in the ordinary shares or ADSs, as applicable, and thereafter as capital gain. However, because we do not maintain calculations of our earnings and profits in accordance with U.S. federal income tax accounting principles, U.S. Holders should expect to treat distributions paid with respect to our ordinary shares and ADSs as dividends. Dividends paid to corporate U.S. Holders generally will not qualify for the dividends received deduction that may otherwise be allowed under the Code. This discussion assumes that distributions made by us, if any, will be paid in U.S. dollars.

Dividends paid to a non-corporate U.S. Holder by a "qualified foreign corporation" may be subject to reduced rates of U.S. federal income taxation if certain holding period and other requirements are met. A qualified foreign corporation generally includes a foreign corporation (other than a PFIC) if (1) its ordinary shares (or ADSs backed by ordinary shares) are readily tradable on an established securities market in the United States or (2) it is eligible for benefits under a comprehensive U.S. income tax treaty that includes an exchange of information program and which the U.S. Treasury Department has determined is satisfactory for these purposes.

IRS guidance indicates that our ADSs (which are listed on the Nasdaq Global Select Market) are readily tradable for purposes of satisfying the conditions required for these reduced tax rates. We do not expect, however, that our ordinary shares will be listed on an established securities market in the United States and therefore do not believe that any dividends paid on our ordinary shares that are not represented by ADSs currently meet the conditions required for these reduced tax rates. There can be no assurance that our ADSs will be considered readily tradable on an established securities market in subsequent years.

The United States does not have a comprehensive income tax treaty with the Cayman Islands. However, in the event that we were deemed to be a PRC resident enterprise under the EIT Law (see "—Taxation in the PRC" above), although no assurance can be given, we might be considered eligible for the benefits of the U.S.-PRC Tax Treaty for the purposes of these rules. U.S. Holders should consult their own tax advisors regarding the availability of the reduced tax rates on dividends paid with respect to our ordinary shares or ADSs in light of their particular circumstances.

Non-corporate U.S. Holders will not be eligible for reduced rates of U.S. federal income taxation on any dividends received from us if we are a PFIC in the taxable year in which such dividends are paid or in the preceding taxable year unless, under certain circumstances, the "deemed sale election" described below under "—Passive Foreign Investment Company Considerations—Status as a PFIC" has been made.

In the event that we were deemed to be a PRC resident enterprise under the EIT Law (see "—Taxation in the PRC" above), U.S. Holders might be subject to PRC withholding taxes on dividends paid by us. In that case, subject to certain conditions and limitations, such PRC withholding tax may be treated as a foreign tax eligible for credit against a U.S. Holder's U.S. federal income tax liability under the U.S. foreign tax credit rules. For the purposes of calculating the U.S. foreign tax credit, dividends paid on our ordinary shares or ADSs, will be treated as income from sources outside the United States and will generally constitute passive category income. If a U.S. Holder is eligible for U.S.-PRC Tax Treaty benefits, any PRC taxes on dividends will not be creditable against such U.S. Holder's U.S. federal income tax liability to the extent such tax is withheld at a rate exceeding the applicable U.S.-PRC Tax Treaty rate. An eligible U.S. Holder who does not elect to claim a foreign tax credit for PRC tax withheld may instead be eligible to claim a deduction, for U.S. federal income tax purposes, in respect of such withholding but only for the year in which such U.S. Holder elects to do so for all creditable foreign income taxes. The U.S. foreign tax credit rules are complex. U.S. Holders should consult their own tax advisors regarding the foreign tax credit rules in light of their particular circumstances.

Taxation of Capital Gains

Subject to the discussion below in "—Passive Foreign Investment Company Considerations," upon the sale, exchange, or other taxable disposition of our ordinary shares or ADSs, a U.S. Holder generally will recognize gain or loss in an amount equal to the difference between the amount realized on such sale or exchange (determined in the case of sales or exchanges in currencies other than U.S. dollars by reference to the spot exchange rate in effect on the date of the sale or exchange or, if sold or exchanged on an established securities market and the U.S. Holder is a cash basis taxpayer or an electing accrual basis taxpayer, the spot exchange rate in effect on the settlement date) and the U.S. Holder's adjusted tax basis in such ordinary shares or ADSs determined in U.S. dollars. A U.S. Holder's initial tax basis will be the U.S. Holder's U.S. dollar purchase price for such ordinary shares or ADSs.

Assuming we are not a PFIC and have not been treated as a PFIC during the U.S. Holder's holding period for its ordinary shares or ADSs, such gain or loss will be capital gain or loss. Under current law, capital gains of non-corporate U.S. Holders derived with respect to capital assets held for more than one year are generally eligible for reduced rates of taxation. The deductibility of capital losses is subject to limitations. Capital gain or loss, if any, recognized by a U.S. Holder generally will be treated as U.S. source income or loss for U.S. foreign tax credit purposes. U.S. Holders are encouraged to consult their own tax advisors regarding the availability of the U.S. foreign tax credit in consideration of their particular circumstances.

If we were treated as a PRC resident enterprise for EIT Law purposes and PRC tax were imposed on any gain (see "—Taxation in the PRC" above), and if a U.S. Holder is eligible for the benefits of the U.S.-PRC Tax Treaty, the holder may be able to treat such gain as PRC source gain under the treaty for U.S. foreign tax credit purposes. A U.S. Holder will be eligible for U.S.-PRC Tax Treaty benefits if (for the purposes of the treaty) such holder is a resident of the United States and satisfies the other requirements specified in the U.S.-PRC Tax Treaty. Because the determination of treaty benefit eligibility is fact-intensive and depends upon a holder's particular circumstances, U.S. Holders should consult their tax advisors regarding U.S.-PRC Tax Treaty benefit eligibility. U.S. Holders are also encouraged to consult their own tax advisors regarding the tax consequences in the event PRC tax were to be imposed on a disposition of ordinary shares or ADSs, including the availability of the U.S. foreign tax credit and the ability and whether to treat any gain as PRC source gain for the purposes of the U.S. foreign tax credit in consideration of their particular circumstances.

Additional Tax on Net Investment Income

An additional 3.8% tax is imposed on the "net investment income" of certain U.S. citizens and resident aliens, and on the undistributed "net investment income" of certain estates and trusts. Among other items, "net investment income" would generally include dividends on and gains from the sale or other disposition of ordinary shares or ADSs. You should consult your own tax advisor regarding the application of this tax.

Passive Foreign Investment Company Considerations

Status as a PFIC. The rules governing PFICs can result in adverse tax consequences to U.S. Holders. We generally will be classified as a PFIC for U.S. federal income tax purposes if, for any taxable year, either: (1) 75% or more of our gross income consists of certain types of passive income, or (2) the average value (determined on a quarterly basis), of our assets that produce, or are held for the production of, passive income is 50% or more of the value of all of our assets.

Passive income generally includes dividends, interest, rents and royalties (other than certain rents and royalties derived in the active conduct of a trade or business), annuities and gains from assets that produce passive income. If a non-U.S. corporation owns at least 25% by value of the stock of another corporation, the non-U.S. corporation is treated for the purposes of the PFIC tests as owning its proportionate share of the assets of the other corporation and as receiving directly its proportionate share of the other corporation's income. Under this rule, we should be deemed to own a proportionate share of the assets and to have received a proportionate share of the income of our principal subsidiaries and joint ventures, including Shanghai Hutchison Pharmaceuticals Limited and Hutchison Whampoa Guangzhou Baiyunshan Chinese Medicine Company Limited for the period up to September 28, 2021 (the effective date of disposal), for the purposes of the PFIC determination.

Additionally, if we are classified as a PFIC in any taxable year with respect to which a U.S. Holder owns ordinary shares or ADSs, we generally will continue to be treated as a PFIC with respect to such U.S. Holder in all succeeding taxable years, regardless of whether we continue to meet the tests described above, unless the U.S. Holder makes the "deemed sale election" described below. Furthermore, if we are treated as a PFIC, then one or more of our subsidiaries may also be treated as PFICs.

Based on certain estimates of our gross income and gross assets (which estimates are inherently imprecise) and the nature of our business, we do not believe that we are currently a PFIC. Notwithstanding the foregoing, the determination of whether we are a PFIC is made annually and depends on particular facts and circumstances (such as the valuation of our assets, including goodwill and other intangible assets) and also may be affected by the application of the PFIC rules, which are subject to differing interpretations. The fair market value of our assets is expected to depend, in part, upon (a) the market price of our ADSs, which is likely to fluctuate, and (b) the composition of our income and assets, which will be affected by how, and how quickly, we spend any cash that is raised in any financing transaction. In light of the foregoing, no assurance can be provided that we are not currently a PFIC or that we will not become a PFIC in any future taxable year. Prospective investors should consult their own tax advisors regarding our PFIC status.

U.S. federal income tax treatment of a shareholder of a PFIC. If we are classified as a PFIC for any taxable year during which a U.S. Holder owns ordinary shares or ADSs, the U.S. Holder, absent certain elections (including the mark-to-market and QEF elections described below), generally will be subject to adverse rules (regardless of whether we continue to be classified as a PFIC) with respect to (1) any "excess distributions" (generally, any distributions received by the U.S. Holder on its ordinary shares or ADSs in a taxable year that are greater than 125% of the average annual distributions received by the U.S. Holder in the three preceding taxable years or, if shorter, the U.S. Holder's holding period) and (2) any gain realized on the sale or other disposition, including a pledge, of such ordinary shares or ADSs.

Under these rules (a) the excess distribution or gain will be allocated ratably over the U.S. Holder's holding period, (b) the amount allocated to the current taxable year and any taxable year prior to the first taxable year in which we are classified as a PFIC will be taxed as ordinary income and (c) the amount allocated to each other taxable year during the U.S. Holder's holding period in which we were classified as a PFIC (i) will be subject to tax at the highest rate of tax in effect for the applicable category of taxpayer for that year and (ii) will be subject to an interest charge at a statutory rate with respect to the resulting tax attributable to each such other taxable year. In addition, non-corporate U.S. Holders will not be eligible for reduced rates of taxation on any dividends received from us if we are a PFIC in the taxable year in which such dividends are paid or in the preceding taxable year.

If we are classified as a PFIC, a U.S. Holder will generally be treated as owning a proportionate amount (by value) of stock or shares owned by us in any direct or indirect subsidiaries that are also PFICs and will be subject to similar adverse rules with respect to any distributions we receive from, and dispositions we make of, the stock or shares of such subsidiaries. U.S. Holders are urged to consult their tax advisors about the application of the PFIC rules to any of our subsidiaries.

If we are classified as a PFIC and then cease to be so classified, a U.S. Holder may make an election (a "deemed sale election") to be treated for U.S. federal income tax purposes as having sold such U.S. Holder's ordinary shares or ADSs on the last day of our taxable year during which we were a PFIC. A U.S. Holder that makes a deemed sale election would then cease to be treated as owning stock in a PFIC. However, gain recognized as a result of making the deemed sale election would be subject to the adverse rules described above and loss would not be recognized.

PFIC "mark-to-market" election. In certain circumstances, a holder of "marketable stock" of a PFIC can avoid certain of the adverse rules described above by making a timely mark-to-market election with respect to such stock. For the purposes of these rules "marketable stock" is stock which is "regularly traded" (traded in greater than de minimis quantities on at least 15 days during each calendar quarter) on a "qualified exchange" or other market within the meaning of applicable U.S. Treasury Regulations. A "qualified exchange" includes a national securities exchange that is registered with the SEC.

A U.S. Holder that makes a timely mark-to-market election must include in gross income, as ordinary income, for each taxable year that we are a PFIC an amount equal to the excess, if any, of the fair market value of the U.S. Holder's ordinary shares or ADSs that are "marketable stock" at the close of the taxable year over the U.S. Holder's adjusted tax basis in such ordinary shares or ADSs. An electing U.S. Holder may also claim an ordinary loss deduction for the excess, if any, of the U.S. Holder's adjusted tax basis in such ordinary shares or ADSs over their fair market value at the close of the taxable year, but this deduction is allowable only to the extent of any net mark-to-market gains previously included in income pursuant to the timely mark-to-market election. The adjusted tax basis of a U.S. Holder's ordinary shares or ADSs with respect to which the timely mark-to-market election applies would be adjusted to reflect amounts included in gross income or allowed as a deduction because of such election. If a U.S. Holder makes an effective mark-to-market election with respect to our ordinary shares or ADSs, gains from an actual sale or other disposition of such ordinary shares or ADSs in a year in which we are a PFIC would be treated as ordinary income, and any losses incurred on such sale or other disposition would be treated as ordinary losses to the extent of any net mark-to-market gains previously included in income.

If we are classified as a PFIC for any taxable year in which a U.S. Holder owns ordinary shares or ADSs but before a timely mark-to-market election is made, the adverse PFIC rules described above will apply to any mark-to-market gain recognized in the year the election is made. Otherwise, a timely mark-to-market election will be effective for the taxable year for which the election is made and all subsequent taxable years unless the ordinary shares or ADSs are no longer regularly traded on a qualified exchange or the IRS consents to the revocation of the election. Our ADSs are listed on the Nasdaq Global Select Market, which is a qualified exchange or other market for the purposes of the mark-to-market election. Consequently, if the ADSs continue to be so listed, and are "regularly traded" for the purposes of these rules (for which no assurance can be given) we expect that the mark-to-market election would be available to a U.S. Holder with respect to our ADSs.

A mark-to-market election is not permitted for the shares of any of our subsidiaries that are also classified as PFICs. Prospective investors should consult their own tax advisors regarding the availability of, and the procedure for, and the effect of making, a mark-to-market election, and whether making the election would be advisable, including in light of their particular circumstances.

PFIC "QEF" election. In some cases, a shareholder of a PFIC can avoid the interest charge and the other adverse PFIC tax consequences described above by obtaining certain information from the PFIC and by making a timely QEF election to be taxed currently on its share of the PFIC's undistributed income. We do not, however, expect to provide the information regarding our income that would be necessary in order for a U.S. Holder to make a timely QEF election if we were classified as a PFIC.

PFIC information reporting requirements. If we are classified as a PFIC in any year with respect to a U.S. Holder, such U.S. Holder will be required to file an annual information return on IRS Form 8621 regarding distributions received on, and any gain realized on the disposition of, our ordinary shares and ADSs, and certain U.S. Holders will be required to file an annual information return (also on IRS Form 8621) relating to their ownership interest.

NO ASSURANCE CAN BE GIVEN THAT WE ARE NOT CURRENTLY A PFIC OR THAT WE WILL NOT BECOME A PFIC IN THE FUTURE. U.S. HOLDERS SHOULD CONSULT THEIR OWN TAX ADVISORS WITH RESPECT TO THE OPERATION OF THE PFIC RULES AND RELATED REPORTING REQUIREMENTS IN LIGHT OF THEIR PARTICULAR CIRCUMSTANCES, INCLUDING THE ADVISABILITY AND EFFECTS OF MAKING ANY ELECTION THAT MAY BE AVAILABLE.

Backup Withholding and Information Reporting and Filing Requirements

Backup withholding and information reporting requirements may apply to distributions on, and proceeds from the sale or disposition of, ordinary shares and ADSs that are held by U.S. Holders. The payor will be required to withhold tax (currently at a rate of 24%) on such payments made within the United States, or by a U.S. payor or a U.S. intermediary (and certain subsidiaries thereof) to a U.S. Holder, other than an exempt recipient, if the U.S. Holder is not otherwise exempt and:

- the holder fails to furnish the holder's taxpayer identification number, which for an individual is ordinarily his or her social security number;
- the holder furnishes an incorrect taxpayer identification number;
- the applicable withholding agent is notified by the IRS that the holder previously failed to properly report payments of interest or dividends; or
- the holder fails to certify under penalties of perjury that the holder has furnished a correct taxpayer identification number and that the IRS has not notified the holder that the holder is subject to backup withholding.

Backup withholding is not an additional tax. Amounts withheld as backup withholding may be credited against a U.S. Holder's U.S. federal income tax liability (if any) or refunded provided the required information is furnished to the IRS in a timely manner. U.S. Holders should consult their tax advisors regarding their qualification for an exemption from backup withholding and the procedures for obtaining such an exemption.

Certain U.S. Holders of specified foreign financial assets with an aggregate value in excess of the applicable dollar threshold are required to report information relating to their holding of ordinary shares or ADSs, subject to certain exceptions (including an exception for shares held in accounts maintained by certain financial institutions) with their tax returns for each year in which they hold such interests. U.S. Holders should consult their own tax advisors regarding the information reporting obligations that may arise from their acquisition, ownership or disposition of our ordinary shares or ADSs.

THE ABOVE DISCUSSION DOES NOT COVER ALL TAX MATTERS THAT MAY BE OF IMPORTANCE TO A PARTICULAR INVESTOR. PROSPECTIVE INVESTORS ARE STRONGLY URGED TO CONSULT THEIR OWN TAX ADVISORS ABOUT THE TAX CONSEQUENCES OF AN INVESTMENT IN OUR ORDINARY SHARES OR ADSs.

F. Dividends and Payment Agents.

Not applicable.

G. Statement by Experts.

Not applicable.

H. Documents on Display.

We are subject to the informational requirements of the Exchange Act and are required to file reports and other information with the SEC. Shareholders may access our reports and other information filed with the SEC by viewing them on the SEC's website, at *www.sec.gov*. We also make available on our website's investor relations page, free of charge, our annual report and the text of our reports on Form 6-K, including any amendments to these reports, as well as certain other SEC filings, as soon as reasonably practicable after they are electronically filed with or furnished to the SEC. The address for our investor relations page is *www.hutch-med.com/ shareholder-information*. The information contained on our website is not incorporated by reference in this annual report.

We are a "foreign private issuer" as such term is defined in Rule 405 under the Securities Act, and are not subject to the same requirements that are imposed upon U.S. domestic issuers by the SEC. Under the Exchange Act, we are subject to reporting obligations that, in certain respects, are less detailed and less frequent than those of U.S. domestic reporting companies. As a result, we do not file the same reports that a U.S. domestic issuer would file with the SEC, although we are required to file or furnish to the SEC the continuous disclosure documents that we are required to file on the AIM market.

We will furnish Deutsche Bank Trust Company Americas, the depositary of our ADSs, with our annual reports, which will include a review of operation and annual audited consolidated financial statements prepared in conformity with U.S. GAAP, and all notices of shareholders' meetings and other reports and communications that are made generally available to our shareholders. The depositary will make such notices, reports and communications available to holders of ADSs and, upon our requests, will mail to all record holders of ADSs the information contained in any notice of a shareholders' meeting received by the depositary from us.

I. Subsidiary information.

Not applicable.

ITEM 11. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

Foreign Exchange Risk

Most of our revenue and expenses are denominated in renminbi, and our consolidated financial statements are presented in U.S. dollars. We do not believe that we currently have any significant direct foreign exchange risk and have not used any derivative financial instruments to hedge our exposure to such risk. Although, in general, our exposure to foreign exchange risks should be limited, the value of your investment in our ADSs will be affected by the exchange rate between the U.S. dollar and the renminbi because the value of our business is effectively denominated in renminbi, while the ADSs will be traded in U.S. dollars.

The value of the renminbi against the U.S. dollar and other currencies may fluctuate and is affected by, among other things, changes in China's political and economic conditions. The conversion of renminbi into foreign currencies, including U.S. dollars, has been based on rates set by the PBOC. On July 21, 2005, the PRC government changed its decade-old policy of pegging the value of the renminbi to the U.S. dollar. Under the revised policy, the renminbi is permitted to fluctuate within a narrow and managed band against a basket of certain foreign currencies. This change in policy resulted in a more than 20% appreciation of the renminbi against the U.S. dollar in the following three years. Between July 2008 and June 2010, this appreciation halted, and the exchange rate between the renminbi and U.S. dollar remained within a narrow band. In June 2010, the PBOC announced that the PRC government would increase the flexibility of the exchange rate, and thereafter allowed the renminbi to appreciate slowly against the U.S. dollar within the narrow band fixed by the PBOC. At various times since then, the PBOC has significantly devalued the renminbi against the U.S. dollar. If we decide to convert renminbi into U.S. dollars for the purpose of making payments for dividends on our ordinary shares or ADSs or for other business purposes, appreciation of the U.S. dollar against the renminbi would have a negative effect on the U.S. dollar amounts available to us.

Credit Risk

Substantially all of our bank deposits are in major financial institutions, which we believe are of high credit quality. We limit the amount of credit exposure to any single financial institution. We make periodic assessments of the recoverability of trade and other receivables and amounts due from related parties. Our historical experience in collection of receivables falls within the recorded allowances, and we believe that we have made adequate provision for uncollectible receivables.

Interest Rate Risk

We have no significant interest-bearing assets except for bank deposits. Our exposure to changes in interest rates is mainly attributable to our bank borrowings, which bear interest at floating interest rates and expose us to cash flow interest rate risk. We have not used any interest rate swaps to hedge our exposure to interest rate risk. We have performed sensitivity analysis for the effects on our results for the year from changes in interest rates on floating rate borrowings. The sensitivity to interest rates used is based on the market forecasts available at the end of the reporting period and under the economic environments in which we operate, with other variables held constant. According to the analysis, the impact on our net loss of a 1.0% interest rate shift would be a maximum increase/decrease of $0.3 million for the year ended December 31, 2021.

ITEM 12. DESCRIPTION OF SECURITIES OTHER THAN EQUITY SECURITIES

A. Debt Securities.

Not applicable.

B. Warrants and Rights.

Not applicable.

C. Other Securities.

Not applicable.

D. American Depositary Shares.

Our ADSs representing our ordinary shares are currently traded on Nasdaq. Dealings in our ADSs on Nasdaq are conducted in U.S. dollars.

ADSs may be held either:

(a) directly: (i) by having an American Depositary Receipt, also referred to as an ADR, which is a certificate evidencing a specific number of ADSs registered in the holder's name; or (ii) by having uncertificated ADSs registered in the holder's name; or

(b) indirectly, by holding a security entitlement in ADSs through a broker or other financial institution that is a direct or indirect participant in The Depository Trust Company, also called DTC.

The depositary for our ADSs is Deutsche Bank Trust Company Americas, whose office is located at 1 Columbus Circle, New York, NY 10019, United States.

Fees and charges our ADS holders may have to pay

ADS holders will be required to pay the following service fees to Deutsche Bank Trust Company America, the depositary of our ADS program, and certain taxes and governmental charges (in addition to any applicable fees, expenses, taxes and other governmental charges payable on the deposited securities represented by ADSs):

Service	Fees
● To any person to which ADSs are issued or to any person to which a distribution is made in respect of ADS distributions pursuant to stock dividends or other free distributions of stock, bonus distributions, stock splits or other distributions (except where converted to cash)	Up to $0.05 per ADS issued
● Cancellation or withdrawal of ADSs, including the case of termination of the deposit agreement	Up to $0.05 per ADS cancelled
● Distribution of cash dividends	Up to $0.05 per ADS held
● Distribution of cash entitlements (other than cash dividends) and/or cash proceeds from the sale of rights, securities and other entitlements	Up to $0.05 per ADS held
● Distribution of ADSs pursuant to exercise of rights	Up to $0.05 per ADS held
● Depositary services	Up to $0.05 per ADS held on the applicable record date(s) established by the depositary bank (an annual fee)

ADS holders will also be responsible for paying certain fees and expenses incurred by the depositary bank and certain taxes and governmental charges (in addition to any applicable fees, expenses, taxes and other governmental charges payable on the deposited securities represented by any of your ADSs) such as:

- Fees for the transfer and registration of ordinary shares charged by the registrar and transfer agent for the ordinary shares in the Cayman Islands (i.e., upon deposit and withdrawal of ordinary shares).
- Expenses incurred for converting foreign currency into U.S. dollars.
- Expenses for cable, telex and fax transmissions and for delivery of securities.
- Taxes and duties upon the transfer of securities, including any applicable stamp duties, any stock transfer charges or withholding taxes (i.e., when ordinary shares are deposited or withdrawn from deposit).
- Fees and expenses incurred in connection with the delivery or servicing of ordinary shares on deposit.
- Fees and expenses incurred in connection with complying with exchange control regulations and other regulatory requirements applicable to ordinary shares, ordinary shares deposited securities, ADSs and ADRs.
- Any applicable fees and penalties thereon.

The depositary fees payable upon the issuance and cancellation of ADSs are typically paid to the depositary bank by the brokers (on behalf of their clients) receiving the newly issued ADSs from the depositary bank and by the brokers (on behalf of their clients) delivering the ADSs to the depositary bank for cancellation. The brokers in turn charge these fees to their clients. Depositary fees payable in connection with distributions of cash or securities to ADS holders and the depositary services fee are charged by the depositary bank to the holders of record of ADSs as of the applicable ADS record date.

The depositary fees payable for cash distributions are generally deducted from the cash being distributed or by selling a portion of distributable property to pay the fees. In the case of distributions other than cash (i.e., share dividends, rights), the depositary bank charges the applicable fee to the ADS record date holders concurrent with the distribution. In the case of ADSs registered in the name of the investor (whether certificated or uncertificated in direct registration), the depositary bank sends invoices to the applicable record date ADS holders. In the case of ADSs held in brokerage and custodian accounts (via DTC), the depositary bank generally collects its fees through the systems provided by DTC (whose nominee is the registered holder of the ADSs held in DTC) from the brokers and custodians holding ADSs in their DTC accounts. The brokers and custodians who hold their clients' ADSs in DTC accounts in turn charge their clients' accounts the amount of the fees paid to the depositary banks.

In the event of refusal to pay the depositary fees, the depositary bank may, under the terms of the deposit agreement, refuse the requested service until payment is received or may set off the amount of the depositary fees from any distribution to be made to the ADS holder.

Fees and other payments made by the depositary to us

The depositary has agreed to pay certain amounts to us in exchange for its appointment as depositary. We may use these funds towards our expenses relating to the establishment and maintenance of the ADR program, including investor relations expenses, or otherwise as we see fit. In 2021, we did not collect any reimbursements from the depositary for expenses related to the administration and maintenance of the facility.

Ordinary Shares and Conversions

Our ordinary shares are admitted to trading on AIM and trade on the SEHK. Dealings in our ordinary shares on the AIM and SEHK are conducted in pound sterlings and H.K. dollars, respectively.

In connection with the initial public offering of our ordinary shares in Hong Kong in June 2021, we established a branch register of members in Hong Kong, or the Hong Kong share register, which will be maintained by our Hong Kong Share Registrar, Computershare Hong Kong Investor Services Limited. Our principal register of members, or the Cayman share register, will continue to be maintained by our Principal Share Registrar, Computershare Investor Services (Jersey) Limited. All ordinary shares offered in our initial public offering in Hong Kong were registered on the Hong Kong share register in order to be listed and traded on the SEHK.

Details on the conversion process between SEHK, Nasdaq and AIM are available at https://www.hutch-med.com/shareholder-information/investor-faqs/.

PART II

ITEM 13. DEFAULTS, DIVIDEND ARREARAGES AND DELINQUENCIES

None.

ITEM 14. MATERIAL MODIFICATIONS TO THE RIGHTS OF SECURITY HOLDERS AND USE OF PROCEEDS

A-D. Material Modifications to the Rights of Security Holders; Assets Securing Securities; Trustees; Paying Agents.

None.

E. Use of Proceeds.

Not applicable.

ITEM 15. CONTROLS AND PROCEDURES

A. Evaluation of Disclosure Controls and Procedures.

As required by Rule 13a-15 under the Exchange Act, management, including our chief executive officer and our chief financial officer, has evaluated the effectiveness of our disclosure controls and procedures as of the end of the period covered by this report. Disclosure controls and procedures refer to controls and other procedures designed to ensure that information required to be disclosed in the reports we file or submit under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the rules and forms of the SEC. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by us in our reports that we file or submit under the Exchange Act is accumulated and communicated to management, including our principal executive and principal financial officers, or persons performing similar functions, as appropriate to allow timely decisions regarding our required disclosure. Based on such evaluation, our management has concluded that, as of December 31, 2021, our disclosure controls and procedures were effective.

B. Management's Annual Report on Internal Control over Financial Reporting.

Our management is responsible for establishing and maintaining adequate internal control over financial reporting, as defined in Rule 13a-15(f) and 15d-15(f) promulgated under the Securities Exchange Act of 1934. Internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of consolidated financial statements in accordance with U.S. GAAP and includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of a company's assets; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of consolidated financial statements in accordance with generally accepted accounting principles, and that a company's receipts and expenditures are being made only in accordance with authorizations of a company's management and directors; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of a company's assets that could have a material effect on the consolidated financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Projections of any evaluation of effectiveness of our internal control over financial reporting to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Our management, with the participation of our chief executive officer and chief financial officer, has assessed the effectiveness of our internal control over financial reporting as of December 31, 2021. In making this assessment, our management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) in Internal Control-Integrated Framework (2013 Framework). Based on this assessment, management concluded that our internal control over financial reporting was effective as of December 31, 2021.

C. Attestation Report of the Independent Registered Public Accounting Firm.

Our independent registered public accounting firm, PricewaterhouseCoopers Zhong Tian LLP ("PricewaterhouseCoopers Zhong Tian") , has audited the effectiveness of our internal control over financial reporting as of December 31, 2021, as stated in its report, which appears in this annual report.

D. Changes in Internal Control over Financial Reporting.

There were no changes in our internal controls over financial reporting during the fiscal year ended December 31, 2021 that have materially and adversely affected, or are reasonably likely to materially and adversely affect, our internal control over financial reporting.

ITEM 16. RESERVED

ITEM 16A. AUDIT COMMITTEE FINANCIAL EXPERTS

Our audit committee consists of Graeme Allan Jack, Paul Rutherford Carter and Karen Jean Ferrante, with Graeme Allan Jack serving as chairman of the committee. Graeme Allan Jack, Paul Rutherford Carter and Karen Jean Ferrante each meet the independence requirements under the rules of the Nasdaq Stock Market and under Rule 10A-3 under the Exchange Act. We have determined that Graeme Allan Jack is an "audit committee financial expert" within the meaning of Item 407 of Regulation S-K. All members of our audit committee meet the requirements for financial literacy under the applicable rules and regulations of the SEC and the Nasdaq Stock Market. For information relating to qualifications and experience of each audit committee member, see Item 6. "Directors, Senior Management and Employees."

ITEM 16B. CODE OF ETHICS

Our board of directors has adopted a code of ethics applicable to all of our employees, officers and directors, including our principal executive officer, principal financial officer, principal accounting officer or controller, and persons performing similar functions. This code is intended to qualify as a "code of ethics" within the meaning of the applicable rules of the SEC. Our code of ethics is available on our website at *https://www.hutch-med.com/shareholder-information/corporate-governance/code-of-ethics/*. Information contained on, or that can be accessed through, our website is not incorporated by reference into this annual report. See Item 6.C. "Board Practices—Code of Ethics" for more information.

ITEM 16C. PRINCIPAL ACCOUNTANT FEES AND SERVICES

Principal Accountant Fees and Services

The following table summarizes the fees charged by PricewaterhouseCoopers Zhong Tian and PricewaterhouseCoopers for certain services rendered to our company, including some of our subsidiaries and joint ventures, during 2021 and 2020.

	For the year ended December 31,	
	2021	2020
	(in thousands)	
Audit fees[(1)]	4,614	3,289
Tax fees[(2)]	406	45
Other service fees[(3)]	—	90
Total[(4)]	5,020	3,424

Notes:

(1) "Audit fees" means the aggregate fees billed in each of the fiscal years for professional services rendered by PricewaterhouseCoopers Zhong Tian and PricewaterhouseCoopers for the audit of our annual financial statements and review of our interim financial statements, filing of our Form F-3 and S-8, and professional services paid by us in connection with follow-on offerings in the United States, initial public offering in Hong Kong and preparation for other capital market transactions.

(2) "Tax fees" means the aggregate fees billed in each of the fiscal years for professional services rendered by PricewaterhouseCoopers for tax compliance and tax advice.

(3) "Other service fees" means the aggregate fees billed for professional services rendered by PricewaterhouseCoopers for information technology system and security review.

(4) The fees disclosed are exclusive of out-of-pocket expenses and taxes on the amounts paid, which totaled approximately $164,000 and $117,000 in 2020 and 2021, respectively.

(5) On June 15, 2021, we engaged PricewaterhouseCoopers Zhong Tian as our independent registered public accounting firm, and dismissed PricewaterhouseCoopers. The fees for 2021 are fees payable to PricewaterhouseCoopers Zhong Tian. See also "Item 16F. Change in Registrant's Certifying Accountant."

Audit Committee Pre-approval Policies and Procedures

Our audit committee reviews and pre-approves the scope and the cost of audit services related to us and permissible non-audit services performed by the independent auditors, other than those for *de minimis* services which are approved by the audit committee prior to the completion of the audit. All of the services related to our company provided by PricewaterhouseCoopers Zhong Tian and PricewaterhouseCoopers listed above have been approved by the audit committee.

ITEM 16D. EXEMPTIONS FROM THE LISTING STANDARDS FOR AUDIT COMMITTEES

Not applicable.

ITEM 16E. PURCHASES OF EQUITY SECURITIES BY THE ISSUER AND AFFILIATED PURCHASERS

None.

ITEM 16F. CHANGE IN REGISTRANT'S CERTIFYING ACCOUNTANT

On June 15, 2021, we engaged PricewaterhouseCoopers Zhong Tian as our independent registered public accounting firm, and dismissed PricewaterhouseCoopers. The change of our independent registered public accounting firm had been approved by the audit committee of our board of directors, and the decision was not made due to any disagreement between us and Pricewaterhouse Coopers.

The reports of PricewaterhouseCoopers on our consolidated financial statements for the fiscal years ended December 31, 2019 and 2020 did not contain an adverse opinion or disclaimer of opinion and were not qualified or modified as to uncertainty, audit scope or accounting principle.

During the fiscal years ended December 31, 2019 and 2020 and the subsequent interim period through June 15, 2021, there have been no (i) disagreements between us and PricewaterhouseCoopers on any matter of accounting principles or practices, financial statement disclosure, or audit scope or procedure, which disagreements if not resolved to the satisfaction of PricewaterhouseCoopers would have caused them to make reference thereto in their reports on the consolidated financial statements for such years, or (ii) reportable events as defined in Item 16F(a)(1)(v) of the instructions to Form 20-F.

We have provided PricewaterhouseCoopers with a copy of the disclosures hereunder and required under Item 16F of Form 20-F and requested from PricewaterhouseCoopers a letter addressed to the Securities and Exchange Commission indicating whether it agrees with such disclosures. A copy of PricewaterhouseCooper's letter dated June 21, 2021 is attached as Exhibit 16.1 to our current report on Form 6-K furnished to the SEC on June 21, 2021.

During each of the fiscal years ended December 31, 2019 and 2020 and the subsequent interim period through June 15, 2021, neither we nor anyone on behalf of us has consulted with PricewaterhouseCoopers Zhong Tian regarding (i) the application of accounting principles to a specific transaction, either completed or proposed, or the type of audit opinion that might be rendered on our consolidated financial statements, and neither a written report nor oral advice was provided to us that PricewaterhouseCoopers Zhong Tian concluded was an important factor considered by us in reaching a decision as to any accounting, audit or financial reporting issue, (ii) any matter that was the subject of a disagreement pursuant to Item 16F(a)(1)(iv) of the instructions to Form 20-F, or (iii) any reportable event pursuant to Item 16F(a)(1)(v) of the instructions to Form 20-F.

ITEM 16G. CORPORATE GOVERNANCE

As permitted by Nasdaq, in lieu of the Nasdaq corporate governance rules, but subject to certain exceptions, we may follow the practices of our home country which for the purpose of such rules is the Cayman Islands. Certain corporate governance practices in the Cayman Islands may differ significantly from corporate governance listing standards as, except for general fiduciary duties and duties of care, Cayman Islands law has no corporate governance regime which prescribes specific corporate governance standards. For example, we follow Cayman Islands corporate governance practices in lieu of the corporate governance requirements of the Nasdaq Global Select Market in respect of the following:

(i) the majority independent director requirement under Section 5605(b)(1) of the Nasdaq listing rules,

(ii) the requirement under Section 5605(d) of the Nasdaq listing rules that a remuneration committee comprised solely of independent directors governed by a remuneration committee charter oversee executive compensation, and

(iii) the requirement under Section 5605(e) of the Nasdaq listing rules that director nominees be selected or recommended for selection by either a majority of the independent directors or a nominations committee comprised solely of independent directors.

Cayman Islands law does not impose a requirement that our board of directors consist of a majority of independent directors, nor does Cayman Islands law impose specific requirements on the establishment of a remuneration committee or nominating committee or nominating process. We voluntarily comply with Hong Kong Corporate Governance Code. See Item 6.C. “Board Practice—Hong Kong Corporate Governance Code” for more details.

ITEM 16H. MINE SAFETY DISCLOSURE

Not applicable.

ITEM 16I. DISCLOSURE REGARDING FOREIGN JURISDICTIONS THAT PREVENT INSPECTION

Not applicable.

PART III

ITEM 17. FINANCIAL STATEMENTS

See Item 18 “Financial Statements.”

ITEM 18. FINANCIAL STATEMENTS

Our consolidated financial statements and the consolidated financial statements of our non-consolidated joint venture, Shanghai Hutchison Pharmaceuticals, and our former non-consolidated joint venture, Hutchison Baiyunshan, are included at the end of this annual report.

ITEM 19. EXHIBITS

EXHIBIT INDEX

1.1*	Amended and Restated Memorandum and Articles of Association of HUTCHMED (China) Limited
2.1	Form of Deposit Agreement and all holders and beneficial owners of ADSs issued thereunder (incorporated by reference to Exhibit 4.1 to Amendment No. 4 to our Registration Statement on Form F-1 (file no. 333-207447) filed with the SEC on March 4, 2016)
2.2	Form of American Depositary Receipt (incorporated by reference to Exhibit 4.1 to Amendment No. 4 to our Registration Statement on Form F-1 (file no. 333-207447) filed with the SEC on March 4, 2016)
2.3	Form of Specimen Certificate for Ordinary Shares (incorporated by reference to Exhibit 4.3 to Amendment No. 2 to our Registration Statement on Form F-1 (file no. 333-207447) filed with the SEC on February 11, 2016)
2.4*	Description of Ordinary Shares
2.5	Description of American Depositary Shares (incorporated by reference to Exhibit 2.5 to our annual report on Form 20-F/A filed with the SEC on April 29, 2020)
4.1	Amended and Restated License and Collaboration Agreement by and between HUTCHMED Limited (formerly known as Hutchison MediPharma Limited) and AstraZeneca AB (publ) dated as of December 7, 2020 (incorporated by reference to Exhibit 4.1 to our annual report on Form 20-F filed with the SEC on March 4, 2021)
4.2*+	Amendment to the Amended and Restated License and Collaboration Agreement by and between HUTCHMED Limited and AstraZeneca AB (publ) dated as of November 29, 2021
4.3	Amended and Restated Exclusive License and Collaboration Agreement by and HUTCHMED Limited, Eli Lilly Trading (Shanghai) Company Limited and HUTCHMED (China) Limited dated as of October 8, 2013 (incorporated by reference to Exhibit 4.2 to our annual report on Form 20-F/A filed with the SEC on May 30, 2019)
4.4	First Amendment to the Amended and Restated Exclusive License and Collaboration Agreement by and among Lilly (Shanghai) Management Company Limited, HUTCHMED Limited and HUTCHMED (China) Limited dated as of December 18, 2018 (incorporated by reference to Exhibit 4.16 to our annual report on Form 20-F filed with the SEC on March 11, 2019)
4.5	English translation of Sino-Foreign Joint Venture Contract by and between Shanghai Traditional Chinese Medicine Co., Ltd. and Shanghai HUTCHMED Investment Limited (formerly Hutchison Chinese Medicine (Shanghai) Investment Limited) dated as of January 6, 2001 (incorporated by reference to Exhibit 4.6 to our annual report on Form 20-F/A filed with the SEC on May 30, 2019)
4.6	English translation of First Amendment to Sino-Foreign Joint Venture Contract by and between Shanghai Traditional Chinese Medicine Co., Ltd. and Shanghai HUTCHMED Investment Limited dated as of July 12, 2001 (incorporated by reference to Exhibit 10.15 to our Registration Statement on Form F-1 (file no. 333-207447) filed with the SEC on October 16, 2015)
4.7	English translation of Second Amendment to Sino-Foreign Joint Venture Contract by and between Shanghai Traditional Chinese Medicine Co., Ltd. and Shanghai HUTCHMED Investment (HK) Limited dated as of November 5, 2007 (incorporated by reference to Exhibit 10.16 to our Registration Statement on Form F-1 (file no. 333-207447) filed with the SEC on October 16, 2015)
4.8	English translation of Third Amendment to Sino-Foreign Joint Venture Contract by and between Shanghai Traditional Chinese Medicine Co., Ltd. and Shanghai HUTCHMED Investment (HK) Limited dated as of June 19, 2012 (incorporated by reference to Exhibit 10.17 to our Registration Statement on Form F-1 (file no. 333-207447) filed with the SEC on October 16, 2015)
4.9	English translation of Fourth Amendment to Sino-Foreign Joint Venture Contract by and between Shanghai Traditional Chinese Medicine Co., Ltd. and Shanghai HUTCHMED Investment (HK) Limited dated as of March 8, 2013 (incorporated by reference to Exhibit 4.10 to our annual report on Form 20-F/A filed with the SEC on May 30, 2019)
4.10	English translation of Sino-Foreign Joint Venture Contract by and between Sinopharm Group Co. Ltd. and Hutchison Chinese Medicine GSP (HK) Holdings Limited dated as of December 18, 2013 (incorporated by reference to Exhibit 4.11 to our annual report on Form 20-F/A filed with the SEC on May 30, 2019)
4.11	Form of Executive Employment Agreement for HUTCHMED Group (HK) Limited executive officers (incorporated by reference to Exhibit 10.23 to our Registration Statement on Form F-1 (file no. 333-207447) filed with the SEC on October 16, 2015)

4.12	English translation of Form of Executive Employment Agreement for HUTCHMED Limited executive officers (incorporated by reference to Exhibit 10.24 to our Registration Statement on Form F-1 (file no. 333-207447) filed with the SEC on October 16, 2015)
4.13	Form of Indemnification Agreement for Directors and Officers (incorporated by reference to Exhibit 10.25 to our Registration Statement on Form F-1 (file no. 333-207447) filed with the SEC on October 16, 2015)
4.14	Second Amendment to the Amended and Restated Exclusive License and Collaboration Agreement by and among Lilly (Shanghai) Management Company Limited, HUTCHMED Limited and HUTCHMED (China) Limited dated as of July 28, 2020 (incorporated by reference to Exhibit 4.14 to our annual report on Form 20-F filed with the SEC on March 4, 2021)
4.15*+	License Agreement by and among Epizyme, Inc. and Hutchison China MediTech Investment Limited (now known as HUTCHMED Group Investment Limited) dated as of August 7, 2021
4.16*	Form of Offer Letter for Hutchison MediPharma (US), Inc. (now known as HUTCHMED International Corporation) executive officer
4.17*	Form of Offer Letter for Hutchison MediPharma International Inc. (now known as HUTCHMED International Corporation) executive officer
8.1*	List of Significant Subsidiaries of the Company
12.1*	Certification of Chief Executive Officer Required by Rule 13a-14(a)
12.2*	Certification of Chief Financial Officer Required by Rule 13a-14(a)
13.1*	Certification of Chief Executive Officer Required by Rule 13a-14(b) and Section 1350 of Chapter 63 of Title 18 of the United States Code
13.2*	Certification of Chief Financial Officer Required by Rule 13a-14(b) and Section 1350 of Chapter 63 of Title 18 of the United States Code
15.1*	Consent of PricewaterhouseCoopers Zhong Tian LLP, an independent registered accounting firm, regarding the consolidated financial statements of HUTCHMED (China) Limited
15.2*	Consent of PricewaterhouseCoopers, an independent registered accounting firm, regarding the consolidated financial statements of HUTCHMED (China) Limited
15.3*	Consent of PricewaterhouseCoopers Zhong Tian LLP, independent accountants, regarding the consolidated financial statements of Shanghai Hutchison Pharmaceuticals Limited
15.4*	Consent of PricewaterhouseCoopers Zhong Tian LLP, independent accountants, regarding the consolidated financial statements of Hutchison Whampoa Guangzhou Baiyunshan Chinese Medicine Company Limited
15.5*	Consent of Conyers Dill & Pearman
16.1	Letter from PricewaterhouseCoopers to the Securities and Exchange Commission dated June 21, 2021 (incorporated herein by reference to Exhibit 16.1 to the current report on Form 6-K furnished to the SEC on June 21, 2021)
101.INS*	XBRL Instance Document
101.SCH*	XBRL Taxonomy Extension Schema Document
101.CAL*	XBRL Taxonomy Extension Calculation Linkbase Document
101.LAB*	XBRL Taxonomy Extension Label Linkbase Document
101.PRE*	XBRL Taxonomy Extension Presentation Linkbase Document
101.DEF*	XBRL Taxonomy Extension Definitions Linkbase Document
104*	Cover Page Interactive Data File (embedded within the Inline XBRL document)

* Filed herewith.
† Furnished herewith.
\+ Portions of the exhibit have been omitted because they are both (i) not material and (ii) would likely cause competitive harm to the company if publicly disclosed.

SIGNATURES

The registrant hereby certifies that it meets all of the requirements for filing on annual report on Form 20-F and that it has duly caused and authorized the undersigned to sign this annual report on its behalf.

HUTCHMED (China) Limited

By: /s/ CHRISTIAN LAWRENCE HOGG
Name: Christian Lawrence Hogg
Title: Chief Executive Officer

Date: March 3, 2022

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

Report of Independent Registered Public Accounting Firm

To the Board of Directors and Shareholders of HUTCHMED (China) Limited

Opinions on the Financial Statements and Internal Control over Financial Reporting

We have audited the accompanying consolidated balance sheet of HUTCHMED (China) Limited (formerly known as "Hutchison China MediTech Limited") and its subsidiaries (the "Company") as of December 31, 2021, and the related consolidated statements of operations, of comprehensive loss, of changes in shareholders' equity and of cash flows for the year ended December 31, 2021, including the related notes (collectively referred to as the "consolidated financial statements"). We also have audited the Company's internal control over financial reporting as of December 31, 2021, based on criteria established in *Internal Control—Integrated Framework* (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO).

In our opinion, the consolidated financial statements referred to above present fairly, in all material respects, the financial position of the Company as of December 31, 2021, and the results of its operations and its cash flows for the year ended December 31, 2021 in conformity with accounting principles generally accepted in the United States of America. Also in our opinion, the Company maintained, in all material respects, effective internal control over financial reporting as of December 31, 2021, based on criteria established in *Internal Control—Integrated Framework* (2013) issued by the COSO.

Basis for Opinions

The Company's management is responsible for these consolidated financial statements, for maintaining effective internal control over financial reporting, and for its assessment of the effectiveness of internal control over financial reporting, included in Management's Annual Report on Internal Control over Financial Reporting appearing under Item 15 of Form 20-F. Our responsibility is to express opinions on the Company's consolidated financial statements and on the Company's internal control over financial reporting based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audits to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud, and whether effective internal control over financial reporting was maintained in all material respects.

Our audits of the consolidated financial statements included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. Our audit of internal control over financial reporting included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, and testing and evaluating the design and operating effectiveness of internal control based on the assessed risk. Our audits also included performing such other procedures as we considered necessary in the circumstances. We believe that our audits provide a reasonable basis for our opinions.

Definition and Limitations of Internal Control over Financial Reporting

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (i) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (ii) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (iii) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Critical Audit Matters

The critical audit matter communicated below is a matter arising from the current period audit of the consolidated financial statements that was communicated or required to be communicated to the audit committee and that (i) relates to accounts or disclosures that are material to the consolidated financial statements and (ii) involved our especially challenging, subjective, or complex judgments. The communication of critical audit matters does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the accounts or disclosures to which it relates.

Allowances for credit losses on accounts receivable and other receivables (except for prepayments)

As described in Note 6 to the consolidated financial statements, as of December 31, 2021, the gross balance of accounts receivable was US$83.6 million and an allowance for credit losses of less than US$0.1 million was made. As described in Note 7 to the consolidated financial statements, as of December 31, 2021, the gross balance of other receivables was US$81.0 million which consisted of the balance of prepayments of US$14.1 million, and no allowance for credit losses was made. The allowances for credit losses were made based on estimate of the current expected credit losses to be incurred over the expected life of these receivables.

The principal considerations for our determination that performing procedures relating to the allowances for credit losses on accounts receivable and other receivables (except for prepayments) is a critical audit matter are the significant estimates and judgments by management when developing the current expected credit losses to be incurred over the expected life of these receivables, which in turn led to a high degree of auditor judgment and significant audit effort in evaluating the audit evidence related to management's significant assumptions, including accounts receivable and other receivables (except for prepayments) portfolio groups and estimated loss rates.

Addressing the matter involved performing procedures and evaluating audit evidence in connection with forming our overall opinion on the consolidated financial statements. These procedures included testing the effectiveness of internal controls relating to management's estimate of allowances for credit losses on accounts receivable and other receivables (except for prepayments). The procedures also included, among others, testing management's process of developing the allowances for credit losses, testing the accuracy and completeness of the underlying data and the mathematical accuracy of the allowances for credit losses, evaluating the appropriateness of the model and methodology used and assessing the reasonableness of portfolio groups of the receivables and estimated loss rates used by management. Assessing the reasonableness of portfolio groups of the receivables used by management involved evaluating their credit risk characteristics. Assessing the reasonableness of estimated loss rates used by management involved evaluating the historical default rates and application of forward-looking information.

/s/ PricewaterhouseCoopers Zhong Tian LLP
Shenzhen, the People's Republic of China
March 3, 2022

We have served as the Company's auditor since 2021.

Report of Independent Registered Public Accounting Firm

To the Board of Directors and Shareholders of HUTCHMED (China) Limited

Opinion on the Financial Statements

We have audited the consolidated balance sheet of HUTCHMED (China) Limited (formerly known as "Hutchison China MediTech Limited") and its subsidiaries (the "Company") as of December 31, 2020, and the related consolidated statements of operations, of comprehensive loss, of changes in shareholders' equity and of cash flows for each of the two years in the period ended December 31, 2020, including the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2020, and the results of its operations and its cash flows for each of the two years in the period ended December 31, 2020 in conformity with accounting principles generally accepted in the United States of America.

Basis for Opinion

These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's consolidated financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits of these consolidated financial statements in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud.

Our audits included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ PricewaterhouseCoopers
Hong Kong
March 4, 2021

We served as the Company's auditor from 2005 to 2021.

HUTCHMED (China) Limited
Consolidated Balance Sheets
(in US$'000, except share data)

	Note	December 31, 2021	December 31, 2020
Assets			
Current assets			
Cash and cash equivalents	5	377,542	235,630
Short-term investments	5	634,158	199,546
Accounts receivable	6	83,580	47,870
Other receivables, prepayments and deposits	7	81,041	27,928
Inventories	8	35,755	19,766
Total current assets		**1,212,076**	**530,740**
Property, plant and equipment	9	41,275	24,170
Right-of-use assets	10	11,879	8,016
Deferred tax assets	25(ii)	9,401	1,515
Investments in equity investees	11	76,479	139,505
Other non-current assets	12	21,551	20,172
Total assets		**1,372,661**	**724,118**
Liabilities and shareholders' equity			
Current liabilities			
Accounts payable	13	41,177	31,612
Other payables, accruals and advance receipts	14	210,839	121,283
Bank borrowings	15	26,905	—
Income tax payable	25(iii)	15,546	1,120
Other current liabilities		17,191	4,382
Total current liabilities		**311,658**	**158,397**
Lease liabilities	10	7,161	6,064
Deferred tax liabilities	25(ii)	2,765	5,063
Long-term bank borrowings	15	—	26,861
Other non-current liabilities		11,563	8,784
Total liabilities		**333,147**	**205,169**
Commitments and contingencies	16		
Company's shareholders' equity			
Ordinary shares; $0.10 par value; 1,500,000,000 shares authorized; 864,530,850 and 727,722,215 shares issued at December 31, 2021 and 2020 respectively	17	86,453	72,772
Additional paid-in capital		1,505,196	822,458
Accumulated losses		(610,328)	(415,591)
Accumulated other comprehensive income		5,572	4,477
Total Company's shareholders' equity		**986,893**	**484,116**
Non-controlling interests		52,621	34,833
Total shareholders' equity		**1,039,514**	**518,949**
Total liabilities and shareholders' equity		**1,372,661**	**724,118**

The accompanying notes are an integral part of these consolidated financial statements.

HUTCHMED (China) Limited
Consolidated Statements of Operations
(in US$'000, except share and per share data)

	Note	Year Ended December 31, 2021	2020	2019
Revenues				
Goods—third parties		266,199	203,606	175,990
—related parties	24(i)	4,256	5,484	7,637
Services—commercialization—third parties		27,428	3,734	2,584
—collaboration research and development—third parties		18,995	9,771	15,532
—research and development—related parties	24(i)	525	491	494
Other collaboration revenue				
—royalties—third parties		15,064	4,890	2,653
—licensing—third parties		23,661	—	—
Total revenues	19	**356,128**	**227,976**	**204,890**
Operating expenses				
Costs of goods—third parties		(229,448)	(178,828)	(152,729)
Costs of goods—related parties		(3,114)	(3,671)	(5,494)
Costs of services—commercialization—third parties		(25,672)	(6,020)	(1,929)
Research and development expenses	21	(299,086)	(174,776)	(138,190)
Selling expenses		(37,827)	(11,334)	(13,724)
Administrative expenses		(89,298)	(50,015)	(39,210)
Total operating expenses		**(684,445)**	**(424,644)**	**(351,276)**
		(328,317)	**(196,668)**	**(146,386)**
Gain on divestment of an equity investee	23	121,310	—	—
Other income/(expense)				
Interest income	27	2,076	3,236	4,944
Other income		2,426	4,600	1,855
Interest expense	27	(592)	(787)	(1,030)
Other expense		(12,643)	(115)	(488)
Total other income/(expense)		**(8,733)**	**6,934**	**5,281**
Loss before income taxes and equity in earnings of equity investees		**(215,740)**	**(189,734)**	**(141,105)**
Income tax expense	25(i)	(11,918)	(4,829)	(3,274)
Equity in earnings of equity investees, net of tax	11	60,617	79,046	40,700
Net loss		**(167,041)**	**(115,517)**	**(103,679)**
Less: Net income attributable to non-controlling interests		(27,607)	(10,213)	(2,345)
Net loss attributable to the Company		**(194,648)**	**(125,730)**	**(106,024)**
Losses per share attributable to the Company—basic and diluted (US$ per share)	26	(0.25)	(0.18)	(0.16)
Number of shares used in per share calculation—basic and diluted	26	792,684,524	697,931,437	665,683,145

The accompanying notes are an integral part of these consolidated financial statements.

HUTCHMED (China) Limited
Consolidated Statements of Comprehensive Loss
(in US$'000)

	Year Ended December 31,		
	2021	2020	2019
Net loss	**(167,041)**	**(115,517)**	**(103,679)**
Other comprehensive income/(loss)			
Foreign currency translation gain/(loss)	2,964	9,530	(4,331)
Total comprehensive loss	**(164,077)**	**(105,987)**	**(108,010)**
Less: Comprehensive income attributable to non-controlling interests	(28,029)	(11,413)	(1,620)
Total comprehensive loss attributable to the Company	**(192,106)**	**(117,400)**	**(109,630)**

The accompanying notes are an integral part of these consolidated financial statements.

HUTCHMED (China) Limited
Consolidated Statements of Changes in Shareholders' Equity
(in US$'000, except share data in' 000)

	Ordinary Shares Number	Ordinary Shares Value	Additional Paid-in Capital	Accumulated Losses	Accumulated Other Comprehensive (Loss)/Income	Total Company's Shareholders' Equity	Non-controlling Interests	Total Shareholders' Equity
As at January 1, 2019	**666,577**	**66,658**	**505,585**	**(183,659)**	**(243)**	**388,341**	**23,243**	**411,584**
Net (loss)/income	—	—	—	(106,024)	—	(106,024)	2,345	(103,679)
Issuances in relation to share option exercises	329	33	218	—	—	251	—	251
Share-based compensation								
Share options	—	—	7,157	—	—	7,157	16	7,173
Long-term incentive plan ("LTIP")	—	—	2,239	—	—	2,239	12	2,251
	—	—	9,396	—	—	9,396	28	9,424
LTIP—treasury shares acquired and held by Trustee	—	—	(346)	—	—	(346)	—	(346)
Transfer between reserves	—	—	51	(51)	—	—	—	—
Foreign currency translation adjustments	—	—	—	—	(3,606)	(3,606)	(725)	(4,331)
As at December 31, 2019	**666,906**	**66,691**	**514,904**	**(289,734)**	**(3,849)**	**288,012**	**24,891**	**312,903**
Net (loss)/income	—	—	—	(125,730)	—	(125,730)	10,213	(115,517)
Issuance in relation to public offering	23,669	2,366	115,975	—	—	118,341	—	118,341
Issuances in relation to private investment in public equity ("PIPE")	36,667	3,667	196,333	—	—	200,000	—	200,000
Issuance costs	—	—	(8,317)	—	—	(8,317)	—	(8,317)
Issuances in relation to share option exercises	480	48	545	—	—	593	—	593
Share-based compensation								
Share options	—	—	8,727	—	—	8,727	10	8,737
LTIP	—	—	7,203	—	—	7,203	16	7,219
	—	—	15,930	—	—	15,930	26	15,956
LTIP—treasury shares acquired and held by Trustee	—	—	(12,904)	—	—	(12,904)	—	(12,904)
Dividends declared to non-controlling shareholders of subsidiaries	—	—	—	—	—	—	(1,462)	(1,462)
Purchase of additional interests in a subsidiary of an equity investee (Note 11)	—	—	(52)	(83)	(4)	(139)	(35)	(174)
Transfer between reserves	—	—	44	(44)	—	—	—	—
Foreign currency translation adjustments	—	—	—	—	8,330	8,330	1,200	9,530
As at December 31, 2020	**727,722**	**72,772**	**822,458**	**(415,591)**	**4,477**	**484,116**	**34,833**	**518,949**
Net (loss)/income	—	—	—	(194,648)	—	(194,648)	27,607	(167,041)
Issuance in relation to public offering	119,600	11,960	602,907	—	—	614,867	—	614,867
Issuance in relation to PIPE	16,393	1,639	98,361	—	—	100,000	—	100,000
Issuance costs	—	—	(29,806)	—	—	(29,806)	—	(29,806)
Issuances in relation to share option exercises	816	82	2,370	—	—	2,452	—	2,452
Share-based compensation								
Share options	—	—	16,339	—	—	16,339	26	16,365
LTIP	—	—	19,808	—	—	19,808	70	19,878
	—	—	36,147	—	—	36,147	96	36,243
LTIP—treasury shares acquired and held by Trustee	—	—	(27,309)	—	—	(27,309)	—	(27,309)
Dividends declared to non-controlling shareholders of subsidiaries	—	—	—	—	—	—	(9,894)	(9,894)
Transfer between reserves	—	—	89	(89)	—	—	—	—
Divestment of an equity investee (Note 23)	—	—	(21)	—	(1,447)	(1,468)	(443)	(1,911)
Foreign currency translation adjustments	—	—	—	—	2,542	2,542	422	2,964
As at December 31, 2021	**864,531**	**86,453**	**1,505,196**	**(610,328)**	**5,572**	**986,893**	**52,621**	**1,039,514**

The accompanying notes are an integral part of these consolidated financial statements.

HUTCHMED (China) Limited
Consolidated Statements of Cash Flows
(in US$'000)

	Note	Year Ended December 31, 2021	2020	2019
Net cash used in operating activities	28	(204,223)	(62,066)	(80,912)
Investing activities				
Purchases of property, plant and equipment		(16,401)	(7,949)	(8,565)
Purchase of leasehold land		(355)	(11,631)	—
Refund/(payment) of leasehold land deposit	12	930	(2,326)	—
Deposits in short-term investments		(1,355,976)	(732,908)	(478,140)
Proceeds from short-term investments		921,364	629,373	597,044
Purchase of a warrant	20	(15,000)	—	—
Proceeds from divestment of an equity investee	23	159,118	—	—
Purchase of a subsidiary company		—	—	(8,080)
Cash acquired in purchase of a subsidiary company		—	—	16,769
Net cash (used in)/generated from investing activities		(306,320)	(125,441)	119,028
Financing activities				
Proceeds from issuances of ordinary shares		717,319	318,934	251
Purchases of treasury shares	18(ii)	(27,309)	(12,904)	(346)
Dividends paid to non-controlling shareholders of subsidiaries		(9,894)	(1,462)	(1,282)
Repayment of loan to a non-controlling shareholder of a subsidiary		(579)	—	—
Proceeds from bank borrowings		—	—	26,807
Repayment of bank borrowings		—	—	(26,923)
Payment of issuance costs		(29,509)	(8,134)	—
Net cash generated from/(used in) financing activities		650,028	296,434	(1,493)
Net increase in cash and cash equivalents		139,485	108,927	36,623
Effect of exchange rate changes on cash and cash equivalents		2,427	5,546	(1,502)
		141,912	114,473	35,121
Cash and cash equivalents				
Cash and cash equivalents at beginning of year		235,630	121,157	86,036
Cash and cash equivalents at end of year		377,542	235,630	121,157
Supplemental disclosure for cash flow information				
Cash paid for interest		425	815	917
Cash paid for tax, net of refunds	25(iii)	5,014	5,940	3,249
Supplemental disclosure for non-cash activities				
Increase in accrued capital expenditures		8,607	298	1,068
Vesting of treasury shares for LTIP	18(ii)	1,450	4,828	944

The accompanying notes are an integral part of these consolidated financial statements.

HUTCHMED (China) Limited
Notes to the Consolidated Financial Statements

1. Organization and Nature of Business

HUTCHMED (China) Limited (formerly known as "Hutchison China MediTech Limited") (the "Company") and its subsidiaries (together the "Group") are principally engaged in researching, developing, manufacturing and marketing pharmaceutical products. The Group and its equity investees have research and development facilities and manufacturing plants in the People's Republic of China (the "PRC") and sell their products mainly in the PRC, including Hong Kong. In addition, the Group has established international operations in the United States of America (the "U.S.") and Europe.

The Company's ordinary shares are listed on the Main Board of The Stock Exchange of Hong Kong Limited ("HKEX") (listing completed in June 2021) and the AIM market of the London Stock Exchange, and its American depositary shares ("ADS") are traded on the Nasdaq Global Select Market.

Liquidity

As at December 31, 2021, the Group had accumulated losses of US$610,328,000 primarily due to its spending in drug research and development activities. The Group regularly monitors current and expected liquidity requirements to ensure that it maintains sufficient cash balances and adequate credit facilities to meet its liquidity requirements in the short and long term. As at December 31, 2021, the Group had cash and cash equivalents of US$377,542,000, short-term investments of US$634,158,000 and unutilized bank borrowing facilities of US$157,430,000. Short-term investments comprised of bank deposits maturing over three months. The Group's operating plan includes the continued receipt of dividends from an equity investee. Dividends received for the years ended December 31, 2021, 2020 and 2019 were US$49,872,000, US$86,708,000 and US$28,135,000 respectively.

Based on the Group's operating plan, the existing cash and cash equivalents, short-term investments and unutilized bank borrowing facilities are considered to be sufficient to meet the cash requirements to fund planned operations and other commitments for at least the next twelve months (the look-forward period used).

2. Particulars of Principal Subsidiaries and Equity Investees

Name	Place of establishment and operations	Equity interest attributable to the Group December 31, 2021	Equity interest attributable to the Group December 31, 2020	Principal activities
Subsidiaries				
HUTCHMED Limited (formerly known as "Hutchison MediPharma Limited")	PRC	99.75 %	99.75 %	Research, development, manufacture and commercialization of pharmaceutical products
HUTCHMED International Corporation (formerly known as "Hutchison MediPharma International Inc.")	U.S.	99.75 %	99.75 %	Provision of professional, scientific and technical support services
Hutchison Whampoa Sinopharm Pharmaceuticals (Shanghai) Company Limited ("HSPL")	PRC	50.87 %	50.87 %	Provision of sales, distribution and marketing services to pharmaceutical manufacturers
Hutchison Hain Organic (Hong Kong) Limited ("HHOHK") (note (a))	Hong Kong	50 %	50 %	Wholesale and trading of healthcare and consumer products
Hutchison Healthcare Limited	PRC	100 %	100 %	Manufacture and distribution of healthcare products
HUTCHMED Science Nutrition Limited (formerly known as "Hutchison Consumer Products Limited")	Hong Kong	100 %	100 %	Wholesale and trading of healthcare and consumer products
Equity investees				
Shanghai Hutchison Pharmaceuticals Limited ("SHPL")	PRC	50 %	50 %	Manufacture and distribution of prescription drug products
Hutchison Whampoa Guangzhou Baiyunshan Chinese Medicine Company Limited ("HBYS") (note (b))	PRC	— %	40 %	Manufacture and distribution of over-the-counter drug products

Notes:

(a) HHOHK is regarded as a subsidiary of the Company, as while both its shareholders have equal representation at the board, in the event of a deadlock, the Group has a casting vote and is therefore able to unilaterally control the financial and operating policies of HHOHK.

(b) On September 28, 2021, the Group completed a transaction to sell its entire investment in HBYS to a third party (Note 23).

3. Summary of Significant Accounting Policies

Principles of Consolidation and Basis of Presentation

The accompanying consolidated financial statements reflect the accounts of the Company and all of its subsidiaries in which a controlling interest is maintained. All inter-company balances and transactions have been eliminated in consolidation. The consolidated financial statements have been prepared in conformity with generally accepted accounting principles in the U.S. ("U.S. GAAP").

Use of Estimates

The preparation of consolidated financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the consolidated financial statements and the reported amounts of revenues and expenses during the reporting period.

Foreign Currency Translation

The Company's presentation currency and functional currency is the U.S. dollar ("US$"). The financial statements of its subsidiaries with a functional currency other than the US$ have been translated into the Company's presentation currency. All assets and liabilities of the subsidiaries are translated using year-end exchange rates and revenues and expenses are translated at average exchange rates for the year. Translation adjustments are reflected in accumulated other comprehensive (loss)/income in shareholders' equity.

Net foreign currency exchange gains of US$1,671,000, US$3,265,000 and US$246,000 were recorded in other income in the consolidated statements of operations for the years ended December 31, 2021, 2020 and 2019 respectively.

Foreign Currency Risk

The Group's operating transactions and its assets and liabilities in the PRC are mainly denominated in Renminbi ("RMB"), which is not freely convertible into foreign currencies. The Group's cash and cash equivalents denominated in RMB are subject to government controls. The value of the RMB is subject to fluctuations from central government policy changes and international economic and political developments that affect the supply and demand of RMB in the foreign exchange market. In the PRC, certain foreign exchange transactions are required by law to be transacted only by authorized financial institutions at exchange rates set by the People's Bank of China (the "PBOC"). Remittances in currencies other than RMB by the Group in the PRC must be processed through the PBOC or other PRC foreign exchange regulatory bodies which require certain supporting documentation in order to complete the remittance.

Allowance for Current Expected Credit Losses and Concentration of Credit Risk

Financial instruments that potentially expose the Group to credit risk consist primarily of cash and cash equivalents, short-term investments, and financial assets not carried at fair value including accounts receivable and other receivables.

The Group recognizes an allowance for current expected credit losses on financial assets not carried at fair value. Current expected credit losses are calculated over the expected life of the financial assets on an individual or a portfolio basis considering information available about the counterparties' credit situation and collectability of the specific cash flows, including information about past events, current conditions and future forecasts.

The Group has no significant concentration of credit risk. The Group places substantially all of its cash and cash equivalents and short-term investments in major financial institutions, which management believes are of high credit quality. The Group has a practice to limit the amount of credit exposure to any particular financial institution. Additionally, the Group has policies in place to ensure that sales are made to customers with an appropriate credit history and the Group performs periodic credit evaluations of its customers. Normally the Group does not require collateral from trade debtors.

Cash and Cash Equivalents

The Group considers all highly liquid investments purchased with original maturities of three months or less to be cash equivalents. Cash and cash equivalents consist primarily of cash on hand and bank deposits and are stated at cost, which approximates fair value.

Short-term Investments

Short-term investments include deposits placed with banks with original maturities of more than three months but less than one year.

Accounts Receivable

Accounts receivable are stated at the amount management expects to collect from customers based on their outstanding invoices. The allowance for credit losses reflects the Group's current estimate of credit losses expected to be incurred over the life of the receivables. The Group considers various factors in establishing, monitoring, and adjusting its allowance for credit losses including the aging of the accounts and aging trends, the historical level of charge-offs, and specific exposures related to particular customers. The Group also monitors other risk factors and forward-looking information, such as country risk, when determining credit limits for customers and establishing adequate allowances for credit losses. Accounts receivable are written off after all reasonable means to collect the full amount (including litigation, where appropriate) have been exhausted.

Inventories

Inventories are stated at the lower of cost or net realizable value. Cost is determined using the weighted average cost method. The cost of finished goods comprises raw materials, direct labor, other direct costs and related production overheads (based on normal operating capacity). Net realizable value is the estimated selling price in the ordinary course of business, less applicable variable selling expenses. A provision for excess and obsolete inventory will be made based primarily on forecasts of product demand and production requirements. The excess balance determined by this analysis becomes the basis for excess inventory charge and the written-down value of the inventory becomes its cost. Written-down inventory is not written up if market conditions improve.

Property, Plant and Equipment

Property, plant and equipment consist of buildings, leasehold improvements, plant and equipment, furniture and fixtures, other equipment and motor vehicles. Property, plant and equipment are stated at cost, net of accumulated depreciation. Depreciation is computed using the straight-line method over the estimated useful lives of the depreciable assets.

Buildings	20 years
Plant and equipment	5-10 years
Furniture and fixtures, other equipment and motor vehicles	4-5 years
Leasehold improvements	Shorter of (a) 5 years or (b) remaining term of lease

Additions and improvements that extend the useful life of an asset are capitalized. Repairs and maintenance costs are expensed as incurred.

Impairment of Long-Lived Assets

The Group evaluates the recoverability of long-lived assets in accordance with authoritative guidance on accounting for the impairment or disposal of long-lived assets. The Group evaluates long-lived assets for impairment whenever events or changes in circumstances indicate that the carrying value of these assets may not be recoverable. If indicators of impairment exist, the first step of the impairment test is performed to assess if the carrying value of the net assets exceeds the undiscounted cash flows of the assets. If yes, the second step of the impairment test is performed in order to determine if the carrying value of the net assets exceeds the fair value. If yes, impairment is recognized for the excess.

Investments in Equity Investees

Investments in equity investees over which the Group has significant influence are accounted for using the equity method. The Group evaluates equity method investments for impairment when events or circumstances suggest that their carrying amounts may not be recoverable. An impairment charge would be recognized in earnings for a decline in value that is determined to be other-than-temporary after assessing the severity and duration of the impairment and the likelihood of recovery before disposal. The investments are recorded at fair value only if impairment is recognized.

Leasehold Land

Leasehold land represents fees paid to acquire the right to use the land on which various plants and buildings are situated for a specified period of time from the date the respective right was granted and are stated at cost less accumulated amortization and impairment loss, if any. Amortization is computed using the straight-line basis over the lease period of 50 years.

Goodwill

Goodwill represents the excess of the purchase price plus fair value of non-controlling interests over the fair value of identifiable assets and liabilities acquired. Goodwill is not amortized, but is tested for impairment at the reporting unit level on at least an annual basis or when an event occurs or circumstances change that would more likely than not reduce the fair value of a reporting unit below its carrying amount. When performing an evaluation of goodwill impairment, the Group has the option to first assess qualitative factors, such as significant events and changes to expectations and activities that may have occurred since the last impairment evaluation, to determine if it is more likely than not that goodwill might be impaired. If as a result of the qualitative assessment, that it is more likely than not that the fair value of the reporting unit is less than its carrying amount, the quantitative fair value test is performed to determine if the fair value of the reporting unit exceeds its carrying value.

Other Intangible Assets

Other intangible assets with finite useful lives are carried at cost less accumulated amortization and impairment loss, if any. Amortization is computed using the straight-line basis over the estimated useful lives of the assets.

Borrowings

Borrowings are recognized initially at fair value, net of debt issuance costs incurred. Borrowings are subsequently stated at amortized cost; any difference between the proceeds (net of debt issuance costs) and the redemption value is recognized in the consolidated statements of operations over the period of the borrowings using the effective interest method.

Ordinary Shares

The Company's ordinary shares are stated at par value of US$0.10 per ordinary share. The difference between the consideration received, net of issuance cost, and the par value is recorded in additional paid-in capital.

Treasury Shares

The Group accounts for treasury shares under the cost method. The treasury shares are purchased for the purpose of the LTIP and held by a trustee appointed by the Group (the "Trustee") prior to vesting.

Share-Based Compensation

Share options

The Group recognizes share-based compensation expense on share options granted to employees and directors based on their estimated grant date fair value using the Polynomial model. This Polynomial pricing model uses various inputs to measure fair value, including the market value of the Company's underlying ordinary shares at the grant date, contractual terms, estimated volatility, risk-free interest rates and expected dividend yields. The Group recognizes share-based compensation expense in the consolidated statements of operations on a graded vesting basis over the requisite service period, and accounts for forfeitures as they occur.

Share options are classified as equity-settled awards. Share-based compensation expense, when recognized, is charged to the consolidated statements of operations with the corresponding entry to additional paid-in capital.

LTIP

The Group recognizes the share-based compensation expense on the LTIP awards based on a fixed or determinable monetary amount on a straight-line basis for each annual tranche awarded over the requisite period. For LTIP awards with performance targets, prior to their determination date, the amount of LTIP awards that is expected to vest takes into consideration the achievement of the performance conditions and the extent to which the performance conditions are likely to be met. Performance conditions vary by awards, and may include targets for shareholder returns, financings, free cash flows, revenues, net profit after taxes and the achievement of clinical and regulatory milestones.

These LTIP awards are classified as liability-settled awards before the determination date (i.e. the date when the achievement of any performance conditions are known), as they settle in a variable number of shares based on a determinable monetary amount, which is determined upon the actual achievement of performance targets. As the extent of achievement of the performance targets is uncertain prior to the determination date, a probability based on management's assessment of the achievement of the performance targets has been assigned to calculate the amount to be recognized as an expense over the requisite period.

After the determination date or if the LTIP awards have no performance conditions, the LTIP awards are classified as equity-settled awards. If the performance target is achieved, the Group will pay the determined monetary amount to the Trustee to purchase ordinary shares of the Company or the equivalent ADS. Any cumulative compensation expense previously recognized as a liability will be transferred to additional paid-in capital, as an equity-settled award. If the performance target is not achieved, no ordinary shares or ADS of the Company will be purchased and the amount previously recorded in the liability will be reversed and included in the consolidated statements of operations.

Defined Contribution Plans

The Group's subsidiaries in the PRC participate in a government-mandated multi-employer defined contribution plan pursuant to which certain retirement, medical and other welfare benefits are provided to employees. The relevant labor regulations require the Group's subsidiaries in the PRC to pay the local labor and social welfare authority's monthly contributions at a stated contribution rate based on the monthly basic compensation of qualified employees. The relevant local labor and social welfare authorities are responsible for meeting all retirement benefits obligations and the Group's subsidiaries in the PRC have no further commitments beyond their monthly contributions. The contributions to the plan are expensed as incurred.

The Group also makes payments to other defined contribution plans for the benefit of employees employed by subsidiaries outside the PRC. The defined contribution plans are generally funded by the relevant companies and by payments from employees.

The Group's contributions to defined contribution plans for the years ended December 31, 2021, 2020 and 2019 amounted to US$7,181,000, US$2,660,000 and US$3,479,000 respectively.

Revenue Recognition

Revenue is measured based on consideration specified in a contract with a customer, and excludes any sales incentives and amounts collected on behalf of third parties. Taxes assessed by a governmental authority that are both imposed on and concurrent with a specific revenue-producing transaction, that are collected by the Group from a customer, are also excluded from revenue. The Group recognizes revenue when it satisfies a performance obligation by transferring control over a good, service or license to a customer.

(i) Goods and services

The Group principally generates revenue from (1) sales of goods, which are the manufacture or purchase and distribution of pharmaceutical products and other consumer health products, and (2) provision of services, which are the provision of sales, distribution and marketing services to pharmaceutical manufacturers. The Group evaluates whether it is the principal or agent for these contracts. Where the Group obtains control of the goods for distribution, it is the principal (i.e. recognizes sales of goods on a gross basis). Where the Group does not obtain control of the goods for distribution, it is the agent (i.e. recognizes provision of services on a net basis). Control is primarily evidenced by taking physical possession and inventory risk of the goods.

Revenue from sales of goods is recognized when the customer takes possession of the goods. This usually occurs upon completed delivery of the goods to the customer site. The amount of revenue recognized is adjusted for expected sales incentives as stipulated in the contract, which are generally issued to customers as direct discounts at the point-of-sale or indirectly in the form of rebates. Sales incentives are estimated using the expected value method. Additionally, sales are generally made with a limited right of return under certain conditions. Revenues are recorded net of provisions for sales discounts and returns.

Revenue from provision of services is recognized when the benefits of the services transfer to the customer over time, which is based on the proportionate value of services rendered as determined under the terms of the relevant contract. Additionally, when the amounts that can be invoiced correspond directly with the value to the customer for performance completed to date, the Group recognizes revenue from provision of services based on amounts that can be invoiced to the customer.

Deferred revenue is recognized if consideration is received in advance of transferring control of the goods or rendering of services. Accounts receivable is recognized if the Group has an unconditional right to bill the customer, which is generally when the customer takes possession of the goods or services are rendered. Payment terms differ by subsidiary and customer, but generally range from 45 to 180 days from the invoice date.

(ii) License and collaboration contracts

The Group's Oncology/Immunology reportable segment includes revenue generated from license and collaboration contracts, which generally contain multiple performance obligations including (1) the license to the commercialization rights of a drug compound and (2) the research and development services for each specified treatment indication, which are accounted for separately if they are distinct, i.e. if a product or service is separately identifiable from other items in the arrangement and if a customer can benefit from it on its own or with other resources that are readily available to the customer.

The transaction price generally includes fixed and variable consideration in the form of upfront payment, research and development cost reimbursements, contingent milestone payments and sales-based royalties. Contingent milestone payments are not included in the transaction price until it becomes probable that a significant reversal of revenue will not occur, which is generally when the specified milestone is achieved. The allocation of the transaction price to each performance obligation is based on the relative standalone selling prices of each performance obligation determined at the inception of the contract. The Group estimates the standalone selling prices based on the income approach. Control of the license to the drug compounds transfers at the inception date of the collaboration agreements and consequently, amounts allocated to this performance obligation are generally recognized at a point in time. Conversely, research and development services for each specified indication are performed over time and amounts allocated to these performance obligations are generally recognized over time using cost inputs as a measure of progress. The Group has determined that research and development expenses provide an appropriate depiction of measure of progress for the research and development services. Changes to estimated cost inputs may result in a cumulative catch-up adjustment. Royalty revenues are recognized as future sales occur as they meet the requirements for the sales-usage based royalty exception.

Deferred revenue is recognized if allocated consideration is received in advance of the Group rendering research and development services or earning royalties on future sales. Accounts receivable is recognized based on the terms of the contract and when the Group has an unconditional right to bill the customer, which is generally when research and development services are rendered.

Research and Development Expenses

Research and development expenses include the following: (i) research and development costs, which are expensed as incurred; (ii) acquired in-process research and development ("IPR&D") expenses, which include the initial costs of externally developed IPR&D projects, acquired directly in a transaction other than a business combination, that do not have an alternative future use; and (iii) milestone payment obligations for externally developed IPR&D projects incurred prior to regulatory approval of the product in the in-licensed territory, which are accrued when the event requiring payment of the milestone occurs (milestone payment obligations incurred upon regulatory approval are recorded as other intangible assets).

Collaborative Arrangements

The Group enters into collaborative arrangements with collaboration partners that fall under the scope of Accounting Standards Codification ("ASC") 808, Collaborative Arrangements ("ASC 808"). The Group records all expenditures for such collaborative arrangements in research and development expenses as incurred, including payments to third party vendors and reimbursements to collaboration partners, if any. Reimbursements from collaboration partners are recorded as reductions to research and development expenses and accrued when they can be contractually claimed.

Government Grants

Grants from governments are recognized at their fair values. Government grants that are received in advance are deferred and recognized in the consolidated statements of operations over the period necessary to match them with the costs that they are intended to compensate. Government grants in relation to the achievement of stages of research and development projects are recognized in the consolidated statements of operations when amounts have been received and all attached conditions have been met. Non-refundable grants received without any further obligations or conditions attached are recognized immediately in the consolidated statements of operations.

Leases

In an operating lease, a lessee obtains control of only the use of the underlying asset, but not the underlying asset itself. An operating lease is recognized as a right-of-use asset with a corresponding liability at the date which the leased asset is available for use by the Group. The Group recognizes an obligation to make lease payments equal to the present value of the lease payments over the lease term. The lease terms may include options to extend or terminate the lease when it is reasonably certain that the Group will exercise that option.

Lease liabilities include the net present value of the following lease payments: (i) fixed payments; (ii) variable lease payments that depend on an index or a rate; and (iii) payments of penalties for terminating the lease if the lease term reflects the lessee exercising that option, if any. Lease liabilities exclude the following payments that are generally accounted for separately: (i) non-lease components, such as maintenance and security service fees and value added tax, and (ii) any payments that a lessee makes before the lease commencement date. The lease payments are discounted using the interest rate implicit in the lease or if that rate cannot be determined, the lessee's incremental borrowing rate being the rate that the lessee would have to pay to borrow the funds in its currency and jurisdiction necessary to obtain an asset of similar value, economic environment and terms and conditions.

An asset representing the right to use the underlying asset during the lease term is recognized that consists of the initial measurement of the operating lease liability, any lease payments made to the lessor at or before the commencement date less any lease incentives received, any initial direct cost incurred by the Group and any restoration costs.

After commencement of the operating lease, the Group recognizes lease expenses on a straight-line basis over the lease term. The right-of-use asset is subsequently measured at cost less accumulated amortization and any impairment provision. The amortization of the right-of-use asset represents the difference between the straight-line lease expense and the accretion of interest on the lease liability each period. The interest amount is used to accrete the lease liability and to amortize the right-of-use asset. There is no amount recorded as interest expense.

Payments associated with short-term leases are recognized as lease expenses on a straight-line basis over the period of the leases.

Subleases of right-of-use assets are accounted for similar to other leases. As an intermediate lessor, the Group separately accounts for the head-lease and sublease unless it is relieved of its primary obligation under the head-lease. Sublease income is recorded on a gross basis separate from the head-lease expenses. If the total remaining lease cost on the head-lease is more than the anticipated sublease income for the lease term, this is an indicator that the carrying amount of the right-of-use asset associated with the head-lease may not be recoverable, and the right-of-use asset will be assessed for impairment.

Income Taxes

The Group accounts for income taxes under the liability method. Under the liability method, deferred income tax assets and liabilities are determined based on the differences between the financial reporting and income tax bases of assets and liabilities and are measured using the income tax rates that will be in effect when the differences are expected to reverse. A valuation allowance is recorded when it is more likely than not that some of the net deferred income tax asset will not be realized.

The Group accounts for an uncertain tax position in the consolidated financial statements only if it is more likely than not that the position is sustainable based on its technical merits and consideration of the relevant tax authority's widely understood administrative practices and precedents. If the recognition threshold is met, the Group records the largest amount of tax benefit that is greater than 50 percent likely to be realized upon ultimate settlement.

The Group recognizes interest and penalties for income taxes, if any, under income tax payable on its consolidated balance sheets and under other expenses in its consolidated statements of operations.

Losses per Share

Basic losses per share is computed by dividing net loss attributable to the Company by the weighted average number of outstanding ordinary shares in issue during the year. Weighted average number of outstanding ordinary shares in issue excludes treasury shares.

Diluted losses per share is computed by dividing net loss attributable to the Company by the weighted average number of outstanding ordinary shares in issue and dilutive ordinary share equivalents outstanding during the year. Dilutive ordinary share equivalents include ordinary shares and treasury shares issuable upon the exercise or settlement of share-based awards or warrants issued by the Company using the treasury stock method. The computation of diluted losses per share does not assume conversion, exercise, or contingent issuance of securities that would have an anti-dilutive effect.

Segment Reporting

Operating segments are reported in a manner consistent with the internal reporting provided to the chief executive officer who is the Group's chief operating decision maker. The chief operating decision maker reviews the Group's internal reporting in order to assess performance and allocate resources.

Profit Appropriation and Statutory Reserves

The Group's subsidiaries and equity investees established in the PRC are required to make appropriations to certain non-distributable reserve funds.

In accordance with the relevant laws and regulations established in the PRC, the Company's subsidiaries registered as wholly-owned foreign enterprise have to make appropriations from their after-tax profits (as determined under generally accepted accounting principles in the PRC ("PRC GAAP")) to reserve funds including general reserve fund, enterprise expansion fund and staff bonus and welfare fund. The appropriation to the general reserve fund must be at least 10% of the after-tax profits calculated in accordance with PRC GAAP. Appropriation is not required if the general reserve fund has reached 50% of the registered capital of the company. Appropriations to the enterprise expansion fund and staff bonus and welfare fund are made at the respective company's discretion. For the Group's equity investees, the amount of appropriations to these funds are made at the discretion of their respective boards.

In addition, Chinese domestic companies must make appropriations from their after-tax profits as determined under PRC GAAP to non-distributable reserve funds including statutory surplus fund and discretionary surplus fund. The appropriation to the statutory surplus fund must be 10% of the after-tax profits as determined under PRC GAAP. Appropriation is not required if the statutory surplus fund has reached 50% of the registered capital of the company. Appropriation to the discretionary surplus fund is made at the respective company's discretion.

The use of the general reserve fund, enterprise expansion fund, statutory surplus fund and discretionary surplus fund is restricted to the offsetting of losses or increases to the registered capital of the respective company. The staff bonus and welfare fund is a liability in nature and is restricted to fund payments of special bonus to employees and for the collective welfare of employees. All these reserves are not permitted to be transferred to the company as cash dividends, loans or advances, nor can they be distributed except under liquidation.

4. Fair Value Disclosures

The following table presents the Group's financial instruments by level within the fair value hierarchy under ASC 820, Fair Value Measurement:

	Fair Value Measurement Using			
	Level 1	Level 2	Level 3	Total
	(in US$'000)			
As at December 31, 2021				
Cash and cash equivalents	377,542	—	—	377,542
Short-term investments	634,158	—	—	634,158
Warrant (Note 20)	—	2,452	—	2,452
As at December 31, 2020				
Cash and cash equivalents	235,630	—	—	235,630
Short-term investments	199,546	—	—	199,546

Accounts receivable, other receivables, accounts payable and other payables are carried at cost, which approximates fair value due to the short-term nature of these financial instruments, and are therefore excluded from the above table. Bank borrowings are floating rate instruments and carried at amortized cost, which approximates their fair values, and are therefore excluded from the above table.

5. Cash and Cash Equivalents and Short-term Investments

	December 31,	
	2021	2020
	(in US$'000)	
Cash and Cash Equivalents		
Cash at bank and on hand	104,620	87,828
Bank deposits maturing in three months or less	272,922	147,802
	377,542	235,630
Short-term Investments		
Bank deposits maturing over three months (note)	634,158	199,546
	1,011,700	435,176

Note: The maturities for short-term investment ranged from 91 to 180 days for the year ended December 31, 2021 and 2020.

Certain cash and bank balances denominated in RMB, US$ and UK Pound Sterling ("£") were deposited with banks in the PRC. The conversion of these balances into foreign currencies is subject to the rules and regulations of foreign exchange control promulgated by the PRC government. Cash and cash equivalents and short-term investments were denominated in the following currencies:

	December 31,	
	2021	2020
	(in US$'000)	
US$	895,935	352,162
RMB	53,455	64,870
Hong Kong dollar ("HK$")	60,535	16,880
£	1,090	954
Euro	685	310
	1,011,700	435,176

6. Accounts Receivable

Accounts receivable from contracts with customers consisted of the following:

	December 31,	
	2021	2020
	(in US$'000)	
Accounts receivable—third parties	82,434	46,743
Accounts receivable—related parties (Note 24(ii))	1,166	1,222
Allowance for credit losses	(20)	(95)
Accounts receivable, net	83,580	47,870

Substantially all accounts receivable are denominated in RMB, US$ and HK$ and are due within one year from the end of the reporting periods. The carrying values of accounts receivable approximate their fair values due to their short-term maturities.

An aging analysis for accounts receivable—third parties based on the relevant invoice dates is as follows:

	December 31,	
	2021	2020
	(in US$'000)	
Not later than 3 months	78,288	42,434
Between 3 months to 6 months	2,867	3,118
Between 6 months to 1 year	78	23
Later than 1 year	1,201	1,168
Account receivable—third parties	82,434	46,743

Movements on the allowance for credit losses:

	2021	2020	2019
		(in US$'000)	
As at January 1	95	16	41
Increase in allowance for credit losses	16	95	16
Decrease in allowance due to subsequent collection	(92)	(18)	(41)
Exchange difference	1	2	—
As at December 31	20	95	16

7. Other receivables, prepayments and deposits

Other receivables, prepayments and deposits consisted of the following:

	December 31,	
	2021	2020
	(in US$'000)	
Dividend receivables (Note 23)	46,387	—
Value-added tax receivables	16,616	14,957
Prepayments	14,128	7,038
Deposits	1,255	905
Amounts due from related parties (Note 24(ii))	1,149	1,142
Leasehold land deposit (Note 12)	—	930
Others	1,506	2,956
	81,041	27,928

No allowance for credit losses have been made for other receivables, prepayments and deposits for the years ended December 31, 2021 and 2020.

8. Inventories

Inventories, net of provision for excess and obsolete inventories, consisted of the following:

	December 31,	
	2021	2020
	(in US$'000)	
Raw materials	15,837	4,502
Finished goods	19,918	15,264
	35,755	19,766

9. Property, Plant and Equipment

Property, plant and equipment consisted of the following:

	Buildings	Leasehold improvements	Plant and equipment	Furniture and fixtures, other equipment and motor vehicles	Construction in progress	Total
			(in US$'000)			
Cost						
As at January 1, 2021	2,372	16,346	5,643	23,040	3,050	50,451
Additions	—	452	24	3,189	19,669	23,334
Disposals	—	(275)	(19)	(705)	—	(999)
Transfers	—	916	197	1,849	(2,962)	—
Exchange differences	60	389	142	584	213	1,388
As at December 31, 2021	2,432	17,828	5,987	27,957	19,970	74,174
Accumulated depreciation						
As at January 1, 2021	1,626	8,652	1,747	14,256	—	26,281
Depreciation	120	2,904	574	3,244	—	6,842
Disposals	—	(223)	(18)	(688)	—	(929)
Exchange differences	42	238	49	376	—	705
As at December 31, 2021	1,788	11,571	2,352	17,188	—	32,899
Net book value						
As at December 31, 2021	644	6,257	3,635	10,769	19,970	41,275

	Buildings	Leasehold improvements	Plant and equipment	Furniture and fixtures, other equipment and motor vehicles	Construction in progress	Total
			(in US$'000)			
Cost						
As at January 1, 2020	2,212	17,022	4,474	19,571	928	44,207
Additions	—	269	59	2,993	4,571	7,892
Disposals	—	(3,103)	(3)	(1,846)	—	(4,952)
Transfers	—	1,014	789	913	(2,716)	—
Exchange differences	160	1,144	324	1,409	267	3,304
As at December 31, 2020	2,372	16,346	5,643	23,040	3,050	50,451
Accumulated depreciation						
As at January 1, 2020	1,406	8,304	1,155	12,487	—	23,352
Depreciation	112	2,701	484	2,646	—	5,943
Disposals	—	(3,051)	(1)	(1,815)	—	(4,867)
Exchange differences	108	698	109	938	—	1,853
As at December 31, 2020	1,626	8,652	1,747	14,256	—	26,281
Net book value						
As at December 31, 2020	746	7,694	3,896	8,784	3,050	24,170

10. Leases

Leases consisted of the following:

	December 31,	
	2021	2020
	(in US$'000)	
Right-of-use assets		
Offices (note)	10,605	6,789
Factories	702	945
Warehouse	281	197
Others	291	85
Total right-of-use assets	11,879	8,016
Lease liabilities—current	4,917	2,785
Lease liabilities—non-current	7,161	6,064
Total lease liabilities	12,078	8,849

Note: Includes US$1.4 million right-of-use asset for corporate offices in Hong Kong that is leased through May 2024 in which the contract has a termination option with 1-month advance notice. The termination option was not recognized as part of the right-of-use asset and lease liability as it is uncertain that the Group will exercise such option.

Lease activities are summarized as follows:

	Year Ended December 31,	
	2021	2020
	(in US$'000)	
Lease expenses:		
Short-term leases with lease terms equal or less than 12 months	106	323
Leases with lease terms greater than 12 months	4,306	3,400
	4,412	3,723
Cash paid on lease liabilities	4,954	3,340
Non-cash: Lease liabilities recognized from obtaining right-of-use assets	7,665	3,098
Non-cash: Lease liabilities changed in relation to modifications and terminations	(33)	2,259

Lease contracts are typically within a period of 1 to 8 years. The weighted average remaining lease term and the weighted average discount rate as at December 31, 2021 was 3.38 years and 3.33% respectively. The weighted average remaining lease term and the weighted average discount rate as at December 31, 2020 was 3.72 years and 3.87% respectively.

Future lease payments are as follows:

	December 31, 2021
	(in US$'000)
Lease payments:	
Not later than 1 year	5,216
Between 1 to 2 years	3,376
Between 2 to 3 years	1,882
Between 3 to 4 years	679
Between 4 to 5 years	680
Later than 5 years	795
Total lease payments	12,628
Less: Discount factor	(550)
Total lease liabilities	12,078

11. Investments in Equity Investees

Investments in equity investees consisted of the following:

	December 31,	
	2021	2020
	(in US$'000)	
SHPL	75,999	79,408
HBYS (note)	—	59,712
Other	480	385
	76,479	139,505

Note: On September 28, 2021, the Group completed a transaction to sell its entire investment in HBYS to a third party (Note 23). The Group has accounted for the investment in HBYS under the equity method up to September 28, 2021.

The equity investees are private companies and there are no quoted market prices available for their shares.

Summarized financial information for the significant equity investees SHPL and HBYS, both under Other Ventures segment, is as follows:

(i) Summarized balance sheets

	SHPL		HBYS	
	December 31,			
	2021	2020	2021	2020
	(in US$'000)			
Current assets	190,260	175,965	—	177,888
Non-current assets	91,605	93,361	—	95,731
Current liabilities	(128,993)	(109,873)	—	(137,179)
Non-current liabilities	(7,131)	(6,739)	—	(16,034)
Net assets	145,741	152,714	—	120,406
Non-controlling interests	—	—	—	(982)
	145,741	152,714	—	119,424

(ii) Summarized statements of operations

	SHPL			HBYS[note (a)]		
	Year Ended December 31,					
	2021	2020	2019	2021[note (b)]	2020	2019
	(in US$'000)					
Revenue	332,648	276,354	272,082	209,528	232,368	215,403
Gross profit	255,089	204,191	194,769	111,066	116,804	115,124
Interest income	1,216	975	582	205	271	160
Finance cost	—	—	—	—	(5)	(16)
Profit before taxation	105,325	77,837	72,324	36,715	107,715	22,926
Income tax expense (note (c))	(15,896)	(10,833)	(11,015)	(4,840)	(16,494)	(3,634)
Net income	89,429	67,004	61,309	31,875	91,221	19,292
Non-controlling interests	—	—	—	(36)	62	505
Net income attributable to the shareholders of equity investee	89,429	67,004	61,309	31,839	91,283	19,797

Notes:

(a) In June 2020, HBYS entered into an agreement with the government to return the land use right for a plot of land in Guangzhou to the government (the "Land Compensation Agreement") for cash consideration which aggregated to RMB679.5 million (approximately US$103.1 million). In November 2020, HBYS completed all material obligations as stipulated in the Land Compensation Agreement and recognized land compensation of RMB569.2 million (approximately US$86.1 million). In June 2021, HBYS received a completion confirmation from the government and became entitled to an additional land compensation bonus of RMB110.3 million (approximately US$17.0 million). HBYS recorded a gain before tax of RMB106.8 million (approximately US$16.4 million) after deducting costs of RMB3.5 million (approximately US$0.6 million).

(b) The summarized statement of operations for HBYS for the year ended December 31, 2021 includes the period when HBYS was the Group's equity investee from January 1, 2021 to September 28, 2021, the completion date of the divestment.

(c) The main entities within each of the SHPL and HBYS groups have been granted the High and New Technology Enterprise ("HNTE") status (the latest renewal of this status covers the years from 2020 to 2022). These entities were eligible to use a preferential income tax rate of 15% for the year ended December 31, 2021 on this basis.

For the years ended December 31, 2021, 2020 and 2019, other equity investees had net income of approximately US$41,000, net losses of approximately US$194,000 and net income of approximately US$294,000 respectively.

(iii) Reconciliation of summarized financial information

Reconciliation of the summarized financial information presented to the carrying amount of investments in equity investees is as follows:

	SHPL			HBYS		
	2021	2020	2019	2021	2020	2019
	(in US$'000)					
Opening net assets after non-controlling interests as at January 1	152,714	146,759	131,778	119,424	44,541	121,984
Impact of change in accounting policy (ASC 842-Leases)	—	—	(2)	—	—	(19)
Net income attributable to the shareholders of equity investee	89,429	67,004	61,309	31,839	91,283	19,797
Purchase of additional interests in a subsidiary of an equity investee (note)	—	—	—	—	(347)	—
Dividends declared	(99,744)	(72,179)	(41,654)	(106,159)	(20,756)	(93,957)
Other comprehensive income/(loss)	3,342	11,130	(4,672)	1,387	4,703	(3,264)
Closing net assets after non-controlling interests as at December 31	145,741	152,714	146,759	46,491	119,424	44,541
Group's share of net assets	72,871	76,357	73,380	23,246	59,712	22,271
Divestment (Note 23)	—	—	—	(23,246)	—	—
Goodwill	3,128	3,051	2,846	—	—	—
Carrying amount of investments as at December 31	75,999	79,408	76,226	—	59,712	22,271

Note: During the year ended December 31, 2020, HBYS acquired an additional 30% interest in a subsidiary and after the acquisition, it became a wholly owned subsidiary of HBYS.

SHPL had the following capital commitments:

	December 31, 2021
	(in US$'000)
Property, plant and equipment	
Contracted but not provided for	155

12. Other Non-Current Assets

	December 31,	
	2021	2020
	(in US$'000)	
Leasehold land (note)	13,169	13,121
Goodwill	3,380	3,307
Warrant (Note 20)	2,452	—
Leasehold land deposit (note)	1,436	1,396
Long term prepayment	951	950
Other intangible asset	163	227
Deferred issuance cost	—	1,171
	21,551	20,172

Note: In December 2020, HUTCHMED Limited acquired a land use right in Shanghai for consideration of US$12.0 million. In addition, a leasehold land deposit amounting to US$2.3 million was required to be paid to the government which is refundable upon reaching specific milestones for the construction of a manufacturing plant on the land. US$0.9 million was returned in January 2021 (Note 7) and US$1.4 million was included in other non-current assets based on the expected timing of the specific milestones.

13. Accounts Payable

	December 31,	
	2021	2020
	(in US$'000)	
Accounts payable—third parties	39,115	26,756
Accounts payable—non-controlling shareholders of subsidiaries (Note 24(iv))	2,062	4,856
	41,177	31,612

Substantially all accounts payable are denominated in RMB and US$ and due within one year from the end of the reporting period. The carrying values of accounts payable approximate their fair values due to their short-term maturities.

An aging analysis based on the relevant invoice dates is as follows:

	December 31,	
	2021	2020
	(in US$'000)	
Not later than 3 months	35,615	26,270
Between 3 months to 6 months	3,705	3,364
Between 6 months to 1 year	588	782
Later than 1 year	1,269	1,196
	41,177	31,612

14. Other Payables, Accruals and Advance Receipts

Other payables, accruals and advance receipts consisted of the following:

	December 31,	
	2021	2020
	(in US$'000)	
Accrued research and development expenses	116,134	72,697
Accrued salaries and benefits	41,786	21,982
Accrued administrative and other general expenses	15,836	10,319
Accrued capital expenditures	11,343	2,736
Accrued selling and marketing expenses	8,412	5,747
Deposits	2,111	1,408
Amounts due to related parties (Note 24(ii))	1,915	401
Deferred government grants	314	374
Others	12,988	5,619
	210,839	121,283

15. Bank Borrowings

Bank borrowings consisted of the following:

	December 31,	
	2021	2020
	(in US$'000)	
Current	26,905	—
Non-current	—	26,861

The weighted average interest rate for outstanding bank borrowings for the years ended December 31, 2021 and 2020 was 1.08% per annum and 1.89% per annum respectively. The carrying amounts of the Group's outstanding bank borrowings were denominated in HK$.

(i) 3-year revolving loan facility and 3-year term loan and revolving loan facilities

In November 2018, the Group through its subsidiary, renewed a 3-year revolving loan facility with a bank in the amount of HK$234,000,000 (US$30,000,000) with an interest rate at the Hong Kong Interbank Offered Rate ("HIBOR") plus 0.85% per annum. This credit facility is guaranteed by the Company. No amount had been drawn from the revolving loan facility and it expired in November 2021.

In May 2019, the Group through its subsidiary, entered into a separate facility agreement with the bank for the provision of additional unsecured credit facilities in the aggregate amount of HK$400,000,000 (US$51,282,000). The 3-year credit facilities include (i) a HK$210,000,000 (US$26,923,000) term loan facility and (ii) a HK$190,000,000 (US$24,359,000) revolving loan facility, both with an interest rate at HIBOR plus 0.85% per annum, and an upfront fee of HK$819,000 (US$105,000) on the term loan. These credit facilities are guaranteed by the Company. The term loan was drawn in October 2019 and is due in May 2022. No amount has been drawn from the revolving loan facility.

(ii) 2-year revolving loan facilities

In August 2018, the Group through its subsidiary, entered into two separate facility agreements with banks for the provision of unsecured credit facilities in the aggregate amount of HK$507,000,000 (US$65,000,000). The first credit facility was a HK$351,000,000 (US$45,000,000) revolving loan facility, with a term of 2 years and an interest rate at HIBOR plus 1.35% per annum. The second credit facility was a HK$156,000,000 (US$20,000,000) revolving loan facility, with a term of 2 years and an interest rate at HIBOR plus 1.35% per annum. These credit facilities were guaranteed by the Company. No amount has been drawn from either of the revolving loan facilities. Both loan facilities expired in August 2020.

In August 2020, the Group through its subsidiary, entered into a 2-year revolving loan facility with a bank in the amount of HK$117,000,000 (US$15,000,000) with an interest rate at HIBOR plus 4.5% per annum. This credit facility is guaranteed by the Company. As at December 31, 2021 and 2020, no amount has been drawn from the revolving loan facility.

(iii) 10-year fixed asset loan facility

In October 2021, a subsidiary entered into a 10-year fixed asset loan facility agreement with a bank for the provision of a secured credit facility in the amount of RMB754,880,000 (US$118,071,000) with an annual interest rate at the 5-year China Loan Prime Rate less 0.65%. This credit facility is guaranteed by the immediate holding company of the subsidiary and secured by the underlying leasehold land and buildings. As at December 31, 2021, no amount has been drawn from the fixed asset loan facility.

The Group's bank borrowings are repayable as from the dates indicated as follows:

	December 31,	
	2021	2020
	(in US$'000)	
Not later than 1 year	26,923	—
Between 1 to 2 years	—	26,923
	26,923	26,923

As at December 31, 2021 and 2020, the Group had unutilized bank borrowing facilities of US$157,430,000 and US$69,359,000 respectively.

16. Commitments and Contingencies

The Group had the following capital commitments:

	December 31, 2021
	(in US$'000)
Property, plant and equipment	
Contracted but not provided for	44,204

The Group does not have any other significant commitments or contingencies.

17. Ordinary Shares

As at December 31, 2021, the Company is authorized to issue 1,500,000,000 ordinary shares.

On January 27, 2020, the Company issued 22,000,000 ordinary shares in the form of 4,400,000 ADS for gross proceeds of US$110.0 million. On February 10, 2020, the Company issued an additional 1,668,315 ordinary shares in the form of 333,663 ADS for gross proceeds of US$8.3 million. Issuance costs totaled US$8.0 million.

On July 2, 2020 and July 3, 2020, the Company issued (1) aggregate 20,000,000 ordinary shares and (2) warrants to a third party for gross proceeds of US$100.0 million through a PIPE. The warrants allowed the third party to purchase up to 16,666,670 ordinary shares of the Company within 18 months of the issuance date for an exercise price of US$6.00 per ordinary share, which have since expired. Issuance costs totaled US$0.2 million.

On November 26, 2020, the Company issued 16,666,670 ordinary shares to a third party for gross proceeds of US$100.0 million through a PIPE. Issuance costs totaled US$0.1 million.

On April 14, 2021, the Company issued 16,393,445 ordinary shares to a third party for gross proceeds of US$100.0 million through a PIPE. Issuance costs totaled US$0.1 million.

On June 30, 2021 and July 15, 2021, the Company issued an aggregate of 119,600,000 ordinary shares in a public offering on the HKEX with over-allotment option exercised in full for aggregate gross proceeds of US$614.9 million. Issuance costs totaled US$29.7 million.

Each ordinary share is entitled to one vote. The holders of ordinary shares are also entitled to receive dividends whenever funds are legally available and when declared by the Board of Directors of the Company.

18. Share-based Compensation

(i) Share-based Compensation of the Company

The Company conditionally adopted a share option scheme on June 4, 2005 (as amended on March 21, 2007) and such scheme has a term of 10 years. It expired in 2016 and no further share options can be granted. Another share option scheme was conditionally adopted on April 24, 2015 (the "Hutchmed Share Option Scheme"). Pursuant to the Hutchmed Share Option Scheme, the Board of Directors of the Company may, at its discretion, offer any employees and directors (including Executive and Non-executive Directors but excluding Independent Non-executive Directors) of the Company, holding companies of the Company and any of their subsidiaries or affiliates, and subsidiaries or affiliates of the Company share options to subscribe for shares of the Company.

As at December 31, 2021, the aggregate number of shares issuable under the Hutchmed Share Option Scheme was 50,059,198 ordinary shares and the aggregate number of shares issuable under the prior share option scheme which expired in 2016 was 705,060 ordinary shares. The Company will issue new shares to satisfy share option exercises. Additionally, the number of shares authorized but unissued was 635,469,150 ordinary shares.

Share options granted are generally subject to a four-year vesting schedule, depending on the nature and the purpose of the grant. Share options subject to the four-year vesting schedule, in general, vest 25% upon the first anniversary of the vesting commencement date as defined in the grant letter, and 25% every subsequent year. However, certain share option grants may have a different vesting schedule as approved by the Board of Directors of the Company. No outstanding share options will be exercisable or subject to vesting after the expiry of a maximum of eight to ten years from the date of grant.

A summary of the Company's share option activity and related information is as follows:

	Number of share options	Weighted average exercise price in US$ per share	Weighted average remaining contractual life (years)	Aggregate intrinsic value (in US$'000)
Outstanding at January 1, 2019	18,554,850	4.57	7.35	19,277
Granted	2,315,000	4.12		
Exercised	(329,000)	0.76		
Cancelled	(1,012,110)	6.33		
Expired	(96,180)	6.51		
Outstanding at December 31, 2019	19,432,560	4.48	6.67	24,316
Granted	15,437,080	4.66		
Exercised	(480,780)	1.23		
Cancelled	(4,486,200)	5.02		
Expired	(741,670)	6.46		
Outstanding at December 31, 2020	29,160,990	4.49	7.21	53,990
Granted	10,174,840	5.96		
Exercised	(815,190)	3.01		
Cancelled	(1,287,650)	5.50		
Expired	(42,400)	5.52		
Outstanding at December 31, 2021	37,190,590	4.88	7.04	82,377
Vested and exercisable at December 31, 2020	11,529,280	3.74	4.57	29,433
Vested and exercisable at December 31, 2021	16,077,770	4.24	4.91	46,491

In estimating the fair value of share options granted, the following assumptions were used in the Polynomial model for awards granted in the periods indicated:

	Year Ended December 31,		
	2021	2020	2019
Weighted average grant date fair value of share options (in US$ per share)	2.24	1.76	1.33
Significant inputs into the valuation model (weighted average):			
Exercise price (in US$ per share)	5.96	4.66	4.12
Share price at effective date of grant (in US$ per share)	5.91	4.66	3.98
Expected volatility (note (a))	41.1 %	42.6 %	38.4 %
Risk-free interest rate (note (b))	1.62 %	0.59 %	0.56 %
Contractual life of share options (in years)	10	10	10
Expected dividend yield (note (c))	0 %	0 %	0 %

Notes:

(a) The Company calculated its expected volatility with reference to the historical volatility prior to the issuances of share options.

(b) For share options exercisable into ordinary shares, the risk-free interest rates reference the sovereign yield of the United Kingdom because the Company's ordinary shares are currently listed on AIM and denominated in £. For share options exercisable into ADS, the risk-free interest rates reference the U.S. Treasury yield curves because the Company's ADS are currently listed on the NASDAQ and denominated in US$.

(c) The Company has not declared or paid any dividends and does not currently expect to do so prior to the exercise of the granted share options, and therefore uses an expected dividend yield of zero in the Polynomial model.

The Company will issue new shares to satisfy share option exercises. The following table summarizes the Company's share option exercises:

	Year Ended December 31,		
	2021	2020	2019
		(in US$'000)	
Cash received from share option exercises	2,452	593	251
Total intrinsic value of share option exercises	2,999	2,475	1,189

The Group recognizes compensation expense on a graded vesting approach over the requisite service period. The following table presents share-based compensation expense included in the Group's consolidated statements of operations:

	Year Ended December 31,		
	2021	2020	2019
		(in US$'000)	
Research and development expenses	8,460	4,061	6,634
Selling and administrative expenses	7,783	4,586	539
Cost of revenues	122	90	—
	16,365	8,737	7,173

As at December 31, 2021, the total unrecognized compensation cost was US$23,051,000, and will be recognized on a graded vesting approach over the weighted average remaining service period of 3.04 years.

(ii) LTIP

The Company grants awards under the LTIP to participating directors and employees, giving them a conditional right to receive ordinary shares of the Company or the equivalent ADS (collectively the "Awarded Shares") to be purchased by the Trustee up to a cash amount. Vesting will depend upon continued employment of the award holder with the Group and will otherwise be at the discretion of the Board of Directors of the Company. Additionally, some awards are subject to change based on annual performance targets prior to their determination date.

LTIP awards prior to the determination date

Performance targets vary by award, and may include targets for shareholder returns, financings, free cash flows, revenues, net profit after taxes and the achievement of clinical and regulatory milestones. As the extent of achievement of the performance targets is uncertain prior to the determination date, a probability based on management's assessment on the achievement of the performance target has been assigned to calculate the amount to be recognized as an expense over the requisite period with a corresponding entry to liability.

LTIP awards after the determination date

Upon the determination date, the Company will pay a determined monetary amount, up to the maximum cash amount based on the actual achievement of the performance target specified in the award, to the Trustee to purchase the Awarded Shares. Any cumulative compensation expense previously recognized as a liability will be transferred to additional paid-in capital, as an equity-settled award. If the performance target is not achieved, no Awarded Shares of the Company will be purchased and the amount previously recorded in the liability will be reversed through share-based compensation expense.

Granted awards under the LTIP are as follows:

Grant date	Maximum cash amount (in US$ millions)	Covered financial years	Performance target determination date
August 5, 2019	0.7	2019	note (a)
October 10, 2019	0.1	note (b)	note (b)
April 20, 2020	5.3	2019	note (d)
April 20, 2020	37.4	2020	note (a)
April 20, 2020	1.9	note (b)	note (b)
April 20, 2020	0.2	note (c)	note (c)
August 12, 2020	2.1	2020	note (a)
August 12, 2020	0.3	note (b)	note (b)
March 26, 2021	57.3	2021	note (a)
September 1, 2021	7.3	2021	note (a)
September 1, 2021	0.5	note (b)	note (b)
October 20, 2021	1.7	note (b)	note (b)
December 14, 2021	0.1	note (b)	note (b)
December 14, 2021	0.1	note (c)	note (c)

Notes:

(a) The annual performance target determination date is the date of the announcement of the Group's annual results for the covered financial year and vesting occurs two business days after the announcement of the Group's annual results for the financial year falling two years after the covered financial year to which the LTIP award relates.

(b) This award does not stipulate performance targets and is subject to a vesting schedule of 25% on each of the first, second, third and fourth anniversaries of the date of grant.

(c) This award does not stipulate performance targets and will be vested on the first anniversary of the date of grant.

(d) This award does not stipulate performance targets and vesting occurs two business days after the announcement of the Group's annual results for the financial year falling two years after the covered financial year to which the LTIP award relates.

The Trustee has been set up solely for the purpose of purchasing and holding the Awarded Shares during the vesting period on behalf of the Company using funds provided by the Company. On the determination date, if any, the Company will determine the cash amount, based on the actual achievement of each annual performance target, for the Trustee to purchase the Awarded Shares. The Awarded Shares will then be held by the Trustee until they are vested.

The Trustee's assets include treasury shares and funds for additional treasury shares, trustee fees and expenses. The number of treasury shares (in the form of ordinary shares or ADS of the Company) held by the Trustee were as follows:

	Number of treasury shares	Cost (in US$'000)
As at January 1, 2019	1,121,030	6,677
Purchased	60,430	346
Vested	(240,150)	(944)
As at December 31, 2019	941,310	6,079
Purchased	3,281,920	12,904
Vested	(712,555)	(4,828)
As at December 31, 2020	3,510,675	14,155
Purchased	4,907,045	27,309
Vested	(278,545)	(1,450)
As at December 31, 2021	8,139,175	40,014

Based on the estimated achievement of performance conditions for 2021 financial year LTIP awards, the determined monetary amount was US$52,056,000 which is recognized to share-based compensation expense over the requisite vesting period to March 2024.

For the years ended December 31, 2021, 2020 and 2019, US$6,618,000, US$7,038,000 and US$262,000 of the LTIP awards were forfeited respectively based on the determined or estimated monetary amount as at the forfeiture date.

The following table presents the share-based compensation expenses recognized under the LTIP awards:

	Year Ended December 31,		
	2021	2020	2019
		(in US$'000)	
Research and development expenses	16,880	7,252	2,640
Selling and administrative expenses	8,451	3,552	1,779
Cost of revenues	294	101	—
	25,625	10,905	4,419
Recorded with a corresponding credit to:			
Liability	14,263	7,778	2,694
Additional paid-in capital	11,362	3,127	1,725
	25,625	10,905	4,419

For the years ended December 31, 2021, 2020 and 2019, US$8,516,000, US$4,092,000 and US$526,000 were reclassified from liability to additional paid-in capital respectively upon LTIP awards reaching the determination date. As at December 31, 2021 and 2020, US$12,836,000 and US$7,089,000 were recorded as liabilities respectively for LTIP awards prior to the determination date.

As at December 31, 2021, the total unrecognized compensation cost was approximately US$53,152,000, which considers expected performance targets and the amounts expected to vest, and will be recognized over the requisite periods.

19. Revenues

The following table presents disaggregated revenue, with sales of goods recognized at a point-in-time and provision of services recognized over time:

	Year Ended December 31, 2021		
	Oncology/ Immunology	Other Ventures	Total
		(in US$'000)	
Goods—Marketed Products	33,937	—	33,937
Goods—Distribution	—	236,518	236,518
Services—Commercialization—Marketed Products	27,428	—	27,428
—Collaboration Research and Development	18,995	—	18,995
—Research and Development	525	—	525
Royalties	15,064	—	15,064
Licensing	23,661	—	23,661
	119,610	236,518	356,128
Third parties	119,085	232,262	351,347
Related parties (Note 24(i))	525	4,256	4,781
	119,610	236,518	356,128

	Year Ended December 31, 2020		
	Oncology/ Immunology	Other Ventures	Total
		(in US$'000)	
Goods—Marketed Products	11,329	—	11,329
Goods—Distribution	—	197,761	197,761
Services—Commercialization—Marketed Products	3,734	—	3,734
—Collaboration Research and Development	9,771	—	9,771
—Research and Development	491	—	491
Royalties	4,890	—	4,890
	30,215	197,761	227,976
Third parties	29,724	192,277	222,001
Related parties (Note 24(i))	491	5,484	5,975
	30,215	197,761	227,976

	Year Ended December 31, 2019		
	Oncology/ Immunology	Other Ventures	Total
		(in US$'000)	
Goods—Marketed Products	8,113	—	8,113
Goods—Distribution	—	175,514	175,514
Services—Commercialization	—	2,584	2,584
—Collaboration Research and Development	15,532	—	15,532
—Research and Development	494	—	494
Royalties	2,653	—	2,653
	26,792	178,098	204,890
Third parties	26,298	170,461	196,759
Related parties (Note 24(i))	494	7,637	8,131
	26,792	178,098	204,890

The following table presents liability balances from contracts with customers:

	December 31,	
	2021	2020
	(in US$'000)	
Deferred revenue		
Current—Oncology/Immunology segment (note (a))	11,078	1,450
Current—Other Ventures segment (note (b))	1,196	147
	12,274	1,597
Non-current—Oncology/Immunology segment (note (a))	878	484
Total deferred revenue (note (c) and (d))	13,152	2,081

Notes:

(a) Oncology/Immunology segment deferred revenue relates to invoiced amounts for royalties which the customer has not yet completed the in-market sale, unamortized upfront and milestone payments and advance consideration received for cost reimbursements which are attributed to research and development services that have not yet been rendered as at the reporting date.

(b) Other Ventures segment deferred revenue relates to payments in advance from customers for goods that have not been transferred and services that have not been rendered to the customer as at the reporting date.

(c) Estimated deferred revenue to be recognized over time as from the date indicated is as follows:

	December 31,	
	2021	2020
	(in US$'000)	
Not later than 1 year	12,274	1,597
Between 1 to 2 years	476	211
Between 2 to 3 years	255	205
Between 3 to 4 years	147	68
	13,152	2,081

(d) As at January 1, 2021, deferred revenue was US$2.1 million, of which US$0.7 million was recognized during the year ended December 31, 2021.

License and collaboration agreement with Eli Lilly

On October 8, 2013, the Group entered into a licensing, co-development and commercialization agreement in China with Eli Lilly and Company ("Lilly") relating to Elunate ("Lilly Agreement"), also known as fruquintinib, a targeted oncology therapy for the treatment of various types of solid tumors. Under the terms of the Lilly Agreement, the Group is entitled to receive a series of payments up to US$86.5 million, including upfront payments and development and regulatory approval milestones. Development costs after the first development milestone are shared between the Group and Lilly. Elunate was successfully commercialized in China in November 2018, and the Group receives tiered royalties in the range of 15% to 20% on all sales in China.

In December 2018, the Group entered into various amendments to the Lilly Agreement (the "2018 Amendment"). Under the terms of the 2018 Amendment, the Group is entitled to determine and conduct future life cycle indications ("LCI") development of Elunate in China beyond the three initial indications specified in the Lilly Agreement and will be responsible for all associated development costs. In return, the Group will receive additional regulatory approval milestones of US$20 million for each LCI approved, for up to three LCI or US$60 million in aggregate, and will increase tiered royalties to a range of 15% to 29% on all Elunate sales in China upon the commercial launch of the first LCI. Additionally, through the 2018 Amendment, Lilly has provided consent, and freedom to operate, for the Group to enter into joint development collaborations with certain third-party pharmaceutical companies to explore combination treatments of Elunate and various immunotherapy agents. The 2018 Amendment also provided the Group rights to promote Elunate in provinces that represent 30% to 40% of the sales of Elunate in China upon the occurrence of certain commercial milestones by Lilly. Such rights were further amended below.

In July 2020, the Group entered into an amendment to the Lilly Agreement (the "2020 Amendment") relating to the expansion of the Group's role in the commercialization of Elunate across all of China. Under the terms of the 2020 Amendment, the Group is responsible for providing promotion and marketing services, including the development and execution of all on-the-ground medical detailing, promotion and local and regional marketing activities, in return for service fees on sales of Elunate made by Lilly. In October 2020, the Group commenced such promotion and marketing services. In addition, development and regulatory approval milestones for an initial indication under the Lilly Agreement were increased by US$10 million in lieu of cost reimbursement.

Upfront and cumulative milestone payments according to the Lilly Agreement received up to December 31, 2021 are summarized as follows:

	(in US$'000)
Upfront payment	6,500
Development milestone payments achieved	40,000

The Lilly Agreement has the following performance obligations: (1) the license for the commercialization rights to Elunate and (2) the research and development services for the specified indications. The transaction price includes the upfront payment, research and development cost reimbursements, milestone payments and sales-based royalties. Milestone payments were not included in the transaction price until it became probable that a significant reversal of revenue would not occur, which is generally when the specified milestone is achieved. The allocation of the transaction price to each performance obligation was based on the relative standalone selling prices of each performance obligation determined at the inception of the contract. Based on this estimation, proportionate amounts of transaction price to be allocated to the license to Elunate and the research and development services were 90% and 10% respectively. Control of the license to Elunate transferred at the inception date of the agreement and consequently, amounts allocated to this performance obligation were recognized at inception. Conversely, research and development services for each specified indication are performed over time and amounts allocated are recognized over time using the prior and estimated future development costs for Elunate as a measure of progress. Royalties are recognized as future sales occur as they meet the requirements for the sales-usage based royalty exception.

The 2018 Amendment is a separate contract as it added distinct research and development services for the LCIs to the Lilly Agreement. The 2020 Amendment related to the promotion and marketing services is a separate contract as it added distinct services to the Lilly Agreement. Such promotion and marketing services are recognized over time based on amounts that can be invoiced to Lilly. The 2020 Amendment related to the additional development and regulatory approval milestone amounts is a modification as it only affected the transaction price of research and development services for a specific indication under the Lilly Agreement, and therefore, such additional milestone amounts will be included in the transaction price accounted under the Lilly Agreement once the specified milestones are achieved.

Revenue recognized under the Lilly Agreement and subsequent amendments is as follows:

	Year Ended December 31,		
	2021	2020	2019
		(in US$'000)	
Goods—Marketed Products	15,792	11,329	8,113
Services—Commercialization—Marketed Products	27,428	3,734	—
—Collaboration Research and Development	4,491	1,991	4,005
Royalties	10,292	4,890	2,653
	58,003	21,944	14,771

License and collaboration agreement with AstraZeneca

On December 21, 2011, the Group and AstraZeneca AB (publ) ("AZ") entered into a global licensing, co-development, and commercialization agreement for Orpathys ("AZ Agreement"), also known as savolitinib, a novel targeted therapy and a highly selective inhibitor of the c-Met receptor tyrosine kinase for the treatment of cancer. Under the terms of the AZ Agreement, the Group is entitled to receive a series of payments up to US$140 million, including upfront payments and development and first-sale milestones. Additionally, the AZ Agreement contains possible significant future commercial sale milestones. Development costs for Orpathys in China will be shared between the Group and AZ, with the Group continuing to lead the development in China. AZ will lead and pay for the development of Orpathys for the rest of the world. Orpathys was successfully commercialized in China in July 2021, and the Group receives fixed royalties of 30% based on all sales in China. Should Orpathys be successfully commercialized outside China, the Group would receive tiered royalties from 9% to 13% on all sales outside of China.

In August 2016 (as amended in December 2020), the Group entered into an amendment to the AZ Agreement whereby the Group shall pay the first approximately US$50 million of phase III clinical trial costs related to developing Orpathys for renal cell carcinoma ("RCC"), and remaining costs will be shared between the Group and AZ. Subject to approval of Orpathys in RCC, the Group would receive additional tiered royalties on all sales outside of China, with the incremental royalty rates determined based on actual sharing of development costs. In November 2021, the Group entered into an additional amendment which revised the sharing between the Group and AZ of development costs for Orpathys in China for non-small cell lung cancer, as well as adding potential development milestones.

Upfront and cumulative milestone payments according to the AZ Agreement received up to December 31, 2021 are summarized as follows:

	(in US$'000)
Upfront payment	20,000
Development milestone payments achieved	25,000
First-sale milestone payment achieved	25,000

The AZ Agreement has the following performance obligations: (1) the license for the commercialization rights to Orpathys and (2) the research and development services for the specified indications. The transaction price includes the upfront payment, research and development cost reimbursements, milestone payments and sales-based royalties. Milestone payments were not included in the transaction price until it became probable that a significant reversal of revenue would not occur, which is generally when the specified milestone is achieved. The allocation of the transaction price to each performance obligation was based on the relative standalone selling prices of each performance obligation determined at the inception of the contract. Based on this estimation, proportionate amounts of transaction price to be allocated to the license to Orpathys and the research and development services were 95% and 5% respectively. Control of the license to Orpathys transferred at the inception date of the agreement and consequently, amounts allocated to this performance obligation were recognized at inception. Conversely, research and development services for each specified indication are performed over time and amounts allocated are recognized over time using the prior and estimated future development costs for Orpathys as a measure of progress.

Revenue recognized under the AZ Agreement and subsequent amendments is as follows:

	Year Ended December 31,		
	2021	2020	2019
		(in US$'000)	
Goods—Marketed Products	6,509	—	—
Services—Collaboration Research and Development	14,113	7,780	11,527
Royalties	4,772	—	—
Licensing	23,661	—	—
	49,055	7,780	11,527

20. In-Licensing arrangement

On August 7, 2021, the Group and Epizyme, Inc. ("Epizyme") entered into a license agreement (the "In-license Agreement") for tazemetostat, a novel inhibitor of EZH2 that is approved by the U.S. Food and Drug Administration for the treatment of certain patients with epithelioid sarcoma and follicular lymphoma. The Group will be responsible for the development and commercialization of tazemetostat in the PRC, Hong Kong, Macau and Taiwan (the "Territory") and also holds rights to manufacture tazemetostat for the Territory. The Group also received a 4-year warrant, exercisable up to August 7, 2025, to purchase up to 5,653,000 shares of Epizyme common stock for an exercise price of US$11.50 per share.

Under the terms of the In-license Agreement and warrant, the Group paid Epizyme a US$25 million upfront payment and is obligated for a series of success-based payments up to US$110 million in development and regulatory milestones and up to US$175 million in sales milestones. Success-based payments are recognized when the related milestone is achieved. After tazemetostat is commercialized in the Territory, the Group will incur tiered royalties based on net sales. As at December 31, 2021, no amounts of development and regulatory milestones, sales milestones or royalties had been paid.

The US$25 million upfront payment was first allocated to the warrant for its initial fair value of US$15 million, and the remainder was allocated to the rights to tazemetostat which were expensed to research and development expense as in-process research and development.

The warrant was recorded as a financial asset at fair value with changes to fair value recognized to the consolidated statements of operations. As at December 31, 2021, the warrant had not been exercised. For the year ended December 31, 2021, a fair value loss of US$12.5 million was recognized to other expenses in the consolidated statements of operations. In estimating the fair value of the warrant, the following assumptions were used in the Black Scholes model for the dates indicated:

	August 7, 2021	December 31, 2021
Fair value of the warrant (in US$'000)	15,000	2,452
Significant inputs into the valuation model:		
Exercise price (in US$ per share)	11.50	11.50
Share price (in US$ per share)	6.47	2.50
Expected volatility (note (a))	74.48 %	72.03 %
Risk-free interest rate (note (b))	0.59 %	1.05 %
Remaining contractual life of the warrant (in years)	4.00	3.60
Expected dividend yield (note (c))	0 %	0 %

Notes:

(a) Expected volatility references the historical volatility for the remaining contractual life of the warrant.

(b) The risk-free interest rates reference the U.S. Treasury yield curves because Epizyme's common stock is currently listed on the NASDAQ and denominated in US$.

(c) Epizyme has not declared or paid any dividends and the Group does not currently expect it to do so within the remaining contractual life of the warrant.

21. Research and Development Expenses

Research and development expenses are summarized as follows:

	Year Ended December 31,		
	2021	2020	2019
		(in US$'000)	
Clinical trial related costs	190,051	105,869	87,777
Personnel compensation and related costs	91,639	63,542	46,246
Other research and development expenses	17,396	5,365	4,167
	299,086	174,776	138,190

The Group has entered into multiple collaborative arrangements under ASC 808 to evaluate the combination of the Group's drug compounds with the collaboration partners' drug compounds. For the years ended December 31, 2021, 2020 and 2019, the Group has incurred research and development expenses of US$18,408,000, US$8,291,000 and US$2,921,000 respectively, related to such collaborative arrangements.

22. Government Grants

Government grants in the Oncology/Immunology segment are primarily given in support of R&D activities and are conditional upon i) the Group spending a predetermined amount, regardless of success or failure of the research and development projects and/or ii) the achievement of certain stages of research and development projects being approved by the relevant PRC government authority. They are refundable to the government if the conditions, if any, are not met. Government grants in the Other Ventures segment are primarily given to promote local initiatives. These government grants may be subject to ongoing reporting and monitoring by the government over the period of the grant.

Government grants, which are deferred and recognized in the consolidated statements of operations over the period necessary to match them with the costs that they are intended to compensate, are recognized in other payable, accruals and advance receipts (Note 14) and other non-current liabilities. For the years ended December 31, 2021, 2020 and 2019, the Group received government grants of US$9,095,000, US$4,724,000 and US$8,742,000 respectively.

Government grants were recognized as reductions in the consolidated statements of operations as follows:

	Year Ended December 31,		
	2021	2020	2019
		(in US$'000)	
Research and development expenses	15,515	1,607	6,133
Other income	318	539	780
	15,833	2,146	6,913

23. Gain on divestment of an equity investee

In March 2021, the Group entered into a sale and purchase agreement (the "SPA") with a third party to sell its entire investment in HBYS with closing subject to regulatory approval in the PRC. On September 28, 2021, the Group completed the divestment, for cash consideration of US$159.1 million.

On May 13, 2021 and September 23, 2021, HBYS had declared dividends to shareholders of US$46.5 million and US$59.7 million respectively which were related to prior year undistributed profits and distributions of a land bonus payment. Based on the SPA, the Group is entitled to a portion of such dividends and the third party will settle these amounts, net of taxes, after HBYS completes the distribution. As at December 31, 2021, US$46.4 million of dividends receivable, net of taxes, from the third party was recorded in other receivables (Note 7).

In addition, the Group and Hutchison Whampoa Enterprises Limited, an affiliate of CK Hutchison Holdings Limited ("CK Hutchison"), entered into a license agreement on June 15, 2021, conditional upon the completion of the divestment, to grant a continuing right to use the "Hutchison Whampoa" brand by HBYS, and the Group agrees to pay HK$12 million (approximately US$1.5 million) per year with aggregate amounts not to exceed HK$120 million (approximately US$15.4 million). On September 28, 2021, the Group recorded the present value of future branding liability payments of US$12.7 million. As at December 31, 2021, US$1.5 million and US$9.8 million were included in amounts due to related parties (Note 24(ii)) and other non-current liabilities respectively.

The gain on divestment of an equity investee was recognized in the consolidated statements of operations as follows:

	Year Ended December 31, 2021
	(in US$'000)
Proceeds	159,118
Dividend receivables–third party (Note 7)	46,387
	205,505
Less: Group's share of net assets of HBYS (Note 11(iii))	(23,246)
Dividend receivables–HBYS	(52,887)
Withholding tax liability on dividend receivables–HBYS	2,644
Branding liability	(12,721)
Accumulated other comprehensive income and reserves	1,911
Transaction costs and others	104
Gain on divestment of an equity investee	121,310
Less: Capital gain tax	(14,373)
Less: Gain on divestment of an equity investee attributable to non-controlling interests	(24,010)
Gain on divestment of an equity investee attributable to the Group	82,927

24. Significant Transactions with Related Parties and Non-Controlling Shareholders of Subsidiaries

The Group has the following significant transactions with related parties and non-controlling shareholders of subsidiaries, which were carried out in the normal course of business at terms determined and agreed by the relevant parties:

(i) Transactions with related parties:

	Year Ended December 31,		
	2021	2020	2019
		(in US$'000)	
Sales to:			
Indirect subsidiaries of CK Hutchison	4,256	5,484	7,637
Revenue from research and development services from:			
An equity investee	525	491	494
Purchases from:			
Equity investees	3,770	3,347	2,465
Rendering of marketing services from:			
Indirect subsidiaries of CK Hutchison	350	332	430
An equity investee	—	—	2,682
	350	332	3,112
Rendering of management services from:			
An indirect subsidiary of CK Hutchison	971	955	931
Entered brand license agreement with:			
An indirect subsidiary of CK Hutchison (note (a))	12,721	—	—

(ii) Balances with related parties included in:

	December 31,	
	2021	2020
	(in US$'000)	
Accounts receivable—related parties		
Indirect subsidiaries of CK Hutchison (note (b))	1,166	1,222
Other receivables, prepayments and deposits		
Equity investees (note (b))	1,149	1,142
Other payables, accruals and advance receipts		
Indirect subsidiaries of CK Hutchison (note (c) and (e))	1,915	401
Other non-current liabilities		
An equity investee (note (d))	736	950
An indirect subsidiary of CK Hutchison (note (e))	9,766	—
	10,502	950

Notes:

(a) The branding rights for HBYS from an indirect subsidiary of CK Hutchison was recognized in the consolidated statements of operations through the gain on divestment of an equity investee (Note 23). For the year ended December 31, 2021, actual cash paid was US$1,538,000.

(b) Balances with related parties are unsecured, repayable on demand and interest-free. The carrying values of balances with related parties approximate their fair values due to their short-term maturities.

(c) Amounts due to indirect subsidiaries of CK Hutchison are unsecured, repayable on demand and interest-bearing if not settled within one month.

(d) Other deferred income represents amounts recognized from granting of promotion and marketing rights.

(e) As at December 31, 2021, branding liability payable of approximately US$1,538,000 and US$9,766,000 were included in amounts due to related parties under other payables, accruals and advance receipts and other non-current liabilities respectively (Note 23).

(iii) Transactions with non-controlling shareholders of subsidiaries:

	Year Ended December 31,		
	2021	2020	2019
		(in US$'000)	
Sales	41,974	36,500	27,343
Purchases	10,660	13,936	13,380
Dividends declared	9,894	1,462	—

(iv) Balances with non-controlling shareholders of subsidiaries included in:

	December 31,	
	2021	2020
	(in US$'000)	
Accounts receivable	8,436	6,184
Accounts payable	2,062	4,856
Other non-current liabilities		
Loan	—	579

25. Income Taxes

(i) Income tax expense

	Year Ended December 31,		
	2021	2020	2019
		(in US$'000)	
Current tax			
HK (note (a))	310	457	321
PRC (note (b) and (c))	15,909	872	708
U.S. and others (note (d))	417	219	636
Total current tax	16,636	1,548	1,665
Deferred income tax (benefits)/expense	(4,718)	3,281	1,609
Income tax expense	11,918	4,829	3,274

Notes:

(a) The Company, three subsidiaries incorporated in the British Virgin Islands and its Hong Kong subsidiaries are subject to Hong Kong profits tax. Under the Hong Kong two-tiered profits tax rates regime, the first HK$2.0 million (US$0.3 million) of assessable profits of qualifying corporations will be taxed at 8.25%, with the remaining assessable profits taxed at 16.5%. Hong Kong profits tax has been provided for at the relevant rates on the estimated assessable profits less estimated available tax losses, if any, of these entities as applicable.

(b) Taxation in the PRC has been provided for at the applicable rate on the estimated assessable profits less estimated available tax losses, if any, in each entity. Under the PRC Enterprise Income Tax Law (the "EIT Law"), the standard enterprise income tax rate is 25%. In addition, the EIT Law provides for a preferential tax rate of 15% for companies which qualify as HNTE. HUTCHMED Limited and its wholly-owned subsidiary HUTCHMED (Suzhou) Limited (formerly known as "Hutchison MediPharma (Suzhou) Limited") qualify as a HNTE up to December 31, 2022 and 2023 respectively.

Pursuant to the EIT law, a 10% withholding tax is levied on dividends paid by PRC companies to their foreign investors. A lower withholding tax rate of 5% is applicable under the China-HK Tax Arrangement if direct foreign investors with at least 25% equity interest in the PRC companies are Hong Kong tax residents, and meet the conditions or requirements pursuant to the relevant PRC tax regulations regarding beneficial ownership. Since the equity holders of the equity investees of the Company are Hong Kong incorporated companies and Hong Kong tax residents, and meet the aforesaid conditions or requirements, the Company has used 5% to provide for deferred tax liabilities on retained earnings which are anticipated to be distributed. As at December 31, 2021, 2020 and 2019, the amounts accrued in deferred tax liabilities relating to withholding tax on dividends were determined on the basis that 100% of the distributable reserves of the equity investees operating in the PRC will be distributed as dividends.

Pursuant to PRC Bulletin on Issues of Enterprise Income Tax and Indirect Transfers of Assets by Non-PRC Resident Enterprises, an indirect transfer of a PRC resident enterprise by a non-PRC resident enterprise, via the transfer of an offshore intermediate holding company, shall be subject to PRC withholding tax under certain conditions.

(c) Current tax in the PRC for the year ended December 31, 2021 includes US$14.4 million arising from the indirect disposal of HBYS (Note 23), calculated at 10% of the excess of the disposal proceeds over the cost of acquiring the equity investment in HBYS.

(d) The Company's subsidiary in the U.S. with operations primarily in New Jersey and New York states is subject to U.S. taxes, primarily federal and state taxes, which have been provided for at approximately 21% (federal) and 0% to 11.5% (state tax) on the estimated assessable profit over the reporting years. Certain income receivable by the Company is subject to U.S. withholding tax of 30%. Two of the Group's subsidiaries are subject to corporate tax in the UK and EU countries at 19% and 20% to 25%, respectively, on the estimated assessable profits in relation to their presence in these countries.

The reconciliation of the Group's reported income tax expense to the theoretical tax amount that would arise using the tax rates of the Company against the Group's loss before income taxes and equity in earnings of equity investees is as follows:

	Year Ended December 31,		
	2021	2020	2019
		(in US$'000)	
Loss before income taxes and equity in earnings of equity investees	(215,740)	(189,734)	(141,105)
Tax calculated at the statutory tax rate of the Company	(35,597)	(31,306)	(23,282)
Tax effects of:			
Different tax rates applicable in different jurisdictions	136	4,025	2,027
Tax valuation allowance	63,975	46,321	25,498
Preferential tax rate difference	(148)	(154)	(177)
Preferential tax deduction and credits	(29,838)	(18,814)	(5,444)
Expenses not deductible for tax purposes	8,684	3,476	4,098
Utilization of previously unrecognized tax losses	(186)	(114)	(285)
Withholding tax on undistributed earnings of PRC entities	3,153	3,962	1,894
Others	1,739	(2,567)	(1,055)
Income tax expense	11,918	4,829	3,274

(ii) Deferred tax assets and liabilities

The significant components of deferred tax assets and liabilities are as follows:

	December 31,	
	2021	2020
	(in US$'000)	
Deferred tax assets		
Cumulative tax losses	186,832	117,064
Others	12,269	6,829
Total deferred tax assets	199,101	123,893
Less: Valuation allowance	(189,700)	(122,378)
Deferred tax assets	9,401	1,515
Deferred tax liabilities		
Undistributed earnings from PRC entities	2,720	4,994
Others	45	69
Deferred tax liabilities	2,765	5,063

The movements in deferred tax assets and liabilities are as follows:

	2021	2020	2019
		(in US$'000)	
As at January 1	(3,548)	(2,343)	(4,256)
Utilization of previously recognized withholding tax on undistributed earnings	5,148	2,323	3,390
(Charged)/Credited to the consolidated statements of operations			
Withholding tax on undistributed earnings of PRC entities	(3,153)	(3,962)	(1,894)
Deferred tax on amortization of intangible assets	19	18	18
Deferred tax on temporary differences, tax loss carried forward and research tax credits	7,852	663	267
Divestment of an equity investee	370	—	—
Exchange differences	(52)	(247)	132
As at December 31	6,636	(3,548)	(2,343)

The deferred tax assets and liabilities are offset when there is a legally enforceable right to set off and when the deferred income taxes relate to the same fiscal authority.

The cumulative tax losses can be carried forward against future taxable income and will expire in the following years:

	December 31,	
	2021	2020
	(in US$'000)	
No expiry date	60,450	53,940
2022	200	195
2023	—	—
2024	4,099	3,998
2025	39,321	38,357
2026	52,452	51,034
2027	67,217	66,555
2028	117,376	114,490
2029	191,554	186,844
2030	265,696	259,163
2031	432,278	—
	1,230,643	774,576

The Company believes that it is more likely than not that future operations outside the U.S. will not generate sufficient taxable income to realize the benefit of the deferred tax assets. Certain of the Company's subsidiaries have had sustained tax losses, which will expire within five years if not utilized in the case of PRC subsidiaries (ten years for HNTEs), and which will not be utilized in the case of Hong Kong subsidiaries as they do not generate taxable profits. Accordingly, a valuation allowance has been recorded against the relevant deferred tax assets arising from the tax losses.

A U.S. subsidiary of the Company has approximately US$2.0 million and US$0.6 million U.S. Federal and New Jersey state research tax credits which will expire between 2039 and 2041 (Federal) and 2026 and 2028 (New Jersey) respectively, if not utilized.

The table below summarizes changes in the deferred tax valuation allowance:

	2021	2020	2019
		(in US$'000)	
As at January 1	122,378	69,399	49,021
Charged to consolidated statements of operations	63,975	46,321	25,498
Utilization of previously unrecognized tax losses	(186)	(114)	(285)
Write-off of tax losses	—	—	(3,142)
Others	(9)	—	—
Exchange differences	3,542	6,772	(1,693)
As at December 31	189,700	122,378	69,399

As at December 31, 2021, 2020 and 2019, the Group did not have any material unrecognized uncertain tax positions.

(iii) Income tax payable

	2021	2020	2019
		(in US$'000)	
As at January 1	1,120	1,828	555
Current tax	16,636	1,548	1,665
Withholding tax upon dividend declaration from PRC entities (note (a))	5,148	2,323	2,581
Tax paid (note (b))	(5,014)	(5,940)	(2,970)
Reclassification from non-current withholding tax	—	812	—
Reclassification to prepaid tax	25	485	—
Divestment of an equity investee (Note 23)	(2,644)	—	—
Exchange difference	275	64	(3)
As at December 31	15,546	1,120	1,828

Notes:
(a) The amount for 2019 excludes a non-current withholding tax of US$0.8 million which is included under other non-current liabilities.

(b) The amount for 2020 is net of the PRC Enterprise Income Tax ("EIT") refund of US$0.4 million received by HSPL. The amount for 2019 excludes the PRC EIT of US$0.3 million prepaid by HSPL which is included under other receivables, prepayments and deposits.

26. Losses Per Share

(i) Basic losses per share

Basic losses per share is calculated by dividing the net loss attributable to the Company by the weighted average number of outstanding ordinary shares in issue during the year. Treasury shares held by the Trustee are excluded from the weighted average number of outstanding ordinary shares in issue for purposes of calculating basic losses per share.

	Year Ended December 31,		
	2021	2020	2019
Weighted average number of outstanding ordinary shares in issue	792,684,524	697,931,437	665,683,145
Net loss attributable to the Company (US$'000)	(194,648)	(125,730)	(106,024)
Losses per share attributable to the Company (US$ per share)	(0.25)	(0.18)	(0.16)

(ii) Diluted losses per share

Diluted losses per share is calculated by dividing net loss attributable to the Company by the weighted average number of outstanding ordinary shares in issue and dilutive ordinary share equivalents outstanding during the year. Dilutive ordinary share equivalents include shares issuable upon the exercise or settlement of share options, LTIP awards and warrants issued by the Company using the treasury stock method.

For the years ended December 31, 2021, 2020 and 2019, the share options, LTIP awards and warrants issued by the Company were not included in the calculation of diluted losses per share because of their anti-dilutive effect. Therefore, diluted losses per share were equal to basic losses per share for the years ended December 31, 2021, 2020 and 2019.

27. Segment Reporting

The Group's operating segments are as follows:

(i) Oncology/Immunology: focuses on discovering, developing, and commercializing targeted therapies and immunotherapies for the treatment of cancer and immunological diseases. Oncology/Immunology is further segregated into two core business areas:

(a) R&D: comprises research and development activities covering drug discovery, development, manufacturing and regulatory functions as well as administrative activities to support research and development operations; and

(b) Marketed Products: comprises the sales, marketing, manufacture and distribution of drug developed from research and development activities.

(ii) Other Ventures: comprises other commercial businesses which include the sales, marketing, manufacture and distribution of other prescription drugs and consumer health products.

The performance of the reportable segments is assessed based on segment operating (loss)/profit.

The segment information is as follows:

	Year Ended December 31, 2021							
	Oncology/Immunology							
	R&D			Marketed Products		Other Ventures		
	PRC	U.S. and Others	Subtotal	PRC	Subtotal	PRC	Unallocated	Total
	(in US$'000)							
Revenue from external customers	43,181	—	43,181	76,429	119,610	236,518	—	356,128
Interest income	809	3	812	—	812	282	982	2,076
Equity in earnings of equity investees, net of tax	20	—	20	—	20	60,597	—	60,617
Segment operating (loss)/profit	(143,876)	(159,770)	(303,646)	6,178	(297,468)	185,240	(42,303)	(154,531)
Interest expense	—	—	—	—	—	—	(592)	(592)
Income tax credit/(expense)	22	7,160	7,182	(1,320)	5,862	(14,573)	(3,207)	(11,918)
Net (loss)/income attributable to the Company	(143,528)	(152,235)	(295,763)	4,032	(291,731)	142,890	(45,807)	(194,648)
Depreciation/amortization	(6,436)	(197)	(6,633)	—	(6,633)	(318)	(239)	(7,190)
Additions to non-current assets (other than financial instruments and deferred tax assets)	25,295	4,321	29,616	—	29,616	1,056	327	30,999

	December 31, 2021							
	Oncology/Immunology							
	R&D			Marketed Products		Other Ventures		
	PRC	U.S. and Others	Subtotal	PRC	Subtotal	PRC	Unallocated	Total
	(in US$'000)							
Total assets	166,802	19,870	186,672	35,978	222,650	225,898	924,113	1,372,661
Property, plant and equipment	38,049	1,862	39,911	—	39,911	746	618	41,275
Right-of-use assets	4,798	3,768	8,566	—	8,566	1,827	1,486	11,879
Leasehold land	13,169	—	13,169	—	13,169	—	—	13,169
Goodwill	—	—	—	—	—	3,380	—	3,380
Other intangible asset	—	—	—	—	—	163	—	163
Investments in equity investees	480	—	480	—	480	75,999	—	76,479

	Year Ended December 31, 2020							
	Oncology/Immunology							
	R&D			Marketed Products		Other Ventures		
	PRC	U.S. and Others	Subtotal	PRC	Subtotal	PRC	Unallocated	Total
	(in US$'000)							
Revenue from external customers	10,262	—	10,262	19,953	30,215	197,761	—	227,976
Interest income	461	—	461	—	461	167	2,608	3,236
Equity in earnings of equity investees, net of tax	(97)	—	(97)	—	(97)	79,143	—	79,046
Segment operating (loss)/profit	(119,740)	(63,482)	(183,222)	7,607	(175,615)	83,888	(18,174)	(109,901)
Interest expense	—	—	—	—	—	—	(787)	(787)
Income tax (expense)/credit	(402)	642	240	(167)	73	(824)	(4,078)	(4,829)
Net (loss)/income attributable to the Company	(120,096)	(62,683)	(182,779)	7,282	(175,497)	72,785	(23,018)	(125,730)
Depreciation/amortization	(5,458)	(119)	(5,577)	—	(5,577)	(292)	(192)	(6,061)
Additions to non-current assets (other than financial instruments and deferred tax assets)	22,574	754	23,328	—	23,328	817	1,090	25,235

	December 31, 2020							
	Oncology/Immunology							
	R&D			Marketed Products		Other Ventures		
	PRC	U.S. and Others	Subtotal	PRC	Subtotal	PRC	Unallocated	Total
	(in US$'000)							
Total assets	127,637	9,957	137,594	5,728	143,322	231,234	349,562	724,118
Property, plant and equipment	22,554	454	23,008	—	23,008	688	474	24,170
Right-of-use assets	2,782	1,375	4,157	—	4,157	2,582	1,277	8,016
Leasehold land	13,121	—	13,121	—	13,121	—	—	13,121
Goodwill	—	—	—	—	—	3,307	—	3,307
Other intangible asset	—	—	—	—	—	227	—	227
Investments in equity investees	385	—	385	—	385	139,120	—	139,505

	Year Ended December 31, 2019							
	Oncology/Immunology							
	R&D			Marketed Products		Other Ventures		
	PRC	U.S. and Others	Subtotal	PRC	Subtotal	PRC	Unallocated	Total
	(in US$'000)							
Revenue from external customers	16,026	—	16,026	10,766	26,792	178,098	—	204,890
Interest income	322	—	322	—	322	109	4,513	4,944
Equity in earnings of equity investees, net of tax	147	—	147	—	147	40,553	—	40,700
Segment operating (loss)/profit	(111,518)	(21,785)	(133,303)	5,887	(127,416)	45,255	(17,214)	(99,375)
Interest expense	—	—	—	—	—	—	(1,030)	(1,030)
Income tax expense	(63)	(197)	(260)	—	(260)	(939)	(2,075)	(3,274)
Net (loss)/income attributable to the Company	(111,308)	(21,926)	(133,234)	5,872	(127,362)	41,488	(20,150)	(106,024)
Depreciation/amortization	(4,448)	(62)	(4,510)	—	(4,510)	(264)	(168)	(4,942)
Additions to non-current assets (other than financial instruments and deferred tax assets)	8,602	1,308	9,910	—	9,910	2,772	148	12,830

Revenue from external customers is after elimination of inter-segment sales. Sales between segments are carried out at mutually agreed terms. The amount eliminated attributable to sales between PRC and U.S. and others under Oncology/Immunology segment was US$46,891,000, US$19,230,000 and US$8,406,000 for the years ended December 31, 2021, 2020, and 2019 respectively.

There were three customers with aggregate revenue of US$147,111,000, which accounted for over 10% of the Group's revenue for the year ended December 31, 2021. There were two customers with aggregate revenue of US$62,493,000, which accounted for over 10% of the Group's revenue for the year ended December 31, 2020. There was one customer with revenue of US$27,343,000, which accounted for over 10% of the Group's revenue for the year ended December 31, 2019.

Unallocated expenses mainly represent corporate expenses which include corporate employee benefit expenses and the relevant share-based compensation expenses. Unallocated assets mainly comprise cash and cash equivalents and short-term investments.

A reconciliation of segment operating loss to net loss is as follows:

	Year Ended December 31,		
	2021	2020	2019
		(in US$'000)	
Segment operating loss	(154,531)	(109,901)	(99,375)
Interest expense	(592)	(787)	(1,030)
Income tax expense	(11,918)	(4,829)	(3,274)
Net loss	(167,041)	(115,517)	(103,679)

28. Note to Consolidated Statements of Cash Flows

Reconciliation of net loss for the year to net cash used in operating activities:

	Year Ended December 31,		
	2021	2020	2019
		(in US$'000)	
Net loss	(167,041)	(115,517)	(103,679)
Adjustments to reconcile net loss to net cash used in operating activities			
Amortization of finance costs	44	43	195
Depreciation and amortization	7,190	6,061	4,942
Gain from purchase of a subsidiary	—	—	(17)
Loss on disposals of property, plant and equipment	70	85	17
Provision for excess and obsolete inventories	(23)	65	316
Provision for credit losses	(76)	77	(25)
Share-based compensation expense—share options	16,365	8,737	7,173
Share-based compensation expense—LTIP	25,625	10,905	4,419
Equity in earnings of equity investees, net of tax	(60,617)	(79,046)	(40,700)
Dividends received from SHPL and HBYS	49,872	86,708	28,135
Changes in right-of-use assets	(3,727)	(2,197)	224
Fair value loss on Warrant	12,548	—	—
Gain from disposal of HBYS	(121,310)	—	—
Unrealized currency translation (gain)/loss	(2,505)	(6,149)	1,679
Changes in income tax balances	6,904	(1,111)	304
Changes in working capital			
Accounts receivable	(35,634)	(4,693)	(271)
Other receivables, prepayments and deposits	(5,758)	(9,602)	(2,734)
Inventories	(16,002)	(3,623)	(4,215)
Accounts payable	9,565	7,651	(1,664)
Other payables, accruals and advance receipts	66,224	37,472	25,953
Lease liabilities	3,079	2,258	(101)
Deferred revenue	11,071	(158)	(709)
Other	(87)	(32)	(154)
Total changes in working capital	32,458	29,273	16,105
Net cash used in operating activities	(204,223)	(62,066)	(80,912)

29. Litigation

From time to time, the Group may become involved in litigation relating to claims arising from the ordinary course of business. The Group believes that there are currently no claims or actions pending against the Group, the ultimate disposition of which could have a material adverse effect on the Group's results of operations, financial position or cash flows. However, litigation is subject to inherent uncertainties and the Group's view of these matters may change in the future. When an unfavorable outcome occurs, there exists the possibility of a material adverse impact on the Group's financial position and results of operations for the periods in which the unfavorable outcome occurs, and potentially in future periods.

On May 17, 2019, Luye Pharma Hong Kong Ltd. ("Luye") issued a notice to the Group purporting to terminate a distribution agreement that granted the Group exclusive commercial rights to Seroquel in the PRC for failure to meet a pre-specified target. The Group disagrees with this assertion and believes that Luye have no basis for termination. As a result, the Group commenced legal proceedings in 2019 in order to seek damages. On October 21, 2021 (and further updated in December 2021), the Group was awarded an amount of RMB253.2 million (equivalent to US$39.6 million) with interest of 5.5% per annum from the date of the award until payment and recovery of costs of US$2.2 million ("Award"). Luye is still pursuing further legal proceedings and no Award amounts have been received as at the issuance date of these consolidated financial statements. Hence no Award amounts have been recognized and no adjustment has been made to Seroquel-related balances as at December 31, 2021. Such Seroquel-related balances include accounts receivable, long-term prepayment, accounts payable and other payables of US$1.2 million, US$0.7 million, US$1.0 million and US$1.3 million respectively.

30. Restricted Net Assets

Relevant PRC laws and regulations permit payments of dividends by the Company's subsidiaries in the PRC only out of their retained earnings, if any, as determined in accordance with PRC accounting standards and regulations. In addition, the Company's subsidiaries in the PRC are required to make certain appropriations of net after-tax profits or increases in net assets to the statutory surplus fund prior to payment of any dividends. In addition, registered share capital and capital reserve accounts are restricted from withdrawal in the PRC, up to the amount of net assets held in each subsidiary. As a result of these and other restrictions under PRC laws and regulations, the Company's subsidiaries in the PRC are restricted in their ability to transfer their net assets to the Group in terms of cash dividends, loans or advances, with restricted portions amounting to US$0.1 million and US$0.2 million as at December 31, 2021 and 2020 respectively, which excludes the Company's subsidiaries with a shareholders' deficit. Even though the Group currently does not require any such dividends, loans or advances from the PRC subsidiaries, for working capital and other funding purposes, the Group may in the future require additional cash resources from the Company's subsidiaries in the PRC due to changes in business conditions, to fund future acquisitions and development, or merely to declare and pay dividends to make distributions to shareholders.

In addition, the Group has certain investments in equity investees in the PRC, where the Group's equity in undistributed earnings amounted to US$54.4 million and US$99.9 million as at December 31, 2021 and 2020 respectively.

31. Additional Information: Company Balance Sheets (Parent Company Only)

	Note	December 31, 2021	December 31, 2020
		(in US$'000)	
Assets			
Current assets			
Cash and cash equivalents		979	21
Short-term investments		55,128	—
Other receivables, prepayments and deposits		934	1,120
Total current assets		**57,041**	**1,141**
Investments in subsidiaries		972,831	506,150
Deferred issuance costs		—	1,171
Total assets		**1,029,872**	**508,462**
Liabilities and shareholders' equity			
Current liabilities			
Other payables, accruals and advance receipts		42,952	24,253
Income tax payable		16	93
Total current liabilities		**42,968**	**24,346**
Other non-current liabilities		11	—
Total liabilities		**42,979**	**24,346**
Commitments and contingencies	16		
Company's shareholders' equity			
Ordinary shares; $0.10 par value; 1,500,000,000 shares authorized; 864,530,850 and 727,722,215 shares issued at December 31, 2021 and 2020 respectively	17	86,453	72,772
Additional paid-in capital		1,505,196	822,458
Accumulated losses		(610,328)	(415,591)
Accumulated other comprehensive income		5,572	4,477
Total Company's shareholders' equity		**986,893**	**484,116**
Total liabilities and shareholders' equity		**1,029,872**	**508,462**

32. Subsequent Events

The Group evaluated subsequent events through March 3, 2022, which is the date when the consolidated financial statements were issued.

In February 2022, a US$15 million milestone payment was triggered and receivable in relation to the initiation of the Phase III study for the primary indication non-small cell lung cancer pursuant to the AZ Agreement.

**SHANGHAI HUTCHISON
PHARMACEUTICALS LIMITED**

Report of Independent Auditors

To the Board of Directors of Shanghai Hutchison Pharmaceuticals Limited

Opinion

We have audited the accompanying consolidated financial statements of Shanghai Hutchison Pharmaceuticals Limited and its subsidiaries (the "Company"), which comprise the consolidated statements of financial position as of December 31, 2021 and 2020, and the related consolidated income statements, consolidated statements of comprehensive income, of changes in equity and of cash flows for each of the three years in the period ended December 31, 2021, including the related notes (collectively referred to as the "consolidated financial statements").

In our opinion, the accompanying consolidated financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2021 and 2020, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2021 in accordance with International Financial Reporting Standards as issued by the International Accounting Standards Board .

Basis for Opinion

We conducted our audit in accordance with auditing standards generally accepted in the United States of America (US GAAS). Our responsibilities under those standards are further described in the Auditors' Responsibilities for the Audit of the Consolidated Financial Statements section of our report. We are required to be independent of the Company and to meet our other ethical responsibilities, in accordance with the relevant ethical requirements relating to our audit. We believe that the audit evidence we have obtained is sufficient and appropriate to provide a basis for our audit opinion.

Responsibilities of Management for the Consolidated Financial Statements

Management is responsible for the preparation and fair presentation of the consolidated financial statements in accordance with International Financial Reporting Standards as issued by the International Accounting Standards Board , and for the design, implementation, and maintenance of internal control relevant to the preparation and fair presentation of consolidatedfinancial statements that are free from material misstatement, whether due to fraud or error.

In preparing the financial statements, management is responsible for assessing the Company's ability to continue as a going concern for at least, but not limited to, twelve months from the end of the reporting period, disclosing, as applicable, matters related to going concern and using the going concern basis of accounting unless management either intends to liquidate the Company or to cease operations, or has no realistic alternative but to do so.

Auditors' Responsibilities for the Audit of the Consolidated Financial Statements

Our objectives are to obtain reasonable assurance about whether the financial statements as a whole are free from material misstatement, whether due to fraud or error, and to issue an auditors' report that includes our opinion. Reasonable assurance is a high level of assurance but is not absolute assurance and therefore is not a guarantee that an audit conducted in accordance with US GAAS will always detect a material misstatement when it exists. The risk of not detecting a material misstatement resulting from fraud is higher than for one resulting from error, as fraud may involve collusion, forgery, intentional omissions, misrepresentations, or the override of internal control. Misstatements are considered material if there is a substantial likelihood that, individually or in the aggregate, they would influence the judgment made by a reasonable user based on the financial statements.

In performing an audit in accordance with US GAAS, we:

- Exercise professional judgment and maintain professional skepticism throughout the audit.
- Identify and assess the risks of material misstatement of the consolidated financial statements, whether due to fraud or error, and design and perform audit procedures responsive to those risks. Such procedures include examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements.

- Obtain an understanding of internal control relevant to the audit in order to design audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control. Accordingly, no such opinion is expressed.

- Evaluate the appropriateness of accounting policies used and the reasonableness of significant accounting estimates made by management, as well as evaluate the overall presentation of the consolidated financial statements.

- Conclude whether, in our judgment, there are conditions or events, considered in the aggregate, that raise substantial doubt about the Company’s ability to continue as a going concern for a reasonable period of time.

We are required to communicate with those charged with governance regarding, among other matters, the planned scope and timing of the audit, significant audit findings, and certain internal control-related matters that we identified during the audit.

/s/ PricewaterhouseCoopers Zhong Tian LLP
Shanghai, the People’s Republic of China
March 3, 2022

Shanghai Hutchison Pharmaceuticals Limited
Consolidated Income Statements
(in US$'000)

	Note	Year Ended December 31, 2021	2020	2019
Revenue	5	332,648	276,354	272,082
Cost of sales		(77,559)	(72,163)	(77,313)
Gross profit		255,089	204,191	194,769
Selling expenses		(131,821)	(111,892)	(110,591)
Administrative expenses		(22,627)	(17,907)	(14,761)
Other net operating income	6	4,759	3,473	2,941
Operating profit	7	**105,400**	**77,865**	**72,358**
Finance costs	15	(116)	(12)	(42)
Profit before taxation		**105,284**	**77,853**	**72,316**
Taxation charge	8	(15,896)	(10,833)	(11,015)
Profit for the year		**89,388**	**67,020**	**61,301**

The accompanying notes are an integral part of these consolidated financial statements.

Shanghai Hutchison Pharmaceuticals Limited
Consolidated Statements of Comprehensive Income
(in US$'000)

	Year Ended December 31,		
	2021	2020	2019
Profit for the year	**89,388**	**67,020**	**61,301**
Other comprehensive income/(loss) that has been or may be reclassified subsequently to profit or loss:			
Exchange translation differences	3,341	11,129	(4,670)
Total comprehensive income	**92,729**	**78,149**	**56,631**

The accompanying notes are an integral part of these consolidated financial statements.

Shanghai Hutchison Pharmaceuticals Limited
Consolidated Statements of Financial Position
(in US$'000)

	Note	December 31, 2021	December 31, 2020
Assets			
Current assets			
Cash and cash equivalents	10	50,038	72,478
Trade and bills receivables	11	17,482	18,421
Other receivables, prepayments and deposits	12	3,350	3,392
Inventories	13	119,390	81,674
Total current assets		**190,260**	**175,965**
Property, plant and equipment	14	73,650	76,932
Right-of-use assets	15	2,445	152
Leasehold land		7,025	7,021
Other intangible asset		722	935
Deferred tax assets	16	7,715	8,315
Total assets		**281,817**	**269,320**
Liabilities and shareholders' equity			
Current liabilities			
Trade payables	17	12,411	11,174
Other payables, accruals and advance receipts	18	111,793	93,534
Current tax liabilities	19	4,089	5,032
Lease liabilities	15	700	133
Total current liabilities		**128,993**	**109,873**
Deferred income		4,983	6,720
Lease liabilities	15	2,148	19
Total liabilities		**136,124**	**116,612**
Shareholders' equity			
Share capital		33,382	33,382
Reserves		112,311	119,326
Total shareholders' equity		**145,693**	**152,708**
Total liabilities and shareholders' equity		**281,817**	**269,320**

The accompanying notes are an integral part of these consolidated financial statements.

Shanghai Hutchison Pharmaceuticals Limited
Consolidated Statements of Changes in Equity
(in US$'000)

	Share capital	Exchange reserve	General reserves	Retained earnings	Total equity
As at January 1, 2019	**33,382**	**(3,854)**	**970**	**101,263**	**131,761**
Profit for the year	—	—	—	61,301	61,301
Other comprehensive loss					
Exchange translation differences	—	(4,670)	—	—	(4,670)
Total comprehensive (loss)/income	—	(4,670)	—	61,301	56,631
Transfer between reserves	—	—	14	(14)	—
Dividends declared to shareholders	—	—	—	(41,654)	(41,654)
As at December 31, 2019	**33,382**	**(8,524)**	**984**	**120,896**	**146,738**
Profit for the year	—	—	—	67,020	67,020
Other comprehensive income					
Exchange translation differences	—	11,129	—	—	11,129
Total comprehensive income	—	11,129	—	67,020	78,149
Transfer between reserves	—	—	14	(14)	—
Dividends declared to shareholders	—	—	—	(72,179)	(72,179)
As at December 31, 2020	**33,382**	**2,605**	**998**	**115,723**	**152,708**
Profit for the year	—	—	—	89,388	89,388
Other comprehensive income					
Exchange translation differences	—	3,341	—	—	3,341
Total comprehensive income	—	3,341	—	89,388	92,729
Transfer between reserves	—	—	31	(31)	—
Dividends declared to shareholders	—	—	—	(99,744)	(99,744)
As at December 31, 2021	**33,382**	**5,946**	**1,029**	**105,336**	**145,693**

The accompanying notes are an integral part of these consolidated financial statements.

Shanghai Hutchison Pharmaceuticals Limited
Consolidated Statements of Cash Flows
(in US$'000)

	Note	Year Ended December 31, 2021	2020	2019
Operating activities				
Net cash generated from operations	20	93,970	112,609	76,784
Interest received		1,116	912	518
Income tax paid	19	(15,976)	(10,232)	(13,618)
Net cash generated from operating activities		79,110	103,289	63,684
Investing activities				
Purchase of property, plant and equipment		(3,362)	(2,437)	(4,592)
Proceeds from disposal of property, plant and equipment		32	63	9
Net cash used in investing activities		(3,330)	(2,374)	(4,583)
Financing activities				
Dividends paid to shareholders		(99,744)	(72,179)	(41,654)
Lease payments	15	(303)	(474)	(595)
Net cash used in financing activities		(100,047)	(72,653)	(42,249)
Net (decrease)/increase in cash and cash equivalents		(24,267)	28,262	16,852
Effect of exchange rate changes on cash and cash equivalents		1,827	2,972	(659)
		(22,440)	31,234	16,193
Cash and cash equivalents				
Cash and cash equivalents at beginning of year		72,478	41,244	25,051
Cash and cash equivalents at end of year		50,038	72,478	41,244

The accompanying notes are an integral part of these consolidated financial statements.

Shanghai Hutchison Pharmaceuticals Limited
Notes to the Consolidated Financial Statements

1. General Information

Shanghai Hutchison Pharmaceuticals Limited (the "Company") and its subsidiaries (together the "Group") are principally engaged in manufacturing, selling and distribution of prescription drug products. The Group has manufacturing plants in the People's Republic of China (the "PRC") and sells mainly in the PRC.

The Company was incorporated in the PRC on April 30, 2001 as a Chinese-Foreign Equity joint venture. The Company is jointly controlled by Shanghai HUTCHMED Investment (HK) Limited ("SHHCMI(HK)L") (formerly known as "Shanghai Hutchison Chinese Medicine (HK) Investment Limited") and Shanghai Traditional Chinese Medicine Co., Ltd ("SHTCML").

These consolidated financial statements are presented in United States dollars ("US$"), unless otherwise stated and have been approved for issue by the Company's Board of Directors on March 3, 2022.

2. Summary of Significant Accounting Policies

The consolidated financial statements of the Company have been prepared in accordance with International Financial Reporting Standards ("IFRS") and interpretations issued by the IFRS Interpretations Committee applicable to companies reporting under IFRS. The consolidated financial statements comply with IFRS as issued by the International Accounting Standards Board ("IASB"). These consolidated financial statements have been prepared under the historical cost convention.

During the year, the Group has adopted all of the new and revised standards, amendments and interpretations issued by the IASB that are relevant to the Group's operations and mandatory for annual periods beginning January 1, 2021. The adoption of these new and revised standards, amendments and interpretations did not have any material effects on the Group's results of operations or financial position.

The following standards, amendments and interpretations were issued but not yet effective for the financial year ended December 31, 2021 and have not been early adopted by the Group:

IFRS 3 (Amendments)[1]	Reference to the Conceptual Framework
IAS 16 (Amendments)[1]	Property, Plant and Equipment: Proceeds before Intended Use
IAS 37 (Amendments)[1]	Onerous Contracts – Costs of Fulfilling a Contract
Annual improvement 2018-2020[1]	Improvements to IFRSs
IAS 1[2]	Disclosure Initiative-Accounting Policies
IAS 1 (Amendments)[2]	Classification of Liabilities as Current or Non-current
IAS 8 (Amendments)[2]	Definition of Accounting Estimates
IAS 12 (Amendments)[2]	Deferred Tax related to Assets and Liabilities arising from a Single Transaction
IFRS 17[2]	Insurance Contracts
IFRS 10 and IAS 28 (Amendments)[3]	Sale or Contribution of Assets between an Investor and its Associate or Joint Venture

(1) Effective for the Group for annual periods beginning on or after January 1, 2022.

(2) Effective for the Group for annual periods beginning on or after January 1, 2023.

(3) Effective date to be determined by the IASB.

The adoption of standards, amendments and interpretations listed above in future periods is not expected to have any material effects on the Group's results of operations or financial position.

(a) Basis of Consolidation

The consolidated financial statements of the Group include the financial statements of the Company and its subsidiaries.

The accounting policies of subsidiaries have been changed where necessary to ensure consistency with the policies adopted by the Group.

Intercompany transactions, balances and unrealized gains on transactions between group companies are eliminated. Unrealized losses are also eliminated unless the transaction provides evidence of an impairment of the transferred asset.

(b) Subsidiaries

Subsidiaries are all entities over which the Group has control. The Group controls an entity when the Group is exposed, or has rights, to variable returns from its involvement with the entity and has the ability to affect those returns through its power to direct the activities of the entity. In the consolidated financial statements, subsidiaries are accounted for as described in Note 2(a) above.

Subsidiaries are fully consolidated from the date on which control is transferred to the Group. They are de-consolidated from the date that control ceases.

(c) Foreign Currency Translation

Items included in the financial statements of each of the Group's companies are measured using the currency of the primary economic environment in which the entity operates (the "functional currency"). The functional currency of the Company and its subsidiaries is Renminbi ("RMB") whereas the consolidated financial statements are presented in US$, which is the Company's presentation currency.

Foreign currency transactions are translated into the functional currency using the exchange rates at the dates of the transactions. Foreign currency gains and losses resulting from the settlement of such transactions and from the translation of monetary assets and liabilities denominated in foreign currencies at year end exchange rates are generally recognized in the consolidated income statements.

The financial statements of the Company and its subsidiaries are translated into the Company's presentation currency using the year end rates of exchange for the statements of financial position items and the average rates of exchange for the year for the income statement items. Exchange translation differences are recognized directly in other comprehensive income.

(d) Property, Plant and Equipment

Property, plant and equipment other than construction in progress are stated at historical cost less accumulated depreciation and any accumulated impairment losses. Historical cost includes the purchase price of the asset and any directly attributable costs of bringing the asset to its working condition and location for its intended use.

Subsequent costs are included in the asset's carrying amount or recognized as a separate asset, as appropriate, only when it is probable that future economic benefits associated with the item will flow to the Group and the cost of the item can be measured reliably. All other repairs and maintenance are charged to the consolidated income statements during the financial period in which they are incurred.

Depreciation is calculated using the straight-line method to allocate asset costs less accumulated impairment losses over their estimated useful lives. The principal estimated useful lives are as follows:

Buildings	20 years
Leasehold improvements	Over the unexpired period of the lease or 5 years, whichever is shorter
Plant and equipment	10 years
Furniture and fixtures, other equipment and motor vehicles	5 years

The assets' useful lives are reviewed and adjusted, if appropriate, at the end of each reporting period. An asset's carrying amount is written down immediately to its recoverable amount if the asset's carrying amount is greater than its estimated recoverable amount.

Gains and losses on disposals are determined by comparing net sales proceeds with the carrying amount of the relevant assets and are recognized in the consolidated income statements.

(e) Construction in Progress

Construction in progress represents buildings, plant and machinery under construction and pending installation and is stated at cost less accumulated impairment losses, if any. Cost includes the costs of construction of buildings and the costs of plant and machinery. No provision for depreciation is made on construction-in-progress until such time as the relevant assets are completed and ready for its intended use. When the assets concerned are brought into use, the costs are transferred to property, plant and equipment and depreciated in accordance with the policy as stated in Note 2(d).

(f) Other Intangible Asset

The Group's other intangible asset represents promotion and marketing rights. Other intangible asset has a definite useful life and is carried at historical cost less accumulated amortization and accumulated impairment losses, if any. Amortization is calculated using the straight-line method to allocate its cost over its estimated useful life of ten years.

(g) Research and Development

Research expenditure is recognized as an expense as incurred. Costs incurred on development projects (relating to the design and testing of new or improved products) are recognized as intangible assets when it is probable that the project will generate future economic benefits by considering its commercial and technological feasibility, and costs can be measured reliably. Other development expenditures are recognized as an expense as incurred. Development costs previously recognized as an expense are not recognized as an asset in a subsequent period. Development costs with a finite useful life that have been capitalized, if any, are amortized on a straight-line basis over the period of expected benefit not exceeding five years. The capitalized development costs are reviewed for impairment whenever events or changes in circumstances indicate that the carrying amount of an asset exceeds its recoverable amount.

Where the research phase and the development phase of an internal project cannot be clearly distinguished, all expenditure incurred on the project is charged to the consolidated income statements.

(h) Impairment of Non-Financial Assets

Assets are reviewed for impairment to determine whether there is any indication that the carrying value of these assets may not be recoverable and have suffered an impairment loss. If any such indication exists, the recoverable amount of the asset is estimated in order to determine the extent of the impairment loss, if any. The recoverable amount is the higher of an asset's fair value less costs to sell and value in use. Such impairment loss is recognized in the consolidated income statements. Assets that have an indefinite useful life such as goodwill or intangible assets not ready to use are not subject to amortization and are tested for impairment annually and when there are indications that the carrying value may not be recoverable.

(i) Inventories

Inventories are stated at the lower of cost or net realizable value. Cost is determined using the weighted average cost method. The cost of finished goods comprises raw materials, direct labor, other direct costs and related production overheads (based on normal operating capacity). Net realizable value is the estimated selling price in the ordinary course of business, less applicable variable selling expenses.

(j) Trade and Other Receivables

Trade and other receivables are recognized initially at fair value, which is the amount of consideration that is unconditional. Trade and other receivables solely represent payments of principal and interest, if any, and the Group holds such financial assets with the objective to collect its contractual cash flows. Therefore, the Group measures them subsequently at amortized cost using the effective interest method, less any loss allowance. The Group applies the IFRS 9 simplified approach to measuring expected credit losses which uses a lifetime expected loss allowance for all trade receivables. To measure the expected credit losses, trade receivables have been grouped based on shared credit risk characteristics and the days past due. All other receivables at amortized cost are considered to have low credit risk, and the loss allowance recognized during the period was therefore limited to 12 months expected losses. The amount of the provision is recognized in the consolidated income statements.

(k) Cash and Cash Equivalents

In the consolidated statements of cash flows, cash and cash equivalents include cash on hand, bank deposits and other short-term highly liquid investments with original maturities of three months or less that are readily convertible to known amounts of cash and which are subject to an insignificant risk of changes in value, if any.

(l) Financial Liabilities and Equity Instruments

Financial liabilities and equity instruments issued by the Group are classified according to the substance of the contractual arrangements entered into and the definitions of a financial liability and an equity instrument. Financial liabilities (including trade and other payables) are initially measured at fair value, and are subsequently measured at amortized cost, using the effective interest method. An equity instrument is any contract that does not meet the definition of a financial liability and evidences a residual interest in the assets of the Group after deducting all of its liabilities.

Ordinary shares are classified as equity. Incremental costs, net of tax, directly attributable to the issue of new shares are shown in equity as a deduction from the proceeds.

(m) Current and Deferred Income Tax

(i) Current income tax

The current income tax charge is calculated on the basis of the tax laws enacted or substantively enacted at the balance sheet date in the country where the Group operates and generates taxable income. Management periodically evaluates positions taken in tax returns with respect to situations in which applicable tax regulation is subject to interpretation. It establishes provisions where appropriate on the basis of amounts expected to be paid to the tax authorities.

(ii) Deferred income tax

Inside basis differences

Deferred income tax is recognized, using the liability method, on temporary differences arising between the tax bases of assets and liabilities and their carrying amounts in the consolidated financial statements. However, deferred tax liabilities are not recognized if they arise from the initial recognition of goodwill and deferred income tax is not accounted for if it arises from initial recognition of an asset or liability in a transaction other than a business combination that at the time of the transaction affects neither accounting nor taxable profit or loss. Deferred income tax is determined using tax rates (and laws) that have been enacted or substantively enacted by the balance sheet date and are expected to apply when the related deferred income tax asset is realized or the deferred income tax liability is settled.

Deferred income tax assets are recognized only to the extent that it is probable that future taxable profit will be available against which the temporary differences can be utilized. Deferred income tax assets and deferred income tax liabilities are offset when there is a legally enforceable right to set off and when the deferred income taxes related to the same fiscal authority.

Outside basis differences

Deferred income tax liabilities are provided on taxable temporary differences arising from investments in subsidiaries, except for deferred income tax liabilities where the timing of the reversal of the temporary difference is controlled by the Group and it is probable that the temporary difference will not reverse in the foreseeable future.

Deferred income tax assets are recognized on deductible temporary differences arising from investments in subsidiaries, only to the extent that it is probable the temporary difference will reverse in the future and there is sufficient taxable profit available against which the temporary difference can be utilized.

(n) Employee Benefits

The employees of the Group participate in defined contribution retirement benefit plans managed by the relevant municipal and provincial governments in the PRC. The assets of these plans are held separately from the Group. The Group is required to make monthly contributions to the plans calculated as a percentage of the employees' salaries. The municipal and provincial governments undertake to assume the retirement benefit obligations to all existing and future retired employees under the plans described above. Other than the monthly contributions, the Group has no further obligations for the payment of the retirement and other post-retirement benefits of its employees.

(o) Provisions

Provisions are recognized when the Group has a present legal or constructive obligation as a result of past events, it is probable that an outflow of resources will be required to settle the obligation, and the amount has been reliably estimated. Provisions are not recognized for future operating losses.

(p) Leases

A lease is recognized as a right-of-use asset with a corresponding liability at the date which the leased asset is available for use by the Group. The Group recognizes an obligation to make lease payments equal to the present value of the lease payments over the lease term. The lease terms may include options to extend or terminate the lease when it is reasonably certain that the Group will exercise that option.

Lease liabilities include the net present value of the following lease payments: (i) fixed payments; (ii) variable lease payments that depend on an index or a rate; and (iii) payments of penalties for terminating the lease if the lease term reflects the lessee exercising that option, if any. Lease liabilities exclude the following payments that are generally accounted for separately: (i) non-lease components, such as maintenance and security service fees and value added tax, and (ii) any payments that a lessee makes before the lease commencement date. The lease payments are discounted using the interest rate implicit in the lease or if that rate cannot be determined, the lessee's incremental borrowing rate being the rate that the lessee would have to pay to borrow the funds in its currency and jurisdiction necessary to obtain an asset of similar value, economic environment and terms and conditions.

An asset representing the right to use the underlying asset during the lease term is recognized that consists of the initial measurement of the lease liability, any lease payments made to the lessor at or before the commencement date less any lease incentives received, any initial direct cost incurred by the Group and any restoration costs.

After commencement of the lease, each lease payment is allocated between lease liability and finance costs. The finance costs are recognized over the lease term so as to produce a constant periodic rate of interest on the remaining balance of the lease liability for each period. The right-of-use asset is depreciated on a straight-line basis over the period of the lease.

Payments associated with short-term leases are recognized as lease expenses on a straight-line basis over the period of the leases.

Leasehold land is accounted under IFRS 16.

(q) Government Incentives

Incentives from government are recognized at their fair values where there is a reasonable assurance that the incentives will be received and all attached conditions will be complied with.

Government incentives relating to costs are deferred and recognized in the consolidated income statements over the period necessary to match them with the costs that they are intended to compensate.

Government grants relating to property, plant and equipment are included in other payables, accruals and advance receipts and non-current liabilities as deferred income and credited to the consolidated income statements on a straight-line basis over the expected lives of the related assets.

(r) Revenue and Income Recognition

Revenue is measured based on consideration specified in a contract with a customer, and excludes any sales incentives and amounts collected on behalf of third parties. Taxes assessed by a governmental authority that are both imposed on and concurrent with a specific revenue-producing transaction, that are collected by the Group from a customer, are also excluded from revenue. The Group recognizes revenue when it satisfies a performance obligation by transferring control over a good to a customer.

The Group principally generates revenue from sales of goods. Revenue from sales of goods is recognized when the customer takes possession of the goods. This usually occurs upon completed delivery of the goods to the customer site. The amount of revenue recognized is adjusted for expected sales incentives as stipulated in the contract, which are generally issued to customers as direct discounts at the point-of-sale or indirectly in the form of rebates. Sales incentives are estimated using the expected value method. Additionally, sales are generally made with a limited right of return under certain conditions. Revenues are recorded net of provisions for sales discounts and returns.

Revenue from provision of services is recognized when the benefits of the services transfer to the customer over time, which is based on the proportionate value of services rendered as determined under the terms of the relevant contract. Additionally, when the amounts that can be invoiced correspond directly with the value to the customer for performance completed to date, the Group recognizes revenue from provision of services based on amounts that can be invoiced to the customer.

Payments in advance from customers are deferred if consideration is received in advance of transferring control of the goods or rendering of services. Accounts receivable is recognized if the Group has an unconditional right to bill the customer, which is generally when the customer takes possession of the goods or services are rendered. Payment terms differ by subsidiary and customer, but generally range from 45 to 180 days from the invoice date.

(s) Interest Income

Interest income is recognized on a time-proportion basis using the effective interest method.

(t) Segment Reporting

Operating segments are reported in a manner consistent with the internal reporting provided to the chief operating decision makers. The Company’s Board of Directors, which is responsible for allocating resources and assessing performance of the operating segments, has been identified as the steering committee that makes strategic decisions.

(u) General Reserves

In accordance with the laws applicable to Foreign Investment Enterprises established in the PRC, the Company makes appropriations to certain non-distributable reserve funds including the general reserve fund, the enterprise expansion fund and the staff bonus and welfare fund. The amount of appropriations to these funds are made at the discretion of the Company’s Board of Directors.

3. Financial Risk Management

(a) Financial risk factors

The Group's activities expose it to a variety of financial risks, including credit risk and liquidity risk. The Group does not use any derivative financial instruments for speculative purposes.

(i) Credit risk

The carrying amounts of cash and cash equivalents, trade receivables (including bills receivables) and other receivables included in the consolidated statements of financial position represent the Group's maximum exposure to credit risk of the counterparty in relation to its financial assets.

Substantially all of the Group's cash and cash equivalents are deposited in major financial institutions, which management believes are of high credit quality. The Group has a practice to limit the amount of credit exposure to any financial institution.

Bills receivables are mostly settled by state-owned banks or other reputable banks and therefore the management considers that they will not expose the Group to any significant credit risk.

The Group has no significant concentrations of credit risk. The Group has policies in place to ensure that the sales of products are made to customers with appropriate credit history and the Group performs periodic credit evaluations of its customers.

Management periodically assesses the recoverability of trade receivables and other receivables. The Group's historical loss rates are adjusted to reflect current and forward-looking information on specific factors affecting the ability of the customers to settle the receivables, and historical experience collecting receivables falls within the recorded allowances.

(ii) Liquidity risk

Prudent liquidity management implies maintaining sufficient cash and cash equivalents and the availability of funding when necessary. The Group's policy is to regularly monitor current and expected liquidity requirements to ensure that it maintains sufficient cash balances and adequate credit facilities to meet its liquidity requirements in the short and long term.

As at December 31, 2021 and 2020, the Group's current financial liabilities were mainly due for settlement within twelve months and the Group expects to meet all liquidity requirements.

(b) Capital risk management

The Group's objectives when managing capital are to safeguard the Group's ability to provide returns for shareholders and benefits for other stakeholders and to maintain an optimal capital structure to reduce the cost of capital.

The Group regularly reviews and manages its capital structure to ensure an optimal balance between higher shareholders' return that might be possible with higher levels of borrowings and the advantages and security afforded by a sound capital position, and makes adjustments to the capital structure in light of changes in economic conditions.

The Group monitors capital on the basis of the liabilities to assets ratio. This ratio is calculated as total liabilities divided by total assets as shown on the consolidated statements of financial position.

Currently, it is the Group's strategy to maintain a reasonable liabilities to assets ratio. The liabilities to assets ratio as at December 31, 2021 and 2020 was as follows:

	December 31,	
	2021	2020
	(in US$'000)	
Total liabilities	136,124	116,612
Total assets	281,817	269,320
Liabilities to assets ratio	48.3 %	43.3 %

(c) Fair value estimation

The Group does not have any financial assets or liabilities which are carried at fair value. The carrying amounts of the Group's current financial assets, including cash and cash equivalents, trade and bills receivables and other receivables, and current financial liabilities, including trade payables and other payables and accruals, approximate their fair values due to their short-term maturities. The carrying amounts of the Group's financial instruments carried at cost or amortized cost are not materially different from their fair values.

The face values less any estimated credit adjustments for financial assets and liabilities with a maturity of less than one year are assumed to approximate their fair values. The fair value of financial liabilities for disclosure purposes is estimated by discounting the future contractual cash flows at the current market interest rate that is available to the Group for similar financial instruments.

4. Critical Accounting Estimates and Judgements

Note 2 includes a summary of the significant accounting policies used in the preparation of the consolidated financial statements. The preparation of consolidated financial statements often requires the use of judgements to select specific accounting methods and policies from several acceptable alternatives. Furthermore, significant estimates and assumptions concerning the future may be required in selecting and applying those methods and policies in the consolidated financial statements. The Group bases its estimates and judgements on historical experience and various other assumptions that it believes are reasonable under the circumstances. Actual results may differ from these estimates and judgements under different assumptions or conditions.

The following is a review of the more significant assumptions and estimates, as well as the accounting policies and methods used in the preparation of the consolidated financial statements.

(a) Sales rebates

Certain sales rebates are provided to customers when their business performance for an agreed period within the year and the whole year meets certain criteria as stipulated in the contracts. Sales rebates are considered variable consideration and the estimate of sales rebates during the year is based on estimated sales transactions for the entire period stipulated and is subject to change based on actual performance and collection status.

(b) Useful lives of property, plant and equipment

The Group has made substantial investments in property, plant and equipment. Changes in technology or changes in the intended use of these assets may cause the estimated period of use or value of these assets to change.

(c) Deferred income tax

Deferred tax is recognized using the liability method on temporary differences arising between the tax bases of assets and liabilities against which the deductible temporary differences and the carry forward of unused tax losses and tax credits can be utilized. Deferred income tax assets are recognized only to the extent that it is probable that future taxable profit will be available against which the temporary differences can be utilized. Where the final outcomes are different from the estimations, such differences will impact the carrying amount of deferred tax in the period in which such determination is made.

5. Revenue and Segment Information

Management has reviewed the Group's internal reporting in order to assess performance and allocate resources, and has determined that the Group has two reportable operating segments as follows:

—Manufacturing business—manufacture and distribution of drug products

—Distribution business—provision of sales, distribution and marketing services to pharmaceutical manufacturers

The operating segments are strategic business units that offer different products and services. They are managed separately because each business requires different technology and marketing approaches. The performance of each of the reportable segments is assessed based on a measure of operating profit/(loss).

The segment information is as follows:

	Year Ended December 31, 2021		
	Manufacturing business PRC	Distribution business PRC	Total
		(in US$'000)	
Revenue from external customers	331,097	1,551	332,648
Interest income	629	587	1,216
Operating profit/(loss)	107,361	(1,961)	105,400
Finance costs	114	2	116
Depreciation/amortization	9,118	50	9,168
Additions to non-current assets (other than financial instruments and deferred tax assets)	5,867	82	5,949

	December 31, 2021		
	Manufacturing business PRC	Distribution business PRC	Total
		(in US$'000)	
Total segment assets	280,632	1,185	281,817

	Year Ended December 31, 2020		
	Manufacturing business PRC	Distribution business PRC	Total
		(in US$'000)	
Revenue from external customers	270,954	5,400	276,354
Interest income	396	579	975
Operating profit/(loss)	78,069	(204)	77,865
Finance costs	11	1	12
Depreciation/amortization	8,670	65	8,735
Additions to non-current assets (other than financial instruments and deferred tax assets)	3,037	57	3,094

	December 31, 2020		
	Manufacturing business PRC	Distribution business PRC	Total
		(in US$'000)	
Total segment assets	261,965	7,355	269,320

	Year Ended December 31, 2019		
	Manufacturing business	Distribution business	
	PRC	PRC	Total
		(in US$'000)	
Revenue from external customers	260,986	11,096	272,082
Interest income	300	282	582
Operating profit/(loss)	74,319	(1,961)	72,358
Finance costs	33	9	42
Depreciation/amortization	7,913	185	8,098
Additions to non-current assets (other than financial instruments and deferred tax assets)	2,958	17	2,975

Revenue from external customers is after elimination of inter-segment sales. The amount eliminated was US$77.8 million for 2021 (2020: US$62.2 million; 2019: US$60.8 million). Sales between segments are carried out at mutually agreed terms. Revenue from external customers from the manufacturing business is for sales of goods which are recognized at a point in time. Revenue from external customers from the distribution business is for provision of services which are recognized over time.

6. Other Net Operating Income

	Year Ended December 31,		
	2021	2020	2019
		(in US$'000)	
Interest income	1,216	975	582
Net foreign exchange gain/(loss)	25	70	(20)
Government Incentives	2,999	2,601	2,370
Other operating income/(loss)	519	(173)	9
	4,759	3,473	2,941

7. Operating Profit

	Year Ended December 31,		
	2021	2020	2019
		(in US$'000)	
Operating profit	105,400	77,865	72,358

Operating profit is stated after charging/(crediting) the following:

	Year Ended December 31,		
	2021	2020	2019
		(in US$'000)	
Cost of inventories recognized as expense	50,637	47,299	55,653
Research and development expense	9,350	6,301	4,422
Depreciation of property, plant and equipment	8,100	7,878	7,148
Loss/(Gain) on disposal of property, plant and equipment	60	(2)	11
Amortization of leasehold land	172	160	161
Amortization of other intangible asset	233	217	218
Depreciation charge of right-of-use assets and lease expenses	663	725	724
Movement on the provision for trade receivables	—	(9)	9
Provision for excess and obsolete inventories	(141)	2,447	1,062
Auditor's remuneration	223	198	194
Employee benefit expenses (Note 9)	100,311	80,728	80,647

8. Taxation Charge

	Year Ended December 31,		
	2021	2020	2019
		(in US$'000)	
Current tax	15,082	12,520	10,300
Deferred income tax (Note 16)	814	(1,687)	715
Taxation charge	15,896	10,833	11,015

The taxation charge on the Group's profit before taxation differs from the theoretical amount that would arise using the Group's weighted average tax rate as follows:

	Year Ended December 31,		
	2021	2020	2019
		(in US$'000)	
Profit before taxation	105,284	77,853	72,316
Tax calculated at the statutory tax rates of respective companies	26,321	19,463	18,079
Tax effects of:			
Expenses not deductible for tax purposes	1,946	1,137	2,938
Utilization of unrecognized temporary differences	(55)	(938)	(1,669)
Tax concession (note)	(12,420)	(8,753)	(8,541)
Under/(over) provision in prior years	104	(76)	208
Taxation charge	15,896	10,833	11,015

Note: The Company has been granted the High and New Technology Enterprise status. Accordingly, the Company is subject to a preferential income tax rate of 15% in 2021 and up to 2022 (2020: 15%; 2019: 15%). Certain research and development expenses are also eligible for super-deduction such that 200% of qualified expenses incurred are deductible against taxable profits for tax purposes (2020: 175%; 2019: 175%).

The weighted average tax rate calculated at the statutory tax rates of respective companies was 25%.The effective tax rate for the year ended December 31, 2021 was 15.1% (2020: 13.9%; 2019: 15.2%).

9. Employee Benefit Expenses

	Year Ended December 31,		
	2021	2020	2019
		(in US$'000)	
Wages, salaries and bonuses	77,335	68,226	60,353
Pension costs—defined contribution plans	8,713	995	7,689
Staff welfare	14,263	11,507	12,605
	100,311	80,728	80,647

Employee benefit expenses of approximately US$20.1 million for the year ended December 31, 2021 (2020: US$16.4 million; 2019: US$18.8 million) are included in cost of sales.

10. Cash and cash equivalents

	December 31,	
	2021	2020
	(in US$'000)	
Cash and cash equivalents	50,038	72,478

The cash and cash equivalents denominated in RMB were deposited with banks in the PRC. The conversion of these RMB denominated balances into foreign currencies is subject to the rules and regulations of foreign exchange control promulgated by the PRC government.

11. Trade and Bills Receivables

	December 31,	
	2021	2020
	(in US$'000)	
Trade receivables—third parties	9,555	13,996
Trade receivables—related parties (Note 22(b))	649	1,384
Bills receivables	7,278	3,041
	17,482	18,421

All trade and bills receivables are denominated in RMB and are due within one year from the end of the reporting period. The carrying values of trade and bills receivables approximate their fair values due to their short-term maturities.

Movements on the provision for trade receivables are as follows:

	2021	2020	2019
		(in US$'000)	
As at January 1	—	9	—
Increase in provision for trade receivables	—	—	9
Decrease in provision due to subsequent collection	—	(9)	—
As at December 31	—	—	9

12. Other Receivables, Prepayments and Deposits

	December 31,	
	2021	2020
	(in US$'000)	
Prepayments to suppliers	1,929	1,356
Interest receivables	283	171
Deposits	877	1,338
Others	261	527
	3,350	3,392

13. Inventories

	December 31,	
	2021	2020
	(in US$'000)	
Raw materials	54,585	31,501
Work in progress	39,668	32,684
Finished goods	25,137	17,489
	119,390	81,674

14. Property, plant and equipment

	Buildings situated in the PRC	Leasehold improvements	Plant and equipment	Furniture and fixtures, other equipment and motor vehicles	Construction in progress	Total
			(in US$'000)			
Cost						
As at January 1, 2021	73,480	578	25,173	12,273	2,685	114,189
Additions	28	68	535	929	1,453	3,013
Disposals	—	(128)	(207)	(481)	(1,230)	(2,046)
Transfers	224	314	298	1,982	(2,818)	—
Exchange differences	1,855	16	639	330	46	2,886
As at December 31, 2021	75,587	848	26,438	15,033	136	118,042
Accumulated depreciation						
As at January 1, 2021	15,699	504	12,288	7,570	1,196	37,257
Depreciation	3,763	100	2,347	1,890	—	8,100
Disposals	—	(128)	(145)	(464)	(1,217)	(1,954)
Transfers	93	(390)	—	297	—	—
Exchange differences	428	8	327	205	21	989
As at December 31, 2021	19,983	94	14,817	9,498	—	44,392
Net book value						
As at December 31, 2021	55,604	754	11,621	5,535	136	73,650

	Buildings situated in the PRC	Leasehold improvements	Plant and equipment	Furniture and fixtures, other equipment and motor vehicles	Construction in progress	Total
			(in US$'000)			
Cost						
As at January 1, 2020	68,213	539	22,606	9,526	2,828	103,712
Additions	—	—	581	935	1,519	3,035
Disposals	—	—	(53)	(134)	—	(187)
Transfers	334	—	361	1,155	(1,850)	—
Exchange differences	4,933	39	1,678	791	188	7,629
As at December 31, 2020	73,480	578	25,173	12,273	2,685	114,189
Accumulated depreciation						
As at January 1, 2020	11,212	383	8,760	5,665	1,116	27,136
Depreciation	3,493	88	2,786	1,511	—	7,878
Disposals	—	—	(35)	(91)	—	(126)
Exchange differences	994	33	777	485	80	2,369
As at December 31, 2020	15,699	504	12,288	7,570	1,196	37,257
Net book value						
As at December 31, 2020	57,781	74	12,885	4,703	1,489	76,932

	Buildings situated in the PRC	Leasehold improvements	Plant and equipment	Furniture and fixtures, other equipment and motor vehicles	Construction in progress	Total
			(in US$'000)			
Cost						
As at January 1, 2019	69,434	480	22,583	7,934	3,508	103,939
Additions	—	73	334	1,511	856	2,774
Disposals	—	—	(41)	(170)	—	(211)
Transfers	620	—	337	500	(1,457)	—
Exchange differences	(1,841)	(14)	(607)	(249)	(79)	(2,790)
As at December 31, 2019	68,213	539	22,606	9,526	2,828	103,712
Accumulated depreciation						
As at January 1, 2019	8,035	300	6,786	4,614	1,146	20,881
Depreciation	3,465	93	2,229	1,361	—	7,148
Disposals	—	—	(28)	(163)	—	(191)
Exchange differences	(288)	(10)	(227)	(147)	(30)	(702)
As at December 31, 2019	11,212	383	8,760	5,665	1,116	27,136
Net book value						
As at December 31, 2019	57,001	156	13,846	3,861	1,712	76,576

15. Leases

Leases consisted of the following:

	December 31,	
	2021	2020
	(in US$'000)	
Right-of-use assets:		
Offices	2,445	152
Lease liabilities—current	700	133
Lease liabilities—non-current	2,148	19
	2,848	152

Lease activities are summarized as follows:

	Year Ended December 31,	
	2021	2020
	(in US$'000)	
Lease expenses: Short-term leases with lease terms equal or less than 12 months	508	245
Depreciation charge of right-of-use assets	663	480
Interest expense (included in finance costs)	116	12
Cash paid on lease liabilities	303	474
Non-cash: Lease liabilities recognized from obtaining right-of-use assets	2,936	58

Lease contracts are typically within a period of 1 to 5 years. The weighted average remaining lease term and weighted average discount rate as at December 31, 2021 was 3.7 years (2020: 0.89 years) and 4.75% (2020: 4.75%) respectively.

Future lease payments are as follows:

	December 31,	
	2021	2020
	(in US$'000)	
Lease payments:		
Not later than 1 year	814	135
Between 1 to 2 years	784	19
Between 2 to 3 years	793	—
Between 3 to 4 years	713	—
Total lease payments	3,104	154
Less: Discount factor	(256)	(2)
Total lease liabilities	2,848	152

16. Deferred Tax Assets

The movements in deferred tax assets are as follows:

	2021	2020	2019
		(in US$'000)	
As at January 1	8,315	6,147	7,091
Credited/(debited) to the consolidated income statements —Accrued expenses, provisions, deferred income, accelerated depreciation and other temporary differences (note)	(814)	1,687	(715)
Exchange differences	214	481	(229)
As at December 31	7,715	8,315	6,147

Note: During the year ended December 31, 2021, the Group utilized US$1.1 million deferred tax assets which was recognized during the year ended December 31, 2019 on temporary differences arising from advertising and promotion expenditures.

The Group's deferred tax assets are mainly temporary differences including accrued expenses, provisions, deferred income, accelerated depreciation and other temporary differences. The potential deferred tax assets in respect of tax losses which have not been recognized in the consolidated financial statements were approximately US$26,000 as at December 31, 2021 (2020: US$0.7 million).

These unrecognized tax losses can be carried forward against future taxable income and will expire in the following years:

	December 31,	
	2021	2020
	(in US$'000)	
2021	—	35
2022	7	7
2023	—	2,550
2024	83	76
2025	7	7
2026	6	—
	103	2,675

17. Trade Payables

	December 31,	
	2021	2020
	(in US$'000)	
Trade payables—third parties	12,030	8,711
Trade payables—related parties (Note 22(b))	381	2,463
	12,411	11,174

All trade payables are denominated in RMB and due within one year from the end of the reporting period. The carrying value of trade payables approximates their fair values due to their short-term maturities.

18. Other Payables, Accruals and Advance Receipts

	December 31,	
	2021	2020
	(in US$'000)	
Accrued salaries and benefits	17,796	17,536
Accrued selling and marketing expenses	68,217	59,930
Value-added tax and tax surcharge payables	9,693	8,794
Payments in advance from customers (note)	11,858	2,750
Others	4,229	4,524
	111,793	93,534

Note: Substantially all customer balances as at December 31, 2020 were recognized to revenue during the year ended December 31, 2021. Additionally, substantially all customer balances as at December 31, 2021 are expected to be recognized to revenue within one year upon transfer of goods or services as the contracts have an expected duration of one year or less.

19. Current Tax Liabilities

	2021	2020	2019
		(in US$'000)	
As at January 1	5,032	2,395	5,671
Current tax (Note 8)	15,082	12,520	10,300
Tax paid	(15,976)	(10,232)	(13,618)
Exchange difference	108	192	42
Transfer (from)/to other receivables	(157)	157	—
As at December 31	4,089	5,032	2,395

20. Notes to the Consolidated Statements of Cash Flows

(a) Reconciliation of profit for the year to net cash generated from operations:

	2021	2020	2019
		(in US$'000)	
Profit for the year	89,388	67,020	61,301
Adjustments to reconcile profit for the year to net cash generated from operations			
Taxation charge	15,896	10,833	11,015
Finance costs	116	12	42
Interest income	(1,216)	(975)	(582)
Depreciation on property, plant and equipment	8,100	7,878	7,148
Loss/(gain) on disposal of property, plant and equipment	60	(2)	11
Amortization of leasehold land	172	160	161
Amortization of other intangible asset	233	217	218
Depreciation charge of right-of-use assets	663	480	571
Provision for excess and obsolete inventories	(141)	2,447	1,062
Movement on the provision for trade receivables	—	(9)	9
Exchange differences	(693)	2,057	(1,439)
Changes in working capital:			
Trade and bills receivables	939	6,360	7,053
Other receivables, prepayments and deposits	(80)	(227)	(218)
Inventories	(37,575)	(11,804)	(8,459)
Trade payables	1,237	905	3,097
Other payables, accruals and advance receipts	18,608	26,511	(3,271)
Deferred income	(1,737)	746	(935)
Total changes in working capital	(18,608)	22,491	(2,733)
Net cash generated from operations	93,970	112,609	76,784

(b) Supplemental disclosure for non-cash activities

During the years ended December 31, 2021, there was a decrease in accruals made for purchases of property, plant and equipment of US$0.3 million (2020 and 2019: an increase of US$0.6 million and a decrease of US$1.8 million respectively).

21. Capital commitments

The Group had the following capital commitments:

	December 31, 2021
	(in US$'000)
Property, plant and equipment	
Contracted but not provided for	155

Capital commitments for property, plant and equipment are mainly for improvements to the Group's plant.

22. Significant Related Party Transactions

The Group has the following significant transactions with related parties which were carried out in the normal course of business at terms determined and agreed by the relevant parties:

(a) Transactions with related parties:

	Year Ended December 31,		
	2021	2020	2019
		(in US$'000)	
Sales of goods to:			
—A fellow subsidiary of SHTCML	12,181	10,465	12,459
—A fellow subsidiary of SHHCMI(HK)L	3,492	2,854	2,255
	15,673	13,319	14,714
Purchase of goods from:			
—SHTCML	10,002	7,922	4,609
—Fellow subsidiaries of SHTCML	1,311	1,016	3,263
	11,313	8,938	7,872
Rendering of research and development services from:			
—A fellow subsidiary of SHHCMI(HK)L	525	491	494
Provision of marketing services to:			
—A fellow subsidiary of SHTCML	1,146	2,781	5,045
—A fellow subsidiary of SHHCMI(HK)L	—	—	2,682
	1,146	2,781	7,727
Leasing office from:			
—SHTCML	247	337	335

No transactions have been entered into with the directors of the Company (being the key management personnel) during the year ended December 31, 2021 (2020 and 2019: nil).

(b) Balances with related parties included in:

	December 31,	
	2021	2020
	(in US$'000)	
Trade and bills receivables		
—A fellow subsidiary of SHTCML	649	1,384
Other receivables, prepayments and deposits		
—A fellow subsidiary of SHTCML	547	946
Right-of-use assets		
—SHTCML	—	87
Trade payables		
—SHTCML	—	2,054
— Fellow subsidiaries of SHTCML	381	409
	381	2,463
Other payables, accruals and advance receipts		
—Fellow subsidiaries of SHHCMI(HK)L	1,149	986
Lease liabilities		
—SHTCML	—	94

Balances with related parties are unsecured, interest-free and repayable on demand. The carrying values of balances with related parties approximate their fair values due to their short-term maturities.

23. Particulars of Principal Subsidiaries

Name	Place of establishment and operation	Nominal value of registered capital		Equity interest attributable to the Group		Type of legal entity	Principal activity
		December 31,					
		2021	2020	2021	2020		
		(in RMB'000)					
Shanghai Shangyao Hutchison Whampoa GSP Company Limited	PRC	20,000	20,000	100 %	100 %	Limited liability company	Distribution of drug products
Hutchison Heze Bio Resources & Technology Co., Limited	PRC	1,500	1,500	100 %	100 %	Limited liability company	Agriculture and sales of Chinese herbs

24. Subsequent Events

The Group evaluated subsequent events through March 3, 2022, which is the date when the consolidated financial statements were issued.

HUTCHISON WHAMPOA GUANGZHOU BAIYUNSHAN CHINESE MEDICINE COMPANY LIMITED

Report of Independent Auditors

To the Board of Directors and Shareholders of Hutchison Whampoa Guangzhou Baiyunshan Chinese Medicine Company Limited

We have audited the accompanying consolidated financial statements of Hutchison Whampoa Guangzhou Baiyunshan Chinese Medicine Company Limited and its subsidiaries (the "Company"), which comprise the consolidated statements of financial position as of September 28, 2021 and December 31, 2020, and the related consolidated income statements, consolidated statements of comprehensive income, of changes in equity and of cash flows for the period from January 1, 2021 to September 28, 2021 and each of the two years in the period ended December 31, 2020.

Management's Responsibility for the Consolidated Financial Statements

Management is responsible for the preparation and fair presentation of the consolidated financial statements in accordance with the basis of preparation mentioned in Note 2(1) to the accompanying consolidated financial statements; this includes the design, implementation, and maintenance of internal control relevant to the preparation and fair presentation of consolidated financial statements that are free from material misstatement, whether due to fraud or error.

Auditors' Responsibility

Our responsibility is to express an opinion on the consolidated financial statements based on our audits. We conducted our audits in accordance with auditing standards generally accepted in the United States of America. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the consolidated financial statements are free from material misstatement.

An audit involves performing procedures to obtain audit evidence about the amounts and disclosures in the consolidated financial statements. The procedures selected depend on our judgment, including the assessment of the risks of material misstatement of the consolidated financial statements, whether due to fraud or error. In making those risk assessments, we consider internal control relevant to the Company's preparation and fair presentation of the consolidated financial statements in order to design audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control. Accordingly, we express no such opinion. An audit also includes evaluating the appropriateness of accounting policies used and the reasonableness of significant accounting estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. We believe that the audit evidence we have obtained is sufficient and appropriate to provide a basis for our audit opinion.

Opinion

In our opinion, the consolidated financial statements referred to above present fairly, in all material respects, the financial position of Hutchison Whampoa Guangzhou Baiyunshan Chinese Medicine Company Limited and its subsidiaries as of September 28, 2021 and December 31, 2020, and the results of their operations and their cash flows for the period from January 1, 2021 to September 28, 2021, and each of the two years in the period ended December 31, 2020 in accordance with the basis of preparation mentioned in Note 2(1) to the accompanying consolidated financial statements.

Emphasis of Matter

We draw attention to Note 2(1) to the accompanying consolidated financial statements, which describes the basis of preparation. On September 28, 2021, an intermediate holding company under HUTCHMED (China) Limited which wholly-owned Guangzhou Hutchison Chinese Medicine (HK) Investment Limited ("GZHCMHK"), sold its entire shareholding in GZHCMHK which jointly controls Hutchison Whampoa Guangzhou Baiyunshan Chinese Medicine Company Limited, to a third party. Our opinion is not modified with respect of this matter.

/s/ PricewaterhouseCoopers Zhong Tian LLP
Guangzhou, the People's Republic of China
December 7, 2021

Hutchison Whampoa Guangzhou Baiyunshan Chinese Medicine Company Limited
Consolidated Income Statements
(in US$'000)

	Note	Period from January 1, 2021 to September 28, 2021	Year Ended December 31, 2020	2019
Revenue	5	209,528	232,368	215,403
Cost of sales		(98,462)	(115,564)	(100,279)
Gross profit		111,066	116,804	115,124
Selling expenses		(74,425)	(74,066)	(74,013)
Administrative expenses		(21,659)	(25,664)	(23,817)
Other net operating income	6	5,306	6,071	5,626
Operating profit	7	**20,288**	**23,145**	**22,920**
Share of profits/(losses) of a joint venture and associated companies, net of tax		29	(84)	60
Finance costs		(24)	(57)	(59)
Gain on return of land	8	16,433	84,667	—
Gain on divestment of a subsidiary		—	37	—
Profit before taxation		**36,726**	**107,708**	**22,921**
Taxation charge	9	(4,840)	(16,494)	(3,634)
Profit for the period/year		**31,886**	**91,214**	**19,287**
Attributable to:				
Shareholders of the Company		31,850	91,276	19,792
Non-controlling interests		36	(62)	(505)
		31,886	91,214	19,287

The accompanying notes are an integral part of these consolidated financial statements.

Hutchison Whampoa Guangzhou Baiyunshan Chinese Medicine Company Limited
Consolidated Statements of Comprehensive Income
(in US$'000)

	Period from January 1, 2021 to September 28, 2021	Year Ended December 31, 2020	2019
Profit for the period/year	**31,886**	**91,214**	**19,287**
Other comprehensive income/(loss) that has been or may be reclassified subsequently to profit or loss:			
Exchange translation differences	1,393	4,728	(3,353)
Total comprehensive income	**33,279**	**95,942**	**15,934**
Attributable to:			
Shareholders of the Company	33,237	95,976	16,529
Non-controlling interests	42	(34)	(595)
	33,279	95,942	15,934

The accompanying notes are an integral part of these consolidated financial statements.

Hutchison Whampoa Guangzhou Baiyunshan Chinese Medicine Company Limited
Consolidated Statements of Financial Position
(in US$'000)

	Note	September 28, 2021	December 31, 2020
Assets			
Current assets			
Cash and cash equivalents	11	73,616	16,602
Trade and bills receivables	12	27,874	67,417
Other receivables, prepayments and deposits	13	26,547	50,121
Inventories	14	62,400	43,748
Total current assets		**190,437**	**177,888**
Property, plant and equipment	15	58,619	60,181
Right-of-use assets	16	420	820
Leasehold land		19,657	8,419
Goodwill		8,825	8,751
Other intangible assets		1,798	2,108
Investments in a joint venture and associated companies		618	584
Deferred tax assets	17	4,420	3,141
Other non-current assets	18	46	11,689
Total assets		**284,840**	**273,581**
Liabilities and shareholders' equity			
Current liabilities			
Trade payables	19	19,048	22,579
Other payables, accruals and advance receipts	20	80,484	98,861
Dividend payable	24(b)	105,774	—
Lease liabilities	16	452	568
Current tax liabilities		16,681	15,171
Total current liabilities		**222,439**	**137,179**
Deferred tax liabilities	17	—	114
Deferred income	21	14,913	15,617
Lease liabilities	16	—	303
Total liabilities		**237,352**	**153,213**
Company's shareholders' equity			
Share capital		24,103	24,103
Reserves		22,361	95,283
Total Company's shareholders' equity		**46,464**	**119,386**
Non-controlling interests		1,024	982
Total shareholders' equity		**47,488**	**120,368**
Total liabilities and shareholder's equity		**284,840**	**273,581**

The accompanying notes are an integral part of these consolidated financial statements.

Hutchison Whampoa Guangzhou Baiyunshan Chinese Medicine Company Limited
Consolidated Statements of Changes in Equity
(in US$'000)

	Attributable to shareholders of the Company						
	Share capital	Exchange reserve	General reserves	Retained earnings	Total	Non-controlling interests	Total equity
As at January 1, 2019	**24,103**	**1,220**	**131**	**96,487**	**121,941**	**3,113**	**125,054**
Profit/(loss) for the year	—	—	—	19,792	19,792	(505)	19,287
Other comprehensive loss							
Exchange translation differences	—	(3,263)	—	—	(3,263)	(90)	(3,353)
Total comprehensive (loss)/income	—	(3,263)	—	19,792	16,529	(595)	15,934
Dividends declared to shareholders	—	—	—	(93,957)	(93,957)	—	(93,957)
As at December 31, 2019	**24,103**	**(2,043)**	**131**	**22,322**	**44,513**	**2,518**	**47,031**
Profit/(loss) for the year	—	—	—	91,276	91,276	(62)	91,214
Other comprehensive income							
Exchange translation differences	—	4,700	—	—	4,700	28	4,728
Total comprehensive income/(loss)	—	4,700	—	91,276	95,976	(34)	95,942
Dividends declared to shareholders	—	—	—	(20,756)	(20,756)	—	(20,756)
Acquisition of additional interest in a subsidiary	—	(9)	(131)	(207)	(347)	(1,537)	(1,884)
Divestment of a subsidiary to non-controlling interest	—	—	—	—	—	35	35
As at December 31, 2020	**24,103**	**2,648**	**—**	**92,635**	**119,386**	**982**	**120,368**
Profit for the period	—	—	—	31,850	31,850	36	31,886
Other comprehensive income							
Exchange translation differences	—	1,387	—	—	1,387	6	1,393
Total comprehensive income	—	1,387	—	31,850	33,237	42	33,279
Dividends declared to shareholders	—	—	—	(106,159)	(106,159)	—	(106,159)
As at September 28, 2021	**24,103**	**4,035**	**—**	**18,326**	**46,464**	**1,024**	**47,488**

The accompanying notes are an integral part of these consolidated financial statements.

Hutchison Whampoa Guangzhou Baiyunshan Chinese Medicine Company Limited
Consolidated Statements of Cash Flows
(in US$'000)

	Note	Period from January 1, 2021 to September 28, 2021	Year Ended December 31, 2020	2019
Operating activities				
Net cash generated from operations	22(a)	17,785	60,756	26,237
Interest received		205	271	160
Finance costs paid		(24)	(57)	(59)
Income tax paid		(4,825)	(4,013)	(3,363)
Net cash generated from operating activities		13,141	56,957	22,975
Investing activities				
Purchase of property, plant and equipment		(1,998)	(2,342)	(3,377)
Purchase of intangible assets		(4)	—	(356)
Proceeds from return of land	8	46,154	40,422	—
Proceeds from disposal of leasehold land		—	231	—
Proceeds from disposal of property, plant and equipment		—	730	—
Government grants received relating to property, plant and equipment		10	963	950
Net cash generated from/(used in) investing activities		44,162	40,004	(2,783)
Financing activities				
Dividends paid to shareholders		—	(100,842)	(14,615)
Acquisition of additional interest in a subsidiary		—	(1,884)	—
Lease payments	16	(427)	(609)	(556)
Net cash used in financing activities		(427)	(103,335)	(15,171)
Net increase/(decrease) in cash and cash equivalents		56,876	(6,374)	5,021
Effect of exchange rate changes on cash and cash equivalents		138	1,555	(443)
		57,014	(4,819)	4,578
Cash and cash equivalents				
Cash and cash equivalents at beginning of period/year		16,602	21,421	16,843
Cash and cash equivalents at end of period/year		73,616	16,602	21,421

The accompanying notes are an integral part of these consolidated financial statements.

Hutchison Whampoa Guangzhou Baiyunshan Chinese Medicine Company Limited
Notes to the Consolidated Financial Statements

1. General Information

Hutchison Whampoa Guangzhou Baiyunshan Chinese Medicine Company Limited (the "Company") and its subsidiaries (together the "Group") are principally engaged in manufacturing, selling and distribution of over-the-counter drug products. The Group has manufacturing plants in the People's Republic of China (the "PRC") and sells mainly in the PRC.

The Company was incorporated in the PRC on April 12, 2005 as a Chinese-Foreign Equity joint venture. The Company is jointly controlled by Guangzhou Hutchison Chinese Medicine (HK) Investment Limited ("GZHCMHK") and Guangzhou Baiyunshan Pharmaceutical Holdings Company Limited ("GBPHCL"). On September 28, 2021, an intermediate holding company under HUTCHMED (China) Limited ("HUTCHMED") which wholly-owned GZHCMHK, sold its entire shareholding in GZHCMHK to a third party.

These consolidated financial statements are presented in United States dollars ("US$"), unless otherwise stated and have been approved for issue by the Company's Board of Directors on September 28, 2021.

2. Summary of Significant Accounting Policies

(1) Basis of Preparation

Except for the comparative periods which have been prepared in accordance with the Regulation S-X Rule 3-09 issued by the United States Securities and Exchange Commission ("SEC"), the consolidated financial statements of the Company have been prepared in accordance with International Financial Reporting Standards ("IFRS") and interpretations issued by the IFRS Interpretations Committee applicable to companies reporting under IFRS. The consolidated financial statements comply with IFRS as issued by the International Accounting Standards Board ("IASB"). These consolidated financial statements have been prepared under the historical cost convention.

As at September 28, 2021, the Group was in a net current liabilities position of US$32.0 million, primarily due to the dividend declaration on May 13, 2021 and September 23, 2021 of US$46.5 million and US$59.7 million respectively. Based on the Group's operating plan, the existing cash and cash equivalents along with the expected net cash to be generated from operating activities are considered to be sufficient to meet the cash requirements to fund planned operations and other commitments for at least the next twelve months (the look-forward period used) from the report issue date, and it is appropriate for the Group to prepare the consolidated financial statements on a going concern basis.

(2) Summary of Significant Accounting Policies

During the period, the Group has adopted all of the new and revised standards, amendments and interpretations issued by the IASB that are relevant to the Group's operations and mandatory for annual periods beginning January 1, 2021. The adoption of these new and revised standards, amendments and interpretations did not have any material effects on the Group's results of operations or financial position.

The following standards, amendments and interpretations were issued but not yet effective for the financial period from January 1, 2021 to September 28, 2021 and have not been early adopted by the Group:

IFRS 3 (Amendments)[1]	Reference to the Conceptual Framework
IAS 16 (Amendments)[1]	Property, Plant and Equipment: Proceeds before Intended Use
IAS 37 (Amendments)[1]	Onerous Contracts – Costs of Fulfilling a Contract
Annual improvement 2018-2020[1]	Improvements to IFRSs
IAS 1[2]	Disclosure Initiative – Accounting Policies
IAS 1 (Amendments)[2]	Classification of Liabilities as Current or Non-current
IAS 8 (Amendments)[2]	Definition of Accounting Estimates
IAS 12 (Amendments)[2]	Deferred Tax related to Assets and Liabilities arising from a Single Transaction
IFRS 17[2]	Insurance Contracts
IFRS 10 and IAS 28 (Amendments)[3]	Sale or Contribution of Assets between an Investor and its Associate or Joint Venture

(1) Effective for the Group for annual periods beginning on or after January 1, 2022.

(2) Effective for the Group for annual periods beginning on or after January 1, 2023.

(3) Effective date to be determined by the IASB.

The adoption of standards, amendments and interpretations listed above in future periods is not expected to have any material effects on the Group's results of operations or financial position.

(a) Basis of Consolidation

The consolidated financial statements of the Group include the financial statements of the Company and its subsidiaries, and also include the Group's interests in a joint venture and associated companies on the basis set out in Notes 2(d) and 2(e) below.

The accounting policies of subsidiaries, the joint venture and associated companies have been changed where necessary to ensure consistency with the policies adopted by the Group.

Intercompany transactions, balances and unrealized gains on transactions between group companies are eliminated. Unrealized losses are also eliminated unless the transaction provides evidence of an impairment of the transferred asset.

Non-controlling interests represent the interests of outside shareholders in the operating results and net assets of subsidiaries.

(b) Subsidiaries

Subsidiaries are all entities over which the Group has control. The Group controls an entity when the Group is exposed, or has rights, to variable returns from its involvement with the entity and has the ability to affect those returns through its power to direct the activities of the entity. In the consolidated financial statements, subsidiaries are accounted for as described in Note 2(a) above.

Subsidiaries are fully consolidated from the date on which control is transferred to the Group. They are de-consolidated from the date that control ceases.

(c) Transactions with Non-controlling Interests

Transactions with non-controlling interests that do not result in a loss of control are accounted for as transactions with equity owners of the Group. For purchases from non-controlling interests, the difference between any consideration paid and the relevant share acquired of the carrying value of net assets of the subsidiary is recorded in equity. Gains or losses on disposals to non-controlling interests are also recorded in equity.

(d) Joint Arrangements

Investments in joint arrangements are classified either as joint operations or joint ventures depending on the contractual rights and obligations of each investor. The Group has assessed the nature of its joint arrangement and determined it to be a joint venture. The joint venture is accounted for using the equity method.

Under the equity method of accounting, the interest in joint venture is initially recognized at cost and adjusted thereafter to recognize the Group's share of the post-acquisition profits or losses and movements in other comprehensive income. The Group determines at each reporting date whether there is any objective evidence that the investment in the joint venture is impaired. If this is the case, the Group calculates the amount of impairment as the difference between the recoverable amount of the joint venture and its carrying value and recognizes the amount in the consolidated income statements.

(e) Associated Companies

An associate is an entity, other than a subsidiary or a joint venture, in which the Group has a long-term equity interest and over which the Group is in position to exercise significant influence over its management, including participation in the financial and operating policy decisions.

The results and net assets of associates are incorporated in these financial statements using the equity method of accounting, except when the investment is classified as held for sale, in which case it is accounted for under IFRS 5, Non-current assets held for sale and discontinued operations. The total carrying amount of such investments is reduced to recognize any identified impairment loss in the value of individual investments.

(f) Foreign Currency Translation

Items included in the financial statements of each of the Group's companies are measured using the currency of the primary economic environment in which the entity operates (the "functional currency"). The functional currency of the Company and its subsidiaries, joint venture and associated companies is Renminbi ("RMB") whereas the consolidated financial statements are presented in US$, which is the Company's presentation currency.

Foreign currency transactions are translated into the functional currency using the exchange rates at the dates of the transactions. Foreign currency gains and losses resulting from the settlement of such transactions and from the translation of monetary assets and liabilities denominated in foreign currencies at year end exchange rates are generally recognized in the consolidated income statements.

The financial statements of the Company, subsidiaries, joint venture and associated companies are translated into the Company's presentation currency using the year end rates of exchange for the statements of financial position items and the average rates of exchange for the year for the income statement items. Exchange translation differences are recognized directly in other comprehensive income.

(g) Property, Plant and Equipment

Property, plant and equipment other than construction in progress are stated at historical cost less accumulated depreciation and any accumulated impairment losses. Historical cost includes the purchase price of the asset and any directly attributable costs of bringing the asset to its working condition and location for its intended use.

Subsequent costs are included in the asset's carrying amount or recognized as a separate asset, as appropriate, only when it is probable that future economic benefits associated with the item will flow to the Group and the cost of the item can be measured reliably. All other repairs and maintenance are charged to the consolidated income statements during the financial period in which they are incurred.

Depreciation is calculated using the straight-line method to allocate asset costs less accumulated impairment losses over their estimated useful lives. The principal estimated useful lives are as follows:

Buildings and facilities	10-30 years
Plant and equipment	10 years
Furniture and fixtures, other equipment and motor vehicles	5 years

The assets' useful lives are reviewed and adjusted, if appropriate, at the end of each reporting period. An asset's carrying amount is written down immediately to its recoverable amount if the asset's carrying amount is greater than its estimated recoverable amount.

Gains and losses on disposals are determined by comparing net sales proceeds with the carrying amount of the relevant assets and are recognized in the consolidated income statements.

(h) Construction in Progress

Construction in progress represents buildings, plant and machinery under construction and pending installation and is stated at cost less accumulated impairment losses, if any. Cost includes the costs of construction of buildings and the costs of plant and machinery. No provision for depreciation is made on construction in progress until such time as the relevant assets are completed and ready for its intended use. When the assets concerned are brought into use, the costs are transferred to property, plant and equipment and depreciated in accordance with the policy as stated in Note 2(g).

(i) Goodwill

Goodwill represents the excess of the cost of an acquisition over the fair value of the Group's share of the net identifiable assets of the acquired subsidiary/business at the date of acquisition, or the excess of fair value of business over its fair value of the net identifiable assets injected into the Company upon its formation. If the cost of acquisition is less than the fair value of the Group's share of the net identifiable assets of the acquired subsidiary, the difference is recognized directly in the consolidated income statements.

Goodwill is retained at the carrying amount as a separate asset, and subject to impairment test annually and when there are indications that the carrying value may not be recoverable.

The profit or loss on disposal of a subsidiary is calculated by reference to the net assets at the date of disposal including the attributable amount of goodwill.

(j) Other Intangible Assets

The Group's other intangible assets mainly include distribution network and drugs licenses contributed from non-controlling shareholders. Other intangible assets have a definite useful life and are carried at historical cost less accumulated amortization and accumulated impairment losses, if any. Amortization is calculated using the straight-line method to allocate costs over the estimated useful lives of ten years.

(k) Research and Development

Research expenditure is recognized as an expense as incurred. Costs incurred on development projects (relating to the design and testing of new or improved products) are recognized as intangible assets when it is probable that the project will generate future economic benefits by considering its commercial and technological feasibility, and costs can be measured reliably. Other development expenditures are recognized as an expense as incurred. Development costs previously recognized as an expense are not recognized as an asset in a subsequent period. Development costs with a finite useful life that have been capitalized, if any, are amortized on a straight-line basis over the period of expected benefit not exceeding five years. The capitalized development costs are reviewed for impairment whenever events or changes in circumstances indicate that the carrying amount of an asset exceeds its recoverable amount.

Where the research phase and the development phase of an internal project cannot be clearly distinguished, all expenditure incurred on the project is charged to the consolidated income statements.

(l) Impairment of Non-Financial Assets

Assets are reviewed for impairment to determine whether there is any indication that the carrying value of these assets may not be recoverable and have suffered an impairment loss. If any such indication exists, the recoverable amount of the asset is estimated in order to determine the extent of the impairment loss, if any. The recoverable amount is the higher of an asset's fair value less costs to sell and value in use. Such impairment loss is recognized in the consolidated income statements. Assets that have an indefinite useful life such as goodwill or intangible assets not ready to use are not subject to amortization and are tested for impairment annually and when there are indications that the carrying value may not be recoverable.

(m) Inventories

Inventories are stated at the lower of cost or net realizable value. Cost is determined using the weighted average cost method. The cost of finished goods comprises raw materials, direct labor, other direct costs and related production overheads (based on normal operating capacity). Net realizable value is the estimated selling price in the ordinary course of business, less applicable variable selling expenses.

(n) Trade and Other Receivables

Trade and other receivables are recognized initially at fair value, which is the amount of consideration that is unconditional. Trade and other receivables solely represent payments of principal and interest, if any, and the Group holds such financial assets with the objective to collect its contractual cash flows. Therefore, the Group measures them subsequently at amortized cost using the effective interest method, less any loss allowance. The Group applies the IFRS 9 simplified approach to measuring expected credit losses which uses a lifetime expected loss allowance for all trade receivables. To measure the expected credit losses, trade receivables have been grouped based on shared credit risk characteristics and the days past due. All other receivables at amortized cost are considered to have low credit risk, and the loss allowance recognized during the period was therefore limited to 12 months expected losses. The amount of the provision is recognized in the consolidated income statements.

(o) Cash and Cash Equivalents

In the consolidated statements of cash flows, cash and cash equivalents include cash on hand, bank deposits and other short-term highly liquid investments with original maturities of three months or less that are readily convertible to known amounts of cash and which are subject to an insignificant risk of changes in value, if any.

(p) Financial Liabilities and Equity Instruments

Financial liabilities and equity instruments issued by the Group are classified according to the substance of the contractual arrangements entered into and the definitions of a financial liability and an equity instrument. Financial liabilities (including trade and other payables) are initially measured at fair value, and are subsequently measured at amortized cost, using the effective interest method. An equity instrument is any contract that does not meet the definition of financial liability and evidences a residual interest in the assets of the Group after deducting all of its liabilities.

Ordinary shares are classified as equity. Incremental costs, net of tax, directly attributable to the issue of new shares are shown in equity as a deduction from the proceeds.

(q) Current and Deferred Income Tax

(i) Current income tax

The current income tax charge is calculated on the basis of the tax laws enacted or substantively enacted at the balance sheet date in the country where the Group operates and generates taxable income. Management periodically evaluates positions taken in tax returns with respect to situations in which applicable tax regulation is subject to interpretation. It establishes provisions where appropriate on the basis of amounts expected to be paid to the tax authorities.

(ii) Deferred income tax

Inside basis differences

Deferred income tax is provided in full, using the liability method, on temporary differences arising between the tax bases of assets and liabilities and their carrying amounts in the consolidated financial statements. However, deferred tax liabilities are not recognized if they arise from the initial recognition of goodwill. Deferred income tax is also not accounted for if it arises from initial recognition of an asset or liability in a transaction other than a business combination that, at the time of the transaction, affects neither accounting nor taxable profit or loss and does not give rise to equal taxable and deductible temporary differences. Deferred income tax is determined using tax rates (and laws) that have been enacted or substantively enacted by the balance sheet date and are expected to apply when the related deferred income tax asset is realized or the deferred income tax liability is settled.

Deferred income tax assets are recognized only to the extent that it is probable that future taxable profit will be available against which the temporary differences can be utilized. Deferred income tax assets and deferred income tax liabilities are offset when there is a legally enforceable right to set off and when the deferred income taxes related to the same fiscal authority.

Outside basis differences

Deferred income tax liabilities are provided on taxable temporary differences arising from investments in subsidiaries, associates and joint arrangements, except for deferred income tax liabilities where the timing of the reversal of the temporary difference is controlled by the Group and it is probable that the temporary difference will not reverse in the foreseeable future. Generally the Group is unable to control the reversal of the temporary difference for associates. Only when there is an agreement in place that gives the Group the ability to control the reversal of the temporary difference in the foreseeable future, deferred tax liability in relation to taxable temporary differences arising from the associate's undistributed profits is not recognized.

Deferred income tax assets are recognized on deductible temporary differences arising from investments in subsidiaries, associates and joint arrangements only to the extent that it is probable the temporary difference will reverse in the future and there is sufficient taxable profit available against which the temporary difference can be utilized.

(r) Employee Benefits

The employees of the Group participate in defined contribution retirement benefit plans managed by the relevant municipal and provincial governments in the PRC. The assets of these plans are held separately from the Group. The Group is required to make monthly contributions to the plans, calculated as a percentage of the employees' salaries. The municipal and provincial governments undertake to assume the retirement benefit obligations to all existing and future retired employees under the plans described above. Other than the monthly contributions, the Group has no further obligations for the payment of the retirement and other post-retirement benefits of its employees.

(s) Provisions

Provisions are recognized when the Group has a present legal or constructive obligation as a result of past events, it is probable that an outflow of resources will be required to settle the obligation, and the amount has been reliably estimated. Provisions are not recognized for future operating losses.

(t) Leases

A lease is recognized as a right-of-use asset with a corresponding liability at the date which the leased asset is available for use by the Group. The Group recognizes an obligation to make lease payments equal to the present value of the lease payments over the lease term. The lease terms may include options to extend or terminate the lease when it is reasonably certain that the Group will exercise that option.

Lease liabilities include the net present value of the following lease payments: (i) fixed payments; (ii) variable lease payments that depend on an index or a rate; and (iii) payments of penalties for terminating the lease if the lease term reflects the lessee exercising that option, if any. Lease liabilities exclude the following payments that are generally accounted for separately: (i) non-lease components, such as maintenance and security service fees and value added tax, and (ii) any payments that a lessee makes before the lease commencement date. The lease payments are discounted using the interest rate implicit in the lease or if that rate cannot be determined, the lessee's incremental borrowing rate being the rate that the lessee would have to pay to borrow the funds in its currency and jurisdiction necessary to obtain an asset of similar value, economic environment and terms and conditions.

An asset representing the right to use the underlying asset during the lease term is recognized that consists of the initial measurement of the lease liability, any lease payments made to the lessor at or before the commencement date less any lease incentives received, any initial direct cost incurred by the Group and any restoration costs.

After commencement of the lease, each lease payment is allocated between lease liability and finance costs. The finance costs are recognized over the lease term so as to produce a constant periodic rate of interest on the remaining balance of the lease liability for each period. The right-of-use asset is depreciated on a straight-line basis over the period of the lease.

Payments associated with short-term leases are recognized as lease expenses on a straight-line basis over the period of the leases.

Leasehold land is accounted under IFRS 16.

(u) Government Incentives

Incentives from government are recognized at their fair values where there is a reasonable assurance that the incentives will be received and all attached conditions will be complied with.

Government incentives relating to costs are deferred and recognized in the consolidated income statements over the period necessary to match them with the costs that they are intended to compensate.

Government grants relating to property, plant and equipment are included in non-current liabilities as deferred income and credited to the consolidated income statements on a straight-line basis over the expected lives of the related assets.

(v) Revenue and Income Recognition

The Group principally generates revenue from sales of goods. Revenue from sales of goods is recognized when the customer takes possession of the goods. This usually occurs upon completed delivery of the goods to the customer site. The amount of revenue recognized is adjusted for expected sales incentives as stipulated in the contract, which are generally issued to customers as direct discounts at the point-of-sale or indirectly in the form of rebates. Sales incentives are estimated using the expected value method. Additionally, sales are generally made with a limited right of return under certain conditions. Revenues are recorded net of provisions for sales discounts and returns.

Revenue from provision of services is recognized when the benefits of the services transfer to the customer over time, which is based on the proportionate value of services rendered as determined under the terms of the relevant contract. Additionally, when the amounts that can be invoiced correspond directly with the value to the customer for performance completed to date, the Group recognizes revenue from provision of services based on amounts that can be invoiced to the customer.

Payments in advance from customers are deferred if consideration is received in advance of transferring control of the goods or rendering of services. Accounts receivable is recognized if the Group has an unconditional right to bill the customer, which is generally when the customer takes possession of the goods or services are rendered. Payment terms differ by subsidiary and customer, but generally range from 45 to 180 days from the invoice date.

(w) Interest income

Interest income is recognized on a time-proportion basis using the effective interest method.

(x) Segment Reporting

Operating segments are reported in a manner consistent with the internal reporting provided to the chief operating decision-makers. The Company's Board of Directors, which is responsible for allocating resources and assessing performance of the operating segments, has been identified as the steering committee that makes strategic decisions.

(y) General Reserves

In accordance with the laws applicable to Foreign Investment Enterprises established in the PRC, the Company makes appropriations to certain non-distributable reserve funds including the general reserve fund, the enterprise expansion fund and the staff bonus and welfare fund. The amount of appropriations to these funds are made at the discretion of the Company's Board of Directors.

3. Financial Risk Management

(a) Financial risk factors

The Group's activities expose it to a variety of financial risks, including credit risk and liquidity risk. The Group does not use any derivative financial instruments for speculative purposes.

(i) Credit risk

The carrying amounts of cash and cash equivalents, trade receivables (including bills receivables) and other receivables included in the consolidated statements of financial position represent the Group's maximum exposure to credit risk of the counterparty in relation to its financial assets.

Substantially all of the Group's cash and cash equivalents are deposited in major financial institutions, which management believes are of high credit quality.

Bills receivables are mostly settled by state-owned banks or other reputable banks and therefore the management considers that they will not expose the Group to any significant credit risk.

The Group has no significant concentrations of credit risk. The Group has policies in place to ensure that the sales of products are made to customers with appropriate credit history and the Group performs periodic credit evaluations of its customers.

Management periodically assesses the recoverability of trade receivables and other receivables. The Group's historical loss rates are adjusted to reflect current and forward-looking information on specific factors affecting the ability of the customers to settle the receivables, and historical experience collecting receivables falls within the recorded allowances.

(ii) Liquidity risk

Prudent liquidity management implies maintaining sufficient cash and cash equivalents and the availability of funding when necessary. The Group's policy is to regularly monitor current and expected liquidity requirements to ensure that it maintains sufficient cash balances and adequate credit facilities to meet its liquidity requirements in the short and long term.

As at September 28, 2021 and December 31, 2020, the Group's current financial liabilities were mainly due for settlement within twelve months and the Group expects to meet all liquidity requirements. As at September 28, 2021, the Group's consolidated current liabilities exceed the consolidated current assets by US$32.0 million, which was mainly attributable to current dividends payable to shareholders (refer to Note 24(b)), for which settlement will occur when sufficient cash and cash equivalents are available. In assessing the Group's liquidity, management prepared a cash flow forecast up to December 31, 2022 taking into consideration of ongoing operations and the settlement of the current dividends payable, which indicates that the Group will have sufficient cash resources to fund planned operations and other commitments for at least the next twelve months (the look-forward period used).

(b) Capital risk management

The Group's objectives when managing capital are to safeguard the Group's ability to provide returns for shareholders and benefits for other stakeholders and to maintain an optimal capital structure to reduce the cost of capital.

The Group regularly reviews and manages its capital structure to ensure an optimal balance between higher shareholders' return that might be possible with higher levels of borrowings and the advantages and security afforded by a sound capital position, and makes adjustments to the capital structure in light of changes in economic conditions.

The Group monitors capital on the basis of the liabilities to assets ratio. This ratio is calculated as total liabilities divided by total assets as shown on the consolidated statements of financial position.

Currently, it is the Group's strategy to maintain a reasonable liabilities to assets ratio. The liabilities to assets ratio as at September 28, 2021 and December 31, 2020 was as follows:

	September 28, 2021	December 31, 2020
	(in US$'000)	
Total liabilities (note)	237,352	153,213
Total assets	284,840	273,581
Liabilities to assets ratio	83.3 %	56.0 %

Note: On May 13, 2021 and September 23, 2021, the Company declared dividends to shareholders of US$46.5 million and US$59.7 million respectively, which were not settled as at September 28, 2021.

(c) Fair value estimation

The Group does not have any financial assets or liabilities which are carried at fair value. The carrying amounts of the Group's current financial assets, including cash and cash equivalents, trade and bills receivables and other receivables, and current financial liabilities, including trade payables, and other payables and accruals and dividend payable, approximate their fair values due to their short-term maturities. The carrying amounts of the Group's financial instruments carried at cost or amortized cost are not materially different from their fair values.

The face values less any estimated credit adjustments for financial assets and liabilities with a maturity of less than one year are assumed to approximate their fair values. The fair value of financial liabilities for disclosure purposes is estimated by discounting the future contractual cash flows at the current market interest rate that is available to the Group for similar financial instruments.

4. Critical Accounting Estimates and Judgements

Note 2 includes a summary of the significant accounting policies used in the preparation of the consolidated financial statements. The preparation of consolidated financial statements often requires the use of judgements to select specific accounting methods and policies from several acceptable alternatives. Furthermore, significant estimates and assumptions concerning the future may be required in selecting and applying those methods and policies in the consolidated financial statements. The Group bases its estimates and judgements on historical experience and various other assumptions that it believes are reasonable under the circumstances. Actual results may differ from these estimates and judgements under different assumptions or conditions.

The following is a review of the more significant assumptions and estimates, as well as the accounting policies and methods used in the preparation of the consolidated financial statements.

(a) Sales rebates

Certain sales rebates are provided to customers when their business performance for the whole year meets certain criteria as stipulated in the contracts. Sales rebates are considered variable consideration and the estimate of sales rebates during the year is based on estimated sales transactions for the entire period stipulated and is subject to change based on actual performance and collection status.

(b) Useful lives of property, plant and equipment

The Group has made substantial investments in property, plant and equipment. Changes in technology or changes in the intended use of these assets may cause the estimated period of use or value of these assets to change.

(c) Impairment of non-financial assets

The Group tests at least annually whether goodwill has suffered any impairment. Other non-financial assets are reviewed for impairment whenever events or changes in circumstances indicate that the carrying amount of the asset exceeds its recoverable amount in accordance with the accounting policy stated in Note 2(l). The recoverable amount of an asset or a cash-generating unit is determined based on the higher of the asset's or the cash-generating unit's fair value less costs to disposal and value-in-use. The value-in-use calculation requires the entity to estimate the future cash flows expected to arise from the asset and a suitable discount rate in order to calculate present value, and the growth rate assumptions in the cash flow projections which has been prepared on the basis of management's assumptions and estimates.

(d) Deferred income tax

Deferred tax is recognized using the liability method on temporary differences arising between the tax bases of assets and liabilities against which the deductible temporary differences and the carry forward of unused tax losses and tax credits can be utilized. Deferred income tax assets are recognized only to the extent that it is probable that future taxable profit will be available against which the temporary differences can be utilized. Where the final outcomes are different from the estimations, such differences will impact the carrying amount of deferred tax in the period in which such determination is made.

5. Revenue and Segment Information

Management has reviewed the Group's internal reporting in order to assess performance and allocate resources, and has determined that the Group has two reportable operating segments as follows:

—Manufacturing business—manufacture and distribution of drug products

—Distribution business—provision of sales, distribution and marketing services to pharmaceutical manufacturers

The operating segments are strategic business units that offer different products and services. They are managed separately because each business requires different technology and marketing approaches. The performance of each of the reportable segments is assessed based on operating profit.

The segment information is as follows:

	Period from January 1, 2021 to September 28, 2021		
	Manufacturing business	Distribution business	
	PRC	PRC	Total
		(in US$'000)	
Revenue from external customers	190,619	18,909	209,528
Interest income	141	64	205
Operating profit	18,212	2,076	20,288
Share of profits of a joint venture and associated companies, net of tax	29	—	29
Finance costs	18	6	24
Depreciation/amortization	5,515	98	5,613
Additions to non-current assets (other than financial instruments and deferred tax assets)	2,405	—	2,405

	As at September 28, 2021		
	Manufacturing business PRC	Distribution business PRC	Total
	(in US$'000)		
Total segment assets	251,178	33,662	284,840

	Year Ended December 31, 2020		
	Manufacturing business PRC	Distribution business PRC	Total
	(in US$'000)		
Revenue from external customers	215,427	16,941	232,368
Interest income	188	83	271
Operating profit	20,833	2,312	23,145
Share of losses of a joint venture and associated companies, net of tax	84	—	84
Finance costs	51	6	57
Depreciation/amortization	6,361	123	6,484
Additions to non-current assets (other than financial instruments and deferred tax assets)	2,432	1	2,433

	December 31, 2020		
	Manufacturing business PRC	Distribution business PRC	Total
	(in US$'000)		
Total segment assets	243,578	30,003	273,581

	Year Ended December 31, 2019		
	Manufacturing business PRC	Distribution business PRC	Total
	(in US$'000)		
Revenue from external customers	202,852	12,551	215,403
Interest income	76	84	160
Operating profit	21,738	1,182	22,920
Share of profits of a joint venture and associated companies, net of tax	60	—	60
Finance costs	40	19	59
Depreciation/amortization	6,411	125	6,536
Additions to non-current assets (other than financial instruments and deferred tax assets)	4,002	—	4,002

Revenue from external customers is after elimination of inter-segment sales. The amount eliminated was US$0.2 million for the period from January 1, 2021 to September 28, 2021 (for the years ended December 31, 2020 and 2019: US$0.1 million and US$0.7 million respectively). Sales between segments are carried out at mutually agreed terms. Revenue from external customers is primarily for sales of goods which are recognized at a point in time, except for provision of services which are recognized over time of US$1.2 million for the period from January 1, 2021 to September 28, 2021 (for the years ended December 31, 2020 and 2019: US$3.7 million and US$3.1 million respectively) and included in the manufacturing business operating segment.

6. Other Net Operating Income

	Period from January 1, 2021 to September 28, 2021	Year Ended December 31, 2020	2019
		(in US$'000)	
Interest income	205	271	160
Gain on disposal of leasehold land	—	166	—
Loss on disposal of property, plant and equipment	(47)	(643)	(162)
Other operating income	5,631	6,734	6,226
Other operating expenses	(483)	(457)	(598)
	5,306	6,071	5,626

7. Operating Profit

	Period from January 1, 2021 to September 28, 2021	Year Ended December 31, 2020	2019
		(in US$'000)	
Operating profit	20,288	23,145	22,920

Operating profit is stated after charging/(crediting) the following:

	Period from January 1, 2021 to September 28, 2021	Year Ended December 31, 2020	2019
		(in US$'000)	
Cost of inventories recognized as expense	87,941	100,906	85,802
Depreciation of property, plant and equipment	4,425	5,283	5,417
Impairment of property, plant and equipment	—	—	525
Loss on disposal of property, plant and equipment	47	643	162
Gain on disposal of leasehold land	—	(166)	—
Amortization of leasehold land	450	236	230
Amortization of other intangible assets	331	414	351
Depreciation charge of right-of-use assets and lease expenses	1,360	1,438	1,227
Movements on the provision for trade receivables	38	(20)	(70)
Movements on the provision for excess and obsolete inventories	41	474	314
Research and development expense	2,057	1,670	1,041
Auditor's remuneration	43	88	87
Employee benefit expenses (Note 10)	31,605	36,822	34,634

8. Gain on return of land

In June 2020, the Group entered into an agreement with the government to return the land use right for a plot of land in Guangzhou to the government (the "Land Compensation Agreement") for cash consideration which aggregated to RMB679.5 million (approximately US$103.1 million). In November 2020, the Group completed all material obligations as stipulated in the Land Compensation Agreement and recognized land compensation of RMB569.2 million (approximately US$86.1 million), resulting in a gain of RMB559.7 million (approximately US$84.7 million). In June 2021, the Group received a completion confirmation from the government and recognized an additional land compensation bonus of RMB110.3 million (approximately US$17.0 million), resulting in a gain of RMB106.8 million (approximately US$16.4 million), after deducting costs of RMB3.5 million (approximately US$0.6 million). As at September 28, 2021, the Group has received RMB584.6 million (approximately US$86.6 million) and has recorded RMB94.9 million (approximately US$14.6 million) in other receivables, prepayments and deposits.

9. Taxation Charge

	Period from January 1, 2021 to September 28, 2021	Year Ended December 31,	
		2020	2019
		(in US$'000)	
Current tax	6,093	17,108	3,925
Deferred income tax (Note 17)	(1,253)	(614)	(291)
Taxation charge	4,840	16,494	3,634

The taxation charge on the Group's profit before taxation differs from the theoretical amount that would arise using the Group's weighted average tax rate as follows:

	Period from January 1, 2021 to September 28, 2021	Year Ended December 31,	
		2020	2019
		(in US$'000)	
Profit before taxation	36,726	107,708	22,921
Tax calculated at the statutory tax rates of respective companies	9,181	26,927	5,730
Tax effects of:			
Expenses not deductible for tax purposes	45	66	56
Tax concession (note)	(3,781)	(10,834)	(2,569)
Tax losses for which no deferred tax assets were recognized	192	339	522
Under/(over) provision in prior years	6	44	(17)
Utilization of tax losses for which no deferred tax assets were recognized previously	(803)	(48)	(88)
Taxation charge	4,840	16,494	3,634

Note: The Company has been granted the High and New Technology Enterprise status. Accordingly, the Company is subject to a preferential income tax rate of 15% and renewed the status in 2021. Certain research and development expenses are also eligible for super-deduction such that 200% of qualified expenses incurred are deductible for tax purposes.

The weighted average tax rate calculated at the statutory tax rates of respective companies was 25%. The effective tax rate for the period from January 1, 2021 to September 28, 2021 was 13.2% (for the years ended December 31, 2020 and 2019: 15.3% and 15.9% respectively).

10. Employee Benefit Expenses

	Period from January 1, 2021 to September 28, 2021	Year Ended December 31,	
		2020	2019
		(in US$'000)	
Wages, salaries and bonuses	23,705	28,380	25,066
Pension costs—defined contribution plans	6,679	6,954	8,282
Staff welfare	1,221	1,488	1,286
	31,605	36,822	34,634

Employee benefit expenses of approximately US$9.1 million for the period from January 1, 2021 to September 28, 2021 (for the years ended December 31, 2020 and 2019: US$11.1 million and US$11.4 million repsectively) are included in cost of sales.

11. Cash and Cash Equivalents

	September 28, 2021	December 31, 2020
	(in US$'000)	
Cash and cash equivalents	73,616	16,602

The cash and cash equivalents denominated in RMB were deposited with banks in the PRC. The conversion of these RMB denominated balances into foreign currencies is subject to the rules and regulations of foreign exchange control promulgated by the PRC government.

12. Trade and Bills Receivables

	September 28, 2021	December 31, 2020
	(in US$'000)	
Trade receivables—third parties	4,290	1,764
Trade receivables—related parties (Note 24(b))	1,975	3,485
Bills receivables	21,609	62,168
	27,874	67,417

All trade and bills receivables are denominated in RMB and are due within one year from the end of the reporting period. The carrying values of trade and bills receivables approximate their fair values due to their short-term maturities.

Movements on the provision for trade receivables are as follows:

	2021	2020	2019
		(in US$'000)	
As at January 1	—	19	90
Increase in provision for trade receivables	38	—	5
Decrease in provision due to subsequent collection	—	(20)	(75)
Exchange differences	—	1	(1)
As at September 28/December 31	38	—	19

The impaired and provided receivables as at September 28, 2021 and December 31, 2019 were aged over 1 year.

13. Other Receivables, Prepayments and Deposits

	September 28, 2021	December 31, 2020
	(in US$'000)	
Prepayments to suppliers	9,671	4,784
Value-added tax receivables	780	538
Land compensation receivable	14,592	43,414
Others	1,504	1,385
	26,547	50,121

14. Inventories

	September 28, 2021	December 31, 2020
	(in US$'000)	
Raw materials	23,126	13,063
Work in progress	17,816	17,303
Finished goods	21,458	13,382
	62,400	43,748

15. Property, Plant and Equipment

	Buildings and facilities	Plant and equipment	Furniture and fixtures, other equipment and motor vehicles	Construction in progress	Total
			(in US$'000)		
Cost					
As at January 1, 2021	61,267	27,769	12,615	1,979	103,630
Additions	396	440	623	943	2,402
Disposals	(3)	(97)	(78)	—	(178)
Transfers	—	358	906	(1,264)	—
Exchange differences	516	234	105	17	872
As at September 28, 2021	62,176	28,704	14,171	1,675	106,726
Accumulated depreciation					
As at January 1, 2021	16,368	16,559	10,522	—	43,449
Depreciation	1,763	1,278	1,384	—	4,425
Disposals	(1)	(61)	(69)	—	(131)
Exchange differences	137	138	89	—	364
As at September 28, 2021	18,267	17,914	11,926	—	48,107
Net book value					
As at September 28, 2021	43,909	10,790	2,245	1,675	58,619

	Buildings and facilities	Plant and equipment	Furniture and fixtures, other equipment and motor vehicles	Construction in progress	Total
			(in US$'000)		
Cost					
As at January 1, 2020	59,099	25,426	11,353	1,311	97,189
Additions	224	168	651	1,390	2,433
Disposals	(2,204)	(187)	(522)	—	(2,913)
Disposal of a subsidiary	(28)	—	(27)	—	(55)
Transfers	28	502	318	(848)	—
Exchange differences	4,148	1,860	842	126	6,976
As at December 31, 2020	61,267	27,769	12,615	1,979	103,630
Accumulated depreciation					
As at January 1, 2020	14,021	14,096	8,755	—	36,872
Depreciation	2,201	1,520	1,562	—	5,283
Disposals	(926)	(150)	(464)	—	(1,540)
Disposal of a subsidiary	(10)	—	(23)	—	(33)
Exchange differences	1,082	1,093	692	—	2,867
As at December 31, 2020	16,368	16,559	10,522	—	43,449
Net book value					
As at December 31, 2020	44,899	11,210	2,093	1,979	60,181

	Buildings and facilities	Plant and equipment	Furniture and fixtures, other equipment and motor vehicles	Construction in progress	Total
			(in US$'000)		
Cost					
As at January 1, 2019	61,319	25,866	10,700	1,423	99,308
Additions	158	415	533	1,395	2,501
Disposals	(1,005)	(673)	(319)	—	(1,997)
Transfers	227	502	741	(1,470)	—
Exchange differences	(1,600)	(684)	(302)	(37)	(2,623)
As at December 31, 2019	59,099	25,426	11,353	1,311	97,189
Accumulated depreciation					
As at January 1, 2019	12,739	12,929	7,707	—	33,375
Depreciation	2,299	1,569	1,549	—	5,417
Disposals	(887)	(294)	(287)	—	(1,468)
Impairment	241	267	17	—	525
Exchange differences	(371)	(375)	(231)	—	(977)
As at December 31, 2019	14,021	14,096	8,755	—	36,872
Net book value					
As at December 31, 2019	45,078	11,330	2,598	1,311	60,317

16. Leases

Leases consisted of the following:

	September 28, 2021	December 31, 2020
	(in US$'000)	
Right-of-use assets:		
Warehouses	420	820
Lease liabilities—current	452	568
Lease liabilities—non-current	—	303
	452	871

Lease activities are summarized as follows:

	Period from January 1, 2021 to September 28, 2021	Year Ended December 31,	
		2020	2019
		(in US$'000)	
Lease expenses: Short-term leases with lease terms equal or less than 12 months	953	887	689
Depreciation charge of right-of-use assets	407	551	538
Interest expense (included in finance costs)	24	57	59
Cash paid on lease liabilities	427	609	556
Non-cash: Lease liabilities recognized from obtaining right-of-use assets	—	—	1,145

Lease contracts are typically within a period of 1 to 6 years. The weighted average remaining lease term and weighted average discount rate as at September 28, 2021 was 0.83 year (as at December 31, 2020 and 2019: 1.56 years and 2.51 years respectively) and 4.75% (as at December 31, 2020 and 2019: 4.75% and 4.77% respectively) respectively.

Future lease payments are as follows:

	September 28, 2021	December 31, 2020
	(in US$'000)	
Lease payments:		
Not later than 1 year	462	598
Between 1 to 2 years	—	307
Total lease payments	462	905
Less: Discount factor	(10)	(34)
Total lease liabilities	452	871

17. Deferred Tax Assets and Liabilities

	September 28, 2021	December 31, 2020
	(in US$'000)	
Deferred tax assets	4,420	3,141
Deferred tax liabilities	—	(114)
Net deferred tax assets	4,420	3,027

The movements in net deferred tax assets are as follows:

	2021	2020	2019
		(in US$'000)	
At January 1	3,027	2,217	1,986
Credited/(debited) to the consolidated income statements			
—Tax losses	326	(396)	(27)
—Accrued expenses, provisions, depreciation allowances	927	1,010	318
Exchange differences	140	196	(60)
At September 28/December 31	4,420	3,027	2,217

The Group's deferred tax assets and liabilities are temporary differences including tax losses, accrued expenses, provisions and depreciation allowances. The potential deferred tax assets in respect of tax losses which have not been recognized in the consolidated financial statements were approximately US$1.6 million as at September 28, 2021 (as at December 31, 2020: US$1.6 million).

These unrecognized tax losses can be carried forward against future taxable income and will expire in the following years:

	September 28, 2021	December 31, 2020
	(in US$'000)	
2021	928	926
2022	1,450	1,836
2023	856	849
2024	1,239	1,334
2025	1,074	1,431
2026	669	—
	6,216	6,376

18. Other Non-Current Assets

	September 28, 2021	December 31, 2020
	(in US$'000)	
Prepayment of leasehold land rights (note)	—	11,160
Others	46	529
	46	11,689

Note: Balance as at December 31, 2020 represented prepayments for a land use right in which the title of the land was in the process of registration, pending remaining administrative procedures. In 2021, the registration was completed, title was transferred to the Company and the balance was reclassified to leasehold land.

19. Trade Payables

	September 28, 2021	December 31, 2020
	(in US$'000)	
Trade payables—third parties	15,519	16,852
Trade payables—related parties (Note 24(b))	3,529	5,727
	19,048	22,579

All trade payables are denominated in RMB and due within one year from the end of the reporting period. The carrying value of trade payables approximates their fair values due to their short-term maturities.

20. Other Payables, Accruals and Advance Receipts

	September 28, 2021	December 31, 2020
	(in US$'000)	
Other payables and accruals		
Accrued salaries and benefits	5,384	4,715
Accrued selling and administrative expenses	35,266	27,872
Value-added tax and tax surcharge payables	2,588	2,207
Deposits received	4,748	5,866
Other payables to manufacturers	8,794	8,794
Others	5,934	6,017
	62,714	55,471
Advance receipts		
Payments in advance from customers (note)	16,310	41,963
Deferred government incentives	1,460	1,427
	17,770	43,390
	80,484	98,861

Note: Substantially all customer balances as at December 31, 2020 were recognized to revenue during the period from January 1, 2021 to September 28, 2021. Additionally, substantially all customer balances as at September 28, 2021 are expected to be recognized to revenue within one year upon transfer of goods or services as the contracts have an expected duration of one year or less.

21. Deferred Income

	September 28, 2021	December 31, 2020
	(in US$'000)	
Deferred government incentives:		
Buildings and other non-current assets	11,272	11,890
Others	3,641	3,727
	14,913	15,617

22. Notes to the Consolidated Statements of Cash Flows

(a) Reconciliation of profit for the period/year to net cash generated from operations:

	Period from January 1, 2021 to September 28, 2021	Year Ended December 31,	
		2020	2019
		(in US$'000)	
Profit for the period/year	31,886	91,214	19,287
Adjustments to reconcile profit for the period/year to net cash generated from operations			
Taxation charge	4,840	16,494	3,634
Finance costs	24	57	59
Interest income	(205)	(271)	(160)
Share of (profits)/losses of a joint venture and associated companies, net of tax	(29)	84	(60)
Depreciation on property, plant and equipment	4,425	5,283	5,417
Depreciation charge of right-of-use assets	407	551	538
Loss on disposal of property, plant and equipment	47	643	162
Gain on return of land	(16,433)	(84,667)	—
Gain on disposal of leasehold land	—	(166)	—
Impairment of property, plant and equipment	—	—	525
Amortization of leasehold land	450	236	230
Amortization of other intangible assets	331	414	351
Movement on the provision for trade receivables	38	(20)	(70)
Movement on the provision for excess and obsolete inventories	41	474	314
Amortization of deferred income	(845)	(1,689)	(2,187)
Gain on divestment of a subsidiary	—	(37)	—
Exchange differences	(470)	794	(1,120)
Changes in working capital:			
Trade and bills receivables	39,505	(19,124)	(1,524)
Other receivables, prepayments and deposits	(5,248)	1,902	(2,886)
Inventories	(18,693)	2,195	60
Other non-current assets	(139)	—	700
Trade payables	(3,531)	9,880	(2,965)
Other payables, accruals and advance receipts	(18,616)	36,509	5,932
Total changes in working capital	(6,722)	31,362	(683)
Net cash generated from operations	17,785	60,756	26,237

(b) Supplemental disclosure for non-cash activities

During the period from January 1, 2021 to September 28, 2021, there was an increase of US$0.4 million in accruals made for purchases of property, plant and equipment (for the years ended December 31, 2020 and 2019: an increase of US$0.1 million and a decrease of US$0.9 million respectively).

23. Capital commitments

The Group had the following capital commitments:

	September 28, 2021
	(in US$'000)
Property, plant and equipment	
Contracted but not provided for	1,290

Capital commitments for property, plant and equipment are mainly for improvements to the Group's plant.

24. Significant Related Party Transactions

The Group has the following significant transactions with related parties which were carried out in the normal course of business at terms determined and agreed by the relevant parties:

(a) Transactions with related parties:

	Period from January 1, 2021 to September 28, 2021	Year Ended December 31,	
		2020	2019
		(in US$'000)	
Sales of goods to:			
—Fellow subsidiaries of GBPHCL	25,043	33,535	23,658
—A fellow subsidiary of GZHCMHK	278	493	210
	25,321	34,028	23,868
Other services income from:			
—An equity investee	—	273	275
—Fellow subsidiaries of GBPHCL	3,576	6,166	5,913
	3,576	6,439	6,188
Purchase of goods from:			
—An equity investee	2,145	2,317	3,216
—Fellow subsidiaries of GBPHCL	24,222	29,594	24,733
	26,367	31,911	27,949
Advertising expenses to:			
—A fellow subsidiary of GBPHCL	4,805	5,733	5,128
Interest paid to:			
—A non-controlling shareholder of a subsidiary	—	5	16
	—	5	16

No transactions have been entered into with the directors of the Company (being the key management personnel) during the period from January 1, 2021 to September 28, 2021 (for the years ended December 31, 2020 and 2019: nil).

(b) Balances with related parties included in:

	September 28, 2021	December 31, 2020
	(in US$'000)	
Trade and bills receivables		
—An equity investee (note (i))	—	305
—Fellow subsidiaries of GBPHCL (note (i))	1,975	3,180
	1,975	3,485
Trade payables		
—Fellow subsidiaries of GBPHCL (note (i))	3,529	5,043
—An equity investee (note (i))	—	684
	3,529	5,727
Other receivables and prepayments—related parties		
—Fellow subsidiaries of GBPHCL (note (i))	1,129	743
—An equity investee (note (i))	156	336
	1,285	1,079
Other payables, accruals and advance receipts		
—Fellow subsidiaries of GZHCMHK (note (i) and (ii))	—	156
—Fellow subsidiaries of GBPHCL (note (i))	2,691	5,484
	2,691	5,640
Dividend payable (Note 3(b))		
—GZHCMHK	52,887	—
—GBPHCL	52,887	—
	105,774	—

Notes:

(i) Balances are unsecured, interest-free and repayable on demand. The carrying values of balances with related parties approximate their fair values due to their short-term maturities.

(ii) Amounts payable to fellow subsidiaries of GZHCMHK were due to entities in HUTCHMED's group. On September 28, 2021, HUTCHMED divested its entire interest in the Company and consequently, subsidiaries in HUTCHMED's group were no longer related parties of the Company.

25. Particulars of Principal Subsidiaries, Joint Venture and Associated Companies

All of the Group's principal subsidiaries, joint venture and associated companies had a place of establishment and operation in the PRC.

Name	Nominal value of registered capital		Equity interest attributable to the Group		Type of legal entity	Principal activity
	September 28, 2021	December 31, 2020	September 28, 2021	December 31, 2020		
	(in RMB'000)					
Hutchison Whampoa Guangzhou Baiyunshan Chinese Medicine (Bozhou) Co. Ltd	100,000	100,000	100 %	100 %	Limited liability company	Manufacture, sales and distribution of drug products
Hutchison Whampoa Guangzhou Baiyunshan Pharmaceuticals Limited	10,000	10,000	100 %	100 %	Limited liability company	Sales and marketing of drug products
Hutchison Whampoa Guangzhou Baiyunshan Health & Wellness Co. Ltd	10,000	10,000	100 %	100 %	Limited liability company	Health supplemented food distribution
Hutchison Whampoa Baiyunshan Lai Da Pharmaceuticals (Shan Tou) Company Limited	10,000	10,000	100 %	100 %	Limited liability company	Manufacture, sales and distribution of drug products
Fuyang Baiyunshan Hutchison Whampoa Chinese Medicine Technology Company Limited	3,650	3,650	75 %	75 %	Limited liability company	Agriculture and sales of Chinese herbs
Wenshan Baiyunshan Hutchison Whampoa Sanqi Co. Ltd.	2,000	2,000	51 %	51 %	Limited liability company	Agriculture and sales of Chinese herbs
Daqing Baiyunshan Hutchison Whampoa Banlangen Technology Company Limited	1,020	1,020	51 %	51 %	Limited liability company	Agriculture and sales of Chinese herbs
Shen Nong Garden Traditional Chinese Medicine Museum	1,000	1,000	100 %	100 %	Non-profit making organization	Promote awareness of Chinese herbs
Guangzhou Hulu Cultural Communications Company Limited	1,000	1,000	100 %	100 %	Limited liability company	Promote awareness of Chinese herbs
Bozhou Baiyunshan Pharmaceuticals Co Ltd ("Old Bozhou") (note)	—	500	—	100 %	Limited liability company	Manufacture, sales and distribution of drug products
Shen Nong Garden Pharmacy Company Limited	200	200	100 %	100 %	Limited liability company	Retail of drug products, health foods and souvenirs
Joint Venture						
Qing Yuan Hutchison Whampoa Baiyunshan Chinese Medicine Company Limited	1,000	1,000	50 %	50 %	Limited liability company	Agriculture and sales of Chinese herbs
Associated companies						
Linyi Shenghe Jiuzhou Pharmaceuticals Company Limited	3,000	3,000	30 %	30 %	Limited liability company	Agriculture and sales of Chinese herbs
Tibet Linzhi Guangzhou Pharmaceutical Development Co. Ltd.	2,000	2,000	20 %	20 %	Limited liability company	Trading of Chinese herbs

Note: In August 2021, Old Bozhou was voluntarily dissolved as it had no ongoing operating activities.

Exhibit 1.1

HUTCHMED (CHINA) LIMITED
和黃醫藥(中國)有限公司

(Formerly known as "Hutchison China MediTech Limited 和黃中國醫藥科技有限公司")

AMENDED AND RESTATED MEMORANDUM AND ARTICLES OF ASSOCIATION

(conditionally adopted by special resolution passed on 29 May 2019 and effective on the date on which the shares of the Company are listed on The Stock Exchange of Hong Kong Limited)

THE COMPANIES LAW

OF THE CAYMAN ISLANDS

COMPANY LIMITED BY SHARES

AMENDED AND RESTATED

MEMORANDUM OF ASSOCIATION OF

HUTCHISON CHINA MEDITECH LIMITED
和黃中國醫藥科技有限公司

(conditionally adopted by special resolution passed on 29 May 2019 and effective on the date on which the shares of the Company are listed on The Stock Exchange of Hong Kong Limited)

1. The name of the Company is **Hutchison China MediTech Limited** 和黃中國醫藥科 技有限公司.

2. The Registered Office of the Company shall be at the offices of Maples Corporate Services Limited, P.O. Box 309, Ugland House, Grand Cayman, KY1-1104, Cayman Islands, or at such other place as the Directors may from time to time decide.

3. The objects for which the Company is established are unrestricted and shall include, but without limitation, the following:

   (a) to act and to perform all the functions of a holding company in all its branches and to coordinate the policy and administration of any subsidiary company or companies wherever incorporated or carrying on business or of any group of companies of which the Company or any subsidiary company is a member or which are in any manner controlled directly or indirectly by the Company; and

   (b) to act as an investment company and for that purpose to subscribe, acquire, hold, dispose, sell, deal in or trade upon any terms, whether conditionally or absolutely, shares, stock, debentures, debenture stock, annuities, notes, mortgages, bonds, obligations and securities, foreign exchange, foreign currency deposits and commodities, issued or guaranteed by any company wherever incorporated, or by any government, sovereign, ruler, commissioners, public body or authority, supreme, municipal, local or otherwise, by original subscription, tender, purchase, exchange, underwriting, participation in syndicates or in any other manner and whether or not fully paid up, and to meet calls thereon.

4. Except as prohibited or limited by the Companies Law, the Company shall have and be capable of exercising all the functions of a natural person of full capacity irrespective of any question of corporate benefit, as provided by Section 27(2) of the Companies Law.

5. The liability of each Member is limited to the amount from time to time unpaid on such Member's shares.

6. The share capital of the Company is US$150,000,000 divided into 1,500,000,000 shares of a nominal or par value of US$0.10 each with power for the Company insofar as is permitted by law, to redeem or purchase any of its shares and to increase or reduce the said capital subject to the provisions of the Companies Law and the Articles of Association and to issue any part of its capital, whether original, redeemed or increased with or without any preference, priority or special privilege or subject to any postponement of rights or to any conditions or restrictions and so that unless the conditions of issue shall otherwise expressly declare every issue of shares whether declared to be preference or otherwise shall be subject to the powers hereinbefore contained.

7. If the Company is registered as exempted, its operations will be carried on subject to the provisions of Section 193 of the Companies Law and, subject to the provisions of the Companies Law and the Articles of Association, it shall have the power to register by way of continuation as a body corporate limited by shares under the laws of any jurisdiction outside the Cayman Islands and to be deregistered in the Cayman Islands.

The Companies Law (Revised)

Company Limited by Shares

AMENDED AND RESTATED

ARTICLES OF ASSOCIATION

OF

Hutchison China MediTech Limited
和黃中國醫藥科技有限公司

(conditionally adopted by special resolution passed on 29 May 2019 and effective on the date on which the shares of the Company are listed on The Stock Exchange of Hong Kong Limited)

INDEX

TABLE A

1. The regulations in Table A in the Schedule to the Companies Law (Revised) do not apply to the Company.

INTERPRETATION

2. (1) In these Articles, unless the context otherwise requires, the words standing in the first column of the following table shall bear the meaning set opposite them respectively in the second column.

WORD	MEANING
"Articles"	these Articles in their present form or as supplemented or amended or substituted from time to time;
"Auditor"	the auditor of the Company for the time being and may include any individual or partnership;
"Board" or "Directors"	the board of directors of the Company or the directors present at a meeting of directors of the Company at which a quorum is present;
"business day"	shall mean a day on which each Designated Stock Exchange generally is open for the business of dealing in securities. For the avoidance of doubt, where the Hong Kong Stock Exchange is closed for the business of dealing in securities in Hong Kong on a business day for the reason of a number 8 or higher typhoon signal, black rainstorm warning or other similar event, such day shall for the purposes of these Articles be counted as a business day;
"capital"	the share capital from time to time of the Company;
"clear days"	in relation to the period of a notice that period excluding the day when the notice is given or deemed to be given and the day for which it is given or on which it is to take effect;
"clearing house"	a clearing house recognised by the laws of the jurisdiction in which the shares of the Company are listed or quoted on a stock exchange in such jurisdiction;
"close associate"	in relation to any Director, shall have the same meaning as defined in the Hong Kong Listing Rules, except that for purposes of Article 105 where the transaction or arrangement to be approved by the Board is a connected transaction referred to in the Hong Kong Listing Rules, it shall have the same meaning as that ascribed to "associate" in the Hong Kong Listing Rules;

"Company"	Hutchison China MediTech Limited 和黃中國醫藥 科技有限公司;
"competent regulatory authority"	a competent regulatory authority in the territory where the shares of the Company are listed or quoted on a stock exchange in such territory;
"CREST"	the relevant system (as defined in the CREST Regulations) which enables title to securities to be evidenced and transferred without a written instrument, administered by Euroclear UK & Ireland as the Operator (as defined in the CREST Regulations);
"CREST Regulations"	the Uncertificated Securities Regulations 2001 (SI 2001 No 3755), as amended, and any applicable rules made under those regulations;
"debenture" and "debenture holder"	include debenture stock and debenture stockholder respectively;
"Designated Stock Exchange"	a stock exchange in respect of which the shares of the Company are listed or quoted and where such stock exchange deems such listing or quotation to be the primary listing or quotation of the shares of the Company including, without limitation, the Hong Kong Stock Exchange, the AIM market operated by the London Stock Exchange and Nasdaq Global Select Market or any of them, as the case may be;
"electronic facilities"	has the meaning given to it in article 62(2);
"electronic/hybrid meeting"	a general meeting held and conducted by either or both: (i) physical attendance by Members and/or proxies at one or more places specified by the Directors and (ii) attendance and participation by electronic means by Members and/or proxies;
"Employees' Share Scheme"	for the purposes of these Articles an employees' share scheme is a scheme for encouraging or facilitating the holding of shares or debentures in the Company by or for the benefit of: (a) the bona fide employees or former employees of the Company, a subsidiary of the Company or a holding company or a subsidiary of the Company's holding company; or (b) the wives, husbands, widows, widowers or children or step-children under the age of 18 of such employees or former employees;

"English Act"	the Companies Act 2006 of England and Wales, including any statutory re-enactment or modification thereof;
"Equity Shares"	any share in the capital of the Company other than shares which as respects dividends carry a right to participate only up to a specified amount in a distribution;
"Euroclear UK & Ireland"	Euroclear UK & Ireland Limited, a company incorporated in England and Wales with registered number 2878738 and the operator of CREST;
"head office"	such office of the Company as the Directors may from time to time determine to be the principal office of the Company;
"Hong Kong Listing Rules"	the Rules Governing the Listing of Securities on The Stock Exchange of Hong Kong Limited;
"Hong Kong Stock Exchange"	The Stock Exchange of Hong Kong Limited;
"Law"	The Companies Law, Cap. 22 (Law 3 of 1961, as consolidated and revised) of the Cayman Islands;
"London Stock Exchange"	London Stock Exchange plc;
"Member"	a duly registered holder from time to time of the shares in the capital of the Company;
"Memorandum"	the memorandum of association of the Company in its present form or as supplemented or amended or substituted from time to time;
"month"	a calendar month;
"Notice"	written notice unless otherwise specifically stated and as further defined in these Articles;
"Office"	the registered office of the Company for the time being;
"ordinary resolution"	a resolution shall be an ordinary resolution when it has been passed by a simple majority of votes cast by such Members as, being entitled so to do, vote in person or, in the case of any Member being a corporation, by its duly authorised representative or, where proxies are allowed, by proxy at a general meeting of which Notice has been duly given in accordance with Article 62;
"paid up"	paid up or credited as paid up;

"physical meeting"	a general meeting held and conducted by physical attendance by Members and/or proxies at one or more places specified by the Directors;
"Register"	the principal register and where applicable, any branch register of Members to be maintained at such place within or outside the Cayman Islands as the Board shall determine from time to time;
"Registration Office"	in respect of any class of share capital such place as the Board may from time to time determine to keep a branch register of Members in respect of that class of share capital and where (except in cases where the Board otherwise directs) the transfers or other documents of title for such class of share capital are to be lodged for registration and are to be registered;
"satellite location"	has the meaning given to it in article 65;
"Seal"	common seal or any one or more duplicate seals of the Company (including a securities seal) for use in the Cayman Islands or in any place outside the Cayman Islands;
"Secretary"	any person, firm or corporation appointed by the Board to perform any of the duties of secretary of the Company and includes any assistant, deputy, temporary or acting secretary;
"special resolution"	a resolution shall be a special resolution when it has been passed by a majority of not less than three-fourths of votes cast by such Members as, being entitled so to do, vote in person or, in the case of any Member being a corporation, by its duly authorised representative or, where proxies are allowed, by proxy at a general meeting of which Notice has been duly given in accordance with Article 62; a special resolution shall be effective for any purpose for which an ordinary resolution is expressed to be required under any provision of these Articles or the Statutes;
"Specified Place"	has the meaning given to it in article 65;
"Statutes"	the Law and every other law of the Legislature of the Cayman Islands for the time being in force applying to or affecting the Company, its memorandum of association and/or these Articles;
"Subsidiary and Holding Company"	the meanings attributed to them in the rules of the London Stock Exchange;
"year"	a calendar year;

"£"	the legal currency of the United Kingdom;
"HK$"	the legal currency of The Hong Kong Special Administrative Region of the People's Republic of China; and
"US$"	the legal currency of the United States of America.

(2) In these Articles, unless there be something within the subject or context inconsistent with such construction:

(a) words importing the singular include the plural and vice versa;

(b) words importing a gender include both gender and the neuter;

(c) words importing persons include companies, associations and bodies of persons whether corporate or not;

(d) the words:

(i) "may" shall be construed as permissive;

(ii) "shall" or "will" shall be construed as imperative;

(e) expressions referring to writing shall, unless the contrary intention appears, be construed as including printing, lithography, photography and other modes of representing words or figures in a visible form, and including where the representation takes the form of electronic display, provided that both the mode of service of the relevant document or notice and the Member's election comply with all applicable Statutes, rules and regulations;

(f) references to any law, ordinance, statute or statutory provision shall be interpreted as relating to any statutory modification or re-enactment thereof for the time being in force;

(g) save as aforesaid words and expressions defined in the Statutes shall bear the same meanings in these Articles if not inconsistent with the subject in the context;

(h) references to a document being executed include references to it being executed under hand or under seal or by electronic signature or by any other method and references to a notice or document include a notice or document recorded or stored in any digital, electronic, electrical, magnetic or other retrievable form or medium and information in visible form whether having physical substance or not; and

(i) Section 8 and Section 19 of the Electronic Transactions Law (2003) of the Cayman Islands, as amended from time to time, shall not apply to these Articles to the extent it imposes obligations or requirements in addition to those set out in these Articles.

SHARE CAPITAL

3. (1) As at the date of adoption of these Articles the authorised capital of the Company is US$150,000,000 divided into 1,500,000,000 Ordinary shares of a par value of US$0.10 each.

(2) Subject to the Law, the Company's Memorandum and Articles of Association and, where applicable, the rules of any Designated Stock Exchange and/or any competent regulatory authority, any power of the Company to purchase or otherwise acquire its own shares shall be exercisable by the Board in such manner, upon such terms and subject to such conditions as it thinks fit. The Company is hereby authorised to make payments in respect of the purchase of its shares out of capital or out of any other account or fund which can be authorised for this purpose in accordance with the Law.

(3) Except as allowed by the Law and subject further to compliance with the rules and regulations of any Designated Stock Exchange and any other competent regulatory authority the Company shall not give financial assistance for the purpose of or in connection with a purchase made or to be made by any person of any shares in the Company.

(4) No share shall be issued to bearer.

(5) The Board may accept the surrender for no consideration of any fully paid share.

ALTERATION OF CAPITAL

4. The Company may from time to time by ordinary resolution in accordance with the Law alter the conditions of its Memorandum to:

(a) increase its capital by such sum, to be divided into shares of such amounts, as the resolution shall prescribe;

(b) consolidate and divide all or any of its capital into shares of larger amount than its existing shares;

(c) divide its shares into several classes and without prejudice to any special rights previously conferred on the holders of existing shares attach thereto respectively any preferential, deferred, qualified or special rights, privileges, conditions or such restrictions which in the absence of any such determination by the Company in general meeting, as the Directors may determine provided always that where the Company issues shares which do not carry voting rights, the words "non-voting" shall appear in the designation of such shares and where the equity capital includes shares with different voting rights, the designation of each class of shares, other than those with the most favourable voting rights, must include the words "restricted voting" or "limited voting";

(d) sub-divide its shares, or any of them, into shares of smaller amount than is fixed by the Memorandum (subject, nevertheless, to the Law), and may by such resolution determine that, as between the holders of the shares resulting from such sub-division, one or more of the shares may have any such preferred, deferred or other rights or be subject to any such restrictions as compared with the other or others as the Company has power to attach to unissued or new shares;

(e) cancel any shares which, at the date of the passing of the resolution, have not been taken, or agreed to be taken, by any person, and diminish the amount of its capital by the amount of the shares so cancelled or, in the case of shares, without par value, diminish the number of shares into which its capital is divided.

5. The Board may settle as it considers expedient any difficulty which arises in relation to any consolidation and division under the last preceding Article and in particular but without prejudice to the generality of the foregoing may issue certificates in respect of fractions of shares or arrange for the sale of the shares representing fractions and the distribution of the net proceeds of sale (after deduction of the expenses of such sale) in due proportion amongst the Members who would have been entitled to the fractions, and for this purpose the Board may authorise some person to transfer the shares representing fractions to their purchaser or resolve that such net proceeds be paid to the Company for the Company's benefit. Such purchaser will not be bound to see to the application of the purchase money nor will his title to the shares be affected by any irregularity or invalidity in the proceedings relating to the sale.

6. The Company may from time to time by special resolution, subject to any confirmation or consent required by the Law, reduce its share capital or any capital redemption reserve or other undistributable reserve in any manner permitted by law.

7. Except so far as otherwise provided by the conditions of issue, or by these Articles, any capital raised by the creation of new shares shall be treated as if it formed part of the original capital of the Company, and such shares shall be subject to the provisions contained in these Articles with reference to the payment of calls and instalments, transfer and transmission, forfeiture, lien, cancellation, surrender, voting and otherwise.

SHARE RIGHTS

8. (1) Subject to the provisions of the Law and the Memorandum and Articles of Association and to any special rights conferred on the holders of any shares or class of shares, any share in the Company (whether forming part of the present capital or not) may be issued with or have attached thereto such rights or restrictions whether in regard to dividend, voting, return of capital or otherwise as the Company may by ordinary resolution determine or, if there has not been any such determination or so far as the same shall not make specific provision, as the Board may determine.

(2) Subject to the provisions of the Law, the rules of any Designated Stock Exchange and the Memorandum and Articles of Association of the Company, and to any special rights conferred on the holders of any shares or attaching to any class of shares, shares may be issued on the terms that they may be, or at the option of the Company or the holder are, liable to be redeemed on such terms and in such manner, including out of capital, as the Board may deem fit.

9. Subject to the Law, any preference shares may be issued or converted into shares that, at a determinable date or at the option of the Company or the holder if so authorised by its Memorandum, are liable to be redeemed on such terms and in such manner as the Company before the issue or conversion may by ordinary resolution of the Members determine.

10. Where the Company purchases for redemption a redeemable share, purchases not made through the market or by tender shall be limited to a maximum price as may from time to time be determined by the Company in general meeting, either generally or with regard to specific purchases. If purchases are by tender, tenders shall be available to all Members alike.

VARIATION OF RIGHTS

11. Subject to the Law and without prejudice to Article 8, all or any of the special rights for the time being attached to the shares or any class of shares may, unless otherwise provided by the terms of issue of the shares of that class, from time to time (whether or not the Company is being wound up) be varied, modified or abrogated either with the consent in writing of the holders of not less than three-fourths in

nominal value of the issued shares of that class or with the sanction of a special resolution passed at a separate general meeting of the holders of the shares of that class. To every such separate general meeting all the provisions of these Articles relating to general meetings of the Company shall, mutatis mutandis, apply, but so that:

(a) the necessary quorum (other than at an adjourned meeting) shall be two persons (or in the case of a Member being a corporation, its duly authorised representative) holding or representing by proxy not less than one-third in nominal value of the issued shares of that class and at any adjourned meeting of such holders, two holders present in person or (in the case of a Member being a corporation) its duly authorised representative or by proxy (whatever the number of shares held by them) shall be a quorum;

(b) every holder of shares of the class shall be entitled on a poll to one vote for every such share held by him; and

(c) any holder of shares of the class present in person or by proxy or authorised representative may demand a poll.

12. The special rights conferred upon the holders of any shares or class of shares shall not, unless otherwise expressly provided in the rights attaching to or the terms of issue of such shares, be deemed to be varied, modified or abrogated by the creation or issue of further shares ranking pari passu therewith.

SHARES

13. (1) Subject to the Law, these Articles (and in particular Article 13(3)), any direction that may be given by the Company in general meeting and, where applicable, the rules of any Designated Stock Exchange and without prejudice to any special rights or restrictions for the time being attached to any shares or any class of shares, the unissued shares of the Company (whether forming part of the original or any increased capital) shall be at the disposal of the Board, which may offer, allot, grant options over or otherwise dispose of them to such persons, at such times and for such consideration and upon such terms and conditions as the Board may in its absolute discretion determine but so that no shares shall be issued at a discount. Neither the Company nor the Board shall be obliged, when making or granting any allotment of, offer of, option over or disposal of shares, to make, or make available, any such allotment, offer, option or shares to Members or others with registered addresses in any particular territory or territories being a territory or territories where, in the absence of a registration statement or other special formalities, this would or might, in the opinion of the Board, be unlawful or impracticable. Members affected as a result of the foregoing sentence shall not be, or be deemed to be, a separate class of Members for any purpose whatsoever.

(2) The Board may issue warrants or convertible securities or securities of similar nature conferring the right upon the holders thereof to subscribe for any class of shares or securities in the capital of the Company on such terms as it may from time to time determine.

(3) (a) Notwithstanding any other provision of these Articles, the Board shall not exercise any power of the Company to allot relevant securities, unless they are authorised to do so by ordinary resolution of the Company in general meeting.

(b) In these Articles "relevant securities" means-

(i) shares in the Company other than shares shown in the Memorandum to have been taken by the subscribers to it or shares allotted in pursuance of an Employees' Share Scheme; and

(ii) any right to subscribe for, or to convert any security into, shares in the Company (other than shares so allotted);

and a reference to the allotment of relevant securities includes the grant of such a right but not the allotment of shares pursuant to such a right.

(c) Authority under this Article may be given for a particular exercise of the power or for its exercise generally, and may be unconditional or subject to conditions.

(d) In relation to the grant of such rights as are mentioned in sub-paragraph (b) (ii) of this Article the maximum amount of relevant securities that may be allotted under an authority given pursuant to this Article shall be treated as a reference to the maximum amount of shares which may be allotted pursuant to the rights.

(e) The Board may allot relevant securities, notwithstanding that any authority given under this Article has expired, if they are allotted in pursuance of an offer or agreement made by the Company before the authority expired.

(4) Unless the Company by special resolution directs otherwise, any new Equity Shares will be offered by the Directors for subscription to the holders of the Equity Shares in such proportions as equal (as nearly as possible) the proportion of Equity Shares held by them respectively at that time. For the purpose of this Article, all Equity Shares will be treated as one class of share and the provisions of the penultimate sentence of Article 13(1) shall apply to any such offer.

(5) The offer will be made by notice specifying the number and class of shares offered, the price per share, and a time (being not less than fourteen (14) days) within which the offer, if not accepted, will be deemed to be declined.

(6) Any shares not taken up at the end of the procedure set out in Article 13(5) may be offered by the Directors to a third party and such shares will be at the disposal of the Directors who may, subject to Article 13(3), allot, grant options over or otherwise dispose of them to such persons at such times and generally on such terms as they think fit. However:

(a) no Shares will be issued at a discount;

(b) no Shares will be issued more than three (3) months after the end of the period for acceptance of the last offer of such Shares under Article 13(5) unless the procedure set out in those Articles is repeated in respect of such Shares; and

(c) no Shares will be issued on terms which are more favourable than those on which they were offered to the Members.

(7) The provisions of Articles 13(4) to 13(6) will not apply to a particular allotment of Equity Shares if these are, or are to be:

(a) wholly or partly paid up otherwise than in cash; or

(b) issued in connection with or pursuant to an Employees' Share Scheme but otherwise will apply to all Equity Shares of the Company which may be issued from time to time.

(8) If, due to any inequality between the number of new shares to be issued and the number of shares held by Members entitled to have the offer of new shares made to them, any difficulty arises in the apportionment of any such new shares amongst the Members, such difficulties will be determined by the Board.

14. The Company may in connection with the issue of any shares exercise all powers of paying commission and brokerage conferred or permitted by the Law. Subject to the Law, the commission may be satisfied by the payment of cash or by the allotment of fully or partly paid shares or partly in one and partly in the other.

15. Except as required by law, no person shall be recognised by the Company as holding any share upon any trust and the Company shall not be bound by or required in any way to recognise (even when having notice thereof) any equitable, contingent, future or partial interest in any share or any fractional part of a share or (except only as otherwise provided by these Articles or by law) any other rights in respect of any share except an absolute right to the entirety thereof in the registered holder.

16. Subject to the Law and these Articles, the Board may at any time after the allotment of shares but before any person has been entered in the Register as the holder, recognise a renunciation thereof by the allottee in favour of some other person and may accord to any allottee of a share a right to effect such renunciation upon and subject to such terms and conditions as the Board considers fit to impose.

SHARE CERTIFICATES

17. Every share certificate shall be issued under the Seal or the signature of a single director (or in either case a facsimile thereof) and shall specify the number and class and distinguishing numbers (if any) of the shares to which it relates, and the amount paid up thereon and may otherwise be in such form as the Directors may from time to time determine. No certificate shall be issued representing shares of more than one class. The Board may by resolution determine, either generally or in any particular case or cases, that any signatures on any such certificates (or certificates in respect of other securities) need not be autographic but may be affixed to such certificates by some mechanical means or may be printed thereon.

18. (1) In the case of a share held jointly by several persons, the Company shall not be bound to issue more than one certificate therefor and delivery of a certificate to one of several joint holders shall be sufficient delivery to all such holders.

(2) Where a share stands in the names of two or more persons, the person first named in the Register shall as regards service of notices and, subject to the provisions of these Articles, all or any other matters connected with the Company, except the transfer of the shares, be deemed the sole holder thereof.

19. Every person whose name is entered, upon an allotment of shares, as a Member in the Register shall be entitled, without payment, to receive one certificate for all such shares of any one class or several certificates each for one or more of such shares of such class upon payment for every certificate after the first of such reasonable out-of-pocket expenses as the Board from time to time determines.

20. Share certificates shall be issued within the relevant time limit as prescribed by the Law or the rules of any Designated Stock Exchange may from time to time determine whichever is the shorter, after allotment or, except in the case of a transfer which the Company is for the time being entitled to refuse to register and does not register, after lodgment of a transfer with the Company.

21. (1) Upon every transfer of shares the certificate held by the transferor shall be given up to be cancelled, and shall forthwith be cancelled accordingly, and a new certificate shall be issued to the transferee in respect of the shares transferred to him at such fee as is provided in paragraph (2) of this Article. If any of the shares included in the certificate so given up shall be retained by the transferor a new certificate for the balance shall be issued to him at the aforesaid fee payable by the transferor to the Company in respect thereof.

(2) The fee referred to in paragraph (1) above shall be an amount not exceeding the relevant maximum amount as any Designated Stock Exchange may from time to time determine provided that the Board may at any time determine a lower amount for such fee.

22. If a share certificate shall be damaged or defaced or alleged to have been lost, stolen or destroyed a new certificate representing the same shares may be issued to the relevant Member upon request and on payment of such fee as prescribed in the rules of any Designated Stock Exchange to be the maximum fee payable or such lesser sum as the Board may determine and, subject to compliance with such terms (if any) as to evidence and indemnity and to payment of the costs and reasonable out-of-pocket expenses of the Company in investigating such evidence and preparing such indemnity as the Board may think fit and, in case of damage or defacement, on delivery of the old certificate to the Company provided always that where share warrants have been issued, no new share warrant shall be issued to replace one that has been lost unless the Directors are satisfied beyond reasonable doubt that the original has been destroyed.

LIEN

23. The Company shall have a first and paramount lien on every share (not being a fully paid share) for all moneys (whether presently payable or not) called or payable at a fixed time in respect of that share. The Company shall also have a first and paramount lien on every share (not being a fully paid share) registered in the name of a Member (whether or not jointly with other Members) for all amounts of money presently payable by such Member or his estate to the Company whether the same shall have been incurred before or after notice to the Company of any equitable or other interest of any person other than such Member, and whether the period for the payment or discharge of the same shall have actually arrived or not, and notwithstanding that the same are joint debts or liabilities of such Member or his estate and any other person, whether a Member of the Company or not. The Company's lien on a share shall extend to all dividends or other moneys payable thereon or in respect thereof. The Board may at any time, generally or in any particular case, waive any lien that has arisen or declare any share exempt in whole or in part, from the provisions of this Article.

24. Subject to these Articles, the Company may sell in such manner as the Board determines any share on which the Company has a lien, but no sale shall be made unless some sum in respect of which the lien exists is presently payable, or the liability or engagement in respect of which such lien exists is liable to be presently fulfilled or discharged nor until the expiration of fourteen clear days after a notice in writing,

stating and demanding payment of the sum presently payable, or specifying the liability or engagement and demanding fulfilment or discharge thereof and giving notice of the intention to sell in default, has been served on the registered holder for the time being of the share or the person entitled thereto by reason of his death or bankruptcy.

25. The net proceeds of the sale shall be received by the Company and applied in or towards payment or discharge of the debt or liability in respect of which the lien exists, so far as the same is presently payable, and any residue shall (subject to a like lien for debts or liabilities not presently payable as existed upon the share prior to the sale) be paid to the person entitled to the share at the time of the sale. To give effect to any such sale the Board may authorise some person to transfer the shares sold to the purchaser thereof. The purchaser shall be registered as the holder of the shares so transferred and he shall not be bound to see to the application of the purchase money, nor shall his title to the shares be affected by any irregularity or invalidity in the proceedings relating to the sale.

CALLS ON SHARES

26. Subject to these Articles and to the terms of allotment, the Board may from time to time make calls upon the Members in respect of any moneys unpaid on their shares (whether on account of the nominal value of the shares or by way of premium), and each Member shall (subject to being given at least fourteen (14) clear days' Notice specifying the time and place of payment) pay to the Company as required by such notice the amount called on his shares. A call may be extended, postponed or revoked in whole or in part as the Board determines but no Member shall be entitled to any such extension, postponement or revocation except as a matter of grace and favour.

27. A call shall be deemed to have been made at the time when the resolution of the Board authorising the call was passed and may be made payable either in one lump sum or by instalments.

28. A person upon whom a call is made shall remain liable for calls made upon him notwithstanding the subsequent transfer of the shares in respect of which the call was made. The joint holders of a share shall be jointly and severally liable to pay all calls and instalments due in respect thereof or other moneys due in respect thereof.

29. If a sum called in respect of a share is not paid before or on the day appointed for payment thereof, the person from whom the sum is due shall pay interest on the amount unpaid from the day appointed for payment thereof to the time of actual payment at such rate (not exceeding twenty per cent. (20%) per annum) as the Board may determine, but the Board may in its absolute discretion waive payment of such interest wholly or in part.

30. No Member shall be entitled to receive any dividend or bonus or to be present and vote (save as proxy for another Member) at any general meeting either personally or by proxy, or be reckoned in a quorum, or exercise any other privilege as a Member until all calls or instalments due by him to the Company, whether alone or jointly with any other person, together with interest and expenses (if any) shall have been paid.

31. On the trial or hearing of any action or other proceedings for the recovery of any money due for any call, it shall be sufficient to prove that the name of the Member sued is entered in the Register as the holder, or one of the holders, of the shares in respect of which such debt accrued, that the resolution making the call is duly recorded in the minute book, and that notice of such call was duly given to the Member sued, in pursuance of these Articles; and it shall not be necessary to prove the appointment of the Directors who made such call, nor any other matters whatsoever, but the proof of the matters aforesaid shall be conclusive evidence of the debt.

32. Any amount payable in respect of a share upon allotment or at any fixed date, whether in respect of nominal value or premium or as an instalment of a call, shall be deemed to be a call duly made and payable on the date fixed for payment and if it is not paid the provisions of these Articles shall apply as if that amount had become due and payable by virtue of a call duly made and notified.

33. On the issue of shares the Board may differentiate between the allottees or holders as to the amount of calls to be paid and the times of payment.

34. The Board may, if it thinks fit, receive from any Member willing to advance the same, and either in money or money's worth, all or any part of the moneys uncalled and unpaid or instalments payable upon any shares held by him and upon all or any of the moneys so advanced (until the same would, but for such advance, become presently payable) pay interest at such rate (if any) as the Board may decide. The Board may at any time repay the amount so advanced upon giving to such Member not less than one (1) month's Notice of its intention in that behalf, unless before the expiration of such notice the amount so advanced shall have been called up on the shares in respect of which it was advanced. Such payment in advance shall not entitle the holder of such share or shares to participate in respect thereof in a dividend subsequently declared.

FORFEITURE OF SHARES

35. (1) If a call remains unpaid after it has become due and payable the Board may give to the person from whom it is due not less than fourteen (14) clear days' Notice:

(a) requiring payment of the amount unpaid together with any interest which may have accrued and which may still accrue up to the date of actual payment; and

(b) stating that if the Notice is not complied with the shares on which the call was made will be liable to be forfeited.

(2) If the requirements of any such Notice are not complied with, any share in respect of which such Notice has been given may at any time thereafter, before payment of all calls and interest due in respect thereof has been made, be forfeited by a resolution of the Board to that effect, and such forfeiture shall include all dividends and bonuses declared in respect of the forfeited share but not actually paid before the forfeiture.

36. When any share has been forfeited, notice of the forfeiture shall be served upon the person who was before forfeiture the holder of the share. No forfeiture shall be invalidated by any omission or neglect to give such Notice.

37. The Board may accept the surrender of any share liable to be forfeited hereunder and, in such case, references in these Articles to forfeiture will include surrender.

38. Any share so forfeited shall be deemed the property of the Company and may be sold, re-allotted or otherwise disposed of to such person, upon such terms and in such manner as the Board determines, and at any time before a sale, re-allotment or disposition the forfeiture may be annulled by the Board on such terms as the Board determines.

39. A person whose shares have been forfeited shall cease to be a Member in respect of the forfeited shares but nevertheless shall remain liable to pay the Company all moneys which at the date of forfeiture were presently payable by him to the Company in respect of the shares, with (if the Directors shall in their discretion so require) interest thereon from the date of forfeiture until payment at such rate (not exceeding twenty per cent. (20%) per annum) as the Board determines. The Board may enforce payment thereof if it thinks fit, and without any deduction or allowance for the value of the forfeited shares, at the date of forfeiture, but his liability shall cease if and when the Company shall have received payment in full of all such moneys in respect of the shares. For the purposes of this Article any sum which, by the terms of issue of a share, is payable thereon at a fixed time which is subsequent to the date of forfeiture, whether on account of the nominal value of the share or by way of premium, shall notwithstanding that time has not yet arrived be deemed to be payable at the date of forfeiture, and the same shall become due and payable immediately upon the forfeiture, but interest thereon shall only be payable in respect of any period between the said fixed time and the date of actual payment.

40. A declaration by a Director or the Secretary that a share has been forfeited on a specified date shall be conclusive evidence of the facts therein stated as against all persons claiming to be entitled to the share, and such declaration shall (subject to the execution of an instrument of transfer by the Company if necessary) constitute a good title to the share, and the person to whom the share is disposed of shall be registered as the holder of the share and shall not be bound to see to the application of the consideration (if any), nor shall his title to the share be affected by any irregularity in or invalidity of the proceedings in reference to the forfeiture, sale or disposal of the share. When any share shall have been forfeited, notice of the declaration shall be given to the Member in whose name it stood immediately prior to the forfeiture, and an entry of the forfeiture, with the date thereof, shall forthwith be made in the register, but no forfeiture shall be in any manner invalidated by any omission or neglect to give such notice or make any such entry.

41. Notwithstanding any such forfeiture as aforesaid the Board may at any time, before any shares so forfeited shall have been sold, re-allotted or otherwise disposed of, permit the shares forfeited to be bought back upon the terms of payment of all calls and interest due upon and expenses incurred in respect of the share, and upon such further terms (if any) as it thinks fit.

42. The forfeiture of a share shall not prejudice the right of the Company to any call already made or instalment payable thereon.

43. The provisions of these Articles as to forfeiture shall apply in the case of non-payment of any sum which, by the terms of issue of a share, becomes payable at a fixed time, whether on account of the nominal value of the share or by way of premium, as if the same had been payable by virtue of a call duly made and notified.

REGISTER OF MEMBERS

44. (1) The Company shall keep in one or more books a Register of its Members and shall enter therein the following particulars, that is to say:

(a) the name and address of each Member, the number and class of shares held by him and the amount paid or agreed to be considered as paid on such shares;

(b) the date on which each person was entered in the Register; and

(c) the date on which any person ceased to be a Member.

(2) The Company may keep an overseas or local or other branch register of Members resident in any place, and the Board may make and vary such regulations as it determines in respect of the keeping of any such register and maintaining a Registration Office in connection therewith.

45. The Register and branch register of Members, as the case may be, shall be open to inspection for at least two (2) hours during business hours by Members without charge or by any other person, upon a maximum payment of HK$2.50 or such lesser sum specified by the Board, at the Office or such other place at which the Register is kept in accordance with the Law or, if appropriate, at the Registration Office. The Register including any overseas or local or other branch register of Members may, after notice has been given by advertisement in an appointed newspaper or any other newspapers in accordance with the requirements of any Designated Stock Exchange or by any electronic means in such manner as may be accepted by the Designated Stock Exchange to that effect, be closed at such times or for such periods not exceeding in the whole thirty (30) days in each year as the Board may determine and either generally or in respect of any class of shares.

RECORD DATES

46. Subject to the rules of any Designated Stock Exchange, notwithstanding any other provision of these Articles the Company or the Directors may fix any date as the record date for:

(a) determining the Members entitled to receive any dividend, distribution, allotment or issue; or

(b) determining the Members entitled to receive notice of and to vote at any general meeting of the Company.

TRANSFER OF SHARES

47. (1) Subject to these Articles, any Member may transfer all or any of his shares by an instrument of transfer in the usual or common form or in a form prescribed by the Designated Stock Exchange or in any other form approved by the Board and may be under hand or, if the transferor or transferee is a clearing house or its nominee(s), by hand or by machine imprinted signature or by such other manner of execution as the Board may approve from time to time.

(2) Notwithstanding the provisions of paragraph (1) above, for so long as any shares are listed on the Designated Stock Exchange, title to such listed shares may be evidenced and transferred in accordance with the laws applicable to and the rules and regulations of the Designated Stock Exchange that are or shall be applicable to such listed shares. The register of members of the Company in respect of its listed shares (whether the principal register or a branch register) may be kept by recording the particulars required by Section 40 of the Law in a form otherwise than legible if such recording otherwise complies with the laws applicable to and the rules and regulations of the Designated Stock Exchange that are or shall be applicable to such listed shares.

48. The instrument of transfer shall be executed by or on behalf of the transferor and the transferee provided that the Board may dispense with the execution of the instrument of transfer by the transferee in any case which it thinks fit in its discretion to do so. Without prejudice to the last preceding Article, the

Board may also resolve, either generally or in any particular case, upon request by either the transferor or transferee, to accept mechanically executed transfers. The transferor shall be deemed to remain the holder of the share until the name of the transferee is entered in the Register in respect thereof. Nothing in these Articles shall preclude the Board from recognising a renunciation of the allotment or provisional allotment of any share by the allottee in favour of some other person.

49. (1) The Board may, in its absolute discretion, and without giving any reason therefor, refuse to register a transfer of any share (not being a fully paid up share) to a person of whom it does not approve, or any share issued under any share incentive scheme for employees upon which a restriction on transfer imposed thereby still subsists, and it may also, without prejudice to the foregoing generality, refuse to register a transfer of any share to more than four (4) joint holders or a transfer of any share (not being a fully paid up share) on which the Company has a lien.

(2) No transfer shall be made to an infant or to a person of unsound mind or under other legal disability.

(3) The Board in so far as permitted by any applicable law may, in its absolute discretion, at any time and from time to time transfer any share upon the Register to any branch register or any share on any branch register to the Register or any other branch register. In the event of any such transfer, the Member requesting such transfer shall bear the cost of effecting the transfer unless the Board otherwise determines.

(4) Unless the Board otherwise agrees (which agreement may be on such terms and subject to such conditions as the Board in its absolute discretion may from time to time determine, and which agreement the Board shall, without giving any reason therefor, be entitled in its absolute discretion to give or withhold), no shares upon the Register shall be transferred to any branch register nor shall shares on any branch register be transferred to the Register or any other branch register and all transfers and other documents of title shall be lodged for registration, and registered, in the case of any shares on a branch register, at the relevant Registration Office, and, in the case of any shares on the Register, at the Office or such other place at which the Register is kept in accordance with the Law.

50. Without limiting the generality of the last preceding Article, the Board may decline to recognise any instrument of transfer unless:-

(a) a fee of such maximum sum as the rules of any Designated Stock Exchange may determine to be payable or such lesser sum as the Board may from time to time require is paid to the Company in respect thereof;

(b) the instrument of transfer is in respect of only one class of share;

(c) the instrument of transfer is lodged at the Office or such other place at which the Register is kept in accordance with the Law or the Registration Office (as the case may be) accompanied by the relevant share certificate(s) and such other evidence as the Board may reasonably require to show the right of the transferor to make the transfer (and, if the instrument of transfer is executed by some other person on his behalf, the authority of that person so to do); and

(d) if applicable, the instrument of transfer is duly and properly stamped.

51. If the Board refuses to register a transfer of any share, it shall, within two (2) months after the date on which the transfer was lodged with the Company, send to each of the transferor and transferee notice of the refusal.

52. (1) Notwithstanding Article 47, the Board may, subject to the Statutes and if permitted by the Law, permit shares of any class to be held in uncertificated form to be transferred without an instrument of transfer by means of a relevant system, including (without limitation) CREST.

(2) Where any class of shares is a participating security and the Company is entitled under the Law, these Articles or any applicable regulations to sell, transfer, dispose of, forfeit, re-allot, accept the surrender of or otherwise enforce a lien over a share held in uncertificated form without an instrument of transfer, the Company shall be entitled, subject to the Law, these Articles, any applicable regulations and the facilities and requirements of the relevant system:

(a) to require the holder of that uncertificated share by notice to change that share into certificated form within the period specified in the notice and to hold that share in certificated form so long as required by the Company;

(b) to require the holder of that uncertificated share by notice to give any instructions necessary to transfer title to that share by means of the relevant system within the period specified in the notice;

(c) to require the holder of that uncertificated share by notice to appoint any person to take any step, including without limitation the giving of any instructions by means of the relevant system, necessary to transfer that share within the period specified in the notice; and

(d) to take any action that the Board considers appropriate to achieve the sale, transfer, disposal of, forfeiture, re-allotment or surrender of that share or otherwise to enforce a lien in respect of it.

53. The registration of transfers of shares or of any class of shares may, after notice has been given by advertisement in any newspapers or by any other means in accordance with the requirements of any Designated Stock Exchange to that effect, be suspended and the register closed at such times and for such periods (not exceeding in the whole thirty (30) days in any year or such longer period as the Members may by ordinary resolution determine provided that such period shall not be extended beyond sixty (60) days in any year) as the Board may determine.

54. The Directors shall, subject always to the Law, any other applicable laws and regulations and the facilities and requirements of any relevant system concerned and these Articles, have power to implement and/or approve any arrangements they may, in their absolute discretion, think fit in relation to the evidencing of title to and transfer of interests in shares in the capital of the Company in the form of depositary interests or similar interests, instruments or securities, and to the extent such arrangements are so implemented, no provision of these Articles shall apply or have effect to the extent that it is in any respect inconsistent with the holding or transfer thereof or the shares in the capital of the Company represented thereby. The Directors may from time to time take such actions and do such things as they may, in their absolute discretion, think fit in relation to the operation of any such arrangements.

TRANSMISSION OF SHARES

55. If a Member dies, the survivor or survivors where the deceased was a joint holder, and his legal personal representatives where he was a sole or only surviving holder, will be the only persons recognised by the Company as having any title to his interest in the shares; but nothing in this Article will release the estate of a deceased Member (whether sole or joint) from any liability in respect of any share which had been solely or jointly held by him.

56. Any person becoming entitled to a share in consequence of the death or bankruptcy or winding- up of a Member may, upon such evidence as to his title being produced as may be required by the Board, elect either to become the holder of the share or to have some person nominated by him registered as the transferee thereof. If he elects to become the holder he shall notify the Company in writing either at the Registration Office or Office, as the case may be, to that effect. If he elects to have another person registered he shall execute a transfer of the share in favour of that person. The provisions of these Articles relating to the transfer and registration of transfers of shares shall apply to such notice or transfer as aforesaid as if the death or bankruptcy of the Member had not occurred and the notice or transfer were a transfer signed by such Member.

57. A person becoming entitled to a share by reason of the death or bankruptcy or winding-up of a Member shall be entitled to the same dividends and other advantages to which he would be entitled if he were the registered holder of the share. However, the Board may, if it thinks fit, withhold the payment of any dividend payable or other advantages in respect of such share until such person shall become the registered holder of the share or shall have effectually transferred such share, but, subject to the requirements of Article 77(2) being met, such a person may vote at meetings.

UNTRACEABLE MEMBERS

58. (1) Without prejudice to the rights of the Company under paragraph (2) of this Article, the Company may cease sending cheques for dividend entitlements or dividend warrants by post if such cheques or warrants have been left uncashed on two consecutive occasions. However, the Company may exercise the power to cease sending cheques for dividend entitlements or dividend warrants after the first occasion on which such a cheque or warrant is returned undelivered.

(2) The Company shall have the power to sell, in such manner as the Board thinks fit, any shares of a Member who is untraceable, but no such sale shall be made unless:

(a) all cheques or warrants in respect of dividends of the shares in question, being not less than three in total number, for any sum payable in cash to the holder of such shares in respect of them sent during the relevant period in the manner authorised by the Articles of the Company have remained uncashed;

(b) so far as it is aware at the end of the relevant period, the Company has not at any time during the relevant period received any indication of the existence of the Member who is the holder of such shares or of a person entitled to such shares by death, bankruptcy or operation of law; and

(c) the Company, if so required by the rules of the Designated Stock Exchange, has caused an advertisement in newspapers, or, subject to the requirements of the rules of the Designated Stock Exchange, by electronic communication in the manner in which notice may be served by the Company, giving notice of its intention to sell such shares, and a period of three (3) months or such shorter period as may be allowed by the Designated Stock Exchange has elapsed since the date of such advertisement and the Designated Stock Exchange has been notified of such intention, where appropriate.

For the purpose of the foregoing, the "relevant period" means the period commencing twelve years before the date of publication of the advertisement referred to in paragraph (c) of this Article and ending at the expiry of the period referred to in that paragraph.

(3) To give effect to any such sale the Board may authorise some person to transfer the said shares and an instrument of transfer signed or otherwise executed by or on behalf of such person shall be as effective as if it had been executed by the registered holder or the person entitled by transmission to such shares, and the purchaser shall not be bound to see to the application of the purchase money nor shall his title to the shares be affected by any irregularity or invalidity in the proceedings relating to the sale. The net proceeds of the sale will belong to the Company and upon receipt by the Company of such net proceeds it shall become indebted to the former Member for an amount equal to such net proceeds. No trust shall be created in respect of such debt and no interest shall be payable in respect of it and the Company shall not be required to account for any money earned from the net proceeds which may be employed in the business of the Company or as it thinks fit. Any sale under this Article shall be valid and effective notwithstanding that the Member holding the shares sold is dead, bankrupt or otherwise under any legal disability or incapacity.

GENERAL MEETINGS

59. An annual general meeting of the Company shall be held in each year (within a period of not more than fifteen (15) months after the holding of the last preceding annual general meeting, unless a longer period would not infringe the rules of the Designated Stock Exchange, if any) at such time and place as may be determined by the Board.

60. Each general meeting, other than an annual general meeting, shall be called an extraordinary general meeting. General meetings may be held in any location or locations in any part of the world as may be determined by the Board.

61. The Board may whenever it thinks fit call extraordinary general meetings. Any one or more Members holding at the date of deposit of the requisition not less than one-tenth of the paid up capital of the Company carrying the right of voting at general meetings of the Company shall at all times have the right, by written requisition to the Board or the Secretary of the Company, to require an extraordinary general meeting to be called by the Board for the transaction of any business specified in such requisition; and such meeting shall be held within two (2) months after the deposit of such requisition. If within twenty-one (21) days of such deposit the Board fails to proceed to convene such meeting the requisitionist(s) himself (themselves) may do so in the same manner, and all reasonable expenses incurred by the requisitionist(s) as a result of the failure of the Board shall be reimbursed to the requisitionist(s) by the Company.

NOTICE OF GENERAL MEETINGS

62. (1) An annual general meeting shall be called by Notice of not less than twenty-one (21) clear days. All other general meetings (including an extraordinary general meeting) shall be called by Notice of not less than fourteen (14) clear days but if permitted by the rules of the Designated Stock Exchange, a general meeting may be called by shorter notice, subject to the Law, if it is so agreed:

(a) in the case of a meeting called as an annual general meeting, by all the Members entitled to attend and vote thereat; and

(b) in the case of any other meeting, by a majority in number of the Members having the right to attend and vote at the meeting, being a majority together representing not less than ninety-five per cent. (95%) of the total voting rights at the meeting of all the Members.

To the extent the general meeting is to be held in Hong Kong or arrangement is to be made for Members to attend the general meeting in Hong Kong, notwithstanding any contrary provisions in these Articles, the Directors shall have the power to provide in every notice calling a general meeting that if a black rainstorm warning or a gale warning is in force in Hong Kong at a specific time on the day of the general meeting as specified in such notice, the general meeting will not be held on that day (the "Scheduled Meeting Day") but will, without further notice be automatically postponed and by virtue of that same notice, be held instead at a time on an alternative day (as specified in such notice) that falls within seven business days of the Scheduled Meeting Day. It shall not be a ground of objection to the validity of such notice that the notice calls a general meeting contingently on whether a black rainstorm warning or a gale warning is in force at the relevant time as specified in such notice.

(2) The notice shall specify the time and place of the meeting and particulars of resolutions to be considered at the meeting and, in case of special business, the general nature of the business. The notice convening an annual general meeting shall specify the meeting as such. A notice of the general meeting which is to be an electronic/hybrid meeting shall state details of the facilities for attendance and participation by electronic means at the meeting ("**electronic facilities**") or shall state where such details will be made available by the Company prior to the meeting. If satellite locations are provided for, the notice may, but shall not be required to, specify in the notice the satellite locations. Notice of every general meeting shall be given to all Members (other than to such Members as, under the provisions of these Articles or the terms of issue of the shares they hold, are not entitled to receive such notices from the Company), to all persons entitled to a share in consequence of the death or bankruptcy or winding-up of a Member and to each of the Directors and the Auditors.

(3) If, after the sending of the notice of an electronic/hybrid meeting but before the meeting is held (or after the adjournment of an electronic/hybrid meeting but before the adjourned meeting is held), the Directors consider that it is impractical, undesirable or unreasonable to hold the meeting at its stated time using electronic facilities they may, without sending a new notice of meeting, change the meeting to a physical meeting or change the electronic facilities (and make details of the new electronic facilities available in the manner stated in the notice of meeting) and/or postpone the time at which the meeting is to be held. An adjourned or postponed general meeting may be held as a physical meeting or an electronic/hybrid meeting irrespective of the form of the general meeting which was adjourned.

63. The accidental omission to give Notice of a meeting or (in cases where instruments of proxy are sent out with the Notice) to send such instrument of proxy to, or the non-receipt of such Notice or such instrument of proxy by, any person entitled to receive such Notice shall not invalidate any resolution passed or the proceedings at that meeting.

PROCEEDINGS AT GENERAL MEETINGS

64. All business shall be deemed special that is transacted at an extraordinary general meeting, and also all business that is transacted at an annual general meeting, with the exception of:

(a) the declaration and sanctioning of dividends;

(b) consideration and adoption of the accounts and balance sheet and the reports of the Directors and Auditors and other documents required to be annexed to the balance sheet;

(c) the election of Directors whether by rotation or otherwise in the place of those retiring;

(d) appointment of Auditors (where special notice of the intention for such appointment is not required by the Law) and other officers;

(e) the fixing of the remuneration of the Auditors, and the voting of remuneration or extra remuneration to the Directors;

(f) the granting of any mandate or authority to the Directors to offer, allot, grant options over, or otherwise dispose of the unissued shares of the Company representing not more than twenty per cent. (20%) (or such other percentage as may from time to time be specified in the Hong Kong Listing Rules) in nominal value of its then existing issued share capital and the number of any securities repurchased pursuant to paragraph (g) of this Article; and

(g) the granting of any mandate or authority to the Directors to repurchase securities of the Company.

65. (1) No business other than the appointment of chairman of a meeting shall be transacted at any general meeting unless a quorum is present at the commencement of the business. Two (2) Members entitled to vote and present in person (in the case of a Member being a corporation) by its duly authorised representative or by proxy shall form a quorum for all purposes. The Board may, at its absolute discretion, arrange for Members to attend a general meeting (including any adjourned or postponed meeting) by simultaneous attendance and participation at meeting location(s) using electronic means at such location or locations in any part of the world (each a "**satellite location**") as the Board may, at its absolute discretion, designate. The Members present in person or by proxy at the meeting location(s) shall be counted in the quorum for, and entitled to vote at, the subject general meeting, and that meeting shall be duly constituted and its proceedings valid provided that the Chairman of the meeting is satisfied that adequate electronic facilities are available throughout the meeting to ensure that Members attending at all the meeting locations are able to hear all those persons present and speak at the Specified Place and at any other meeting location held by electronic means and be heard by all other persons in the same way, but under no circumstances shall the inability of one or more Members or proxies to access, or continue to access, the electronic facilities despite adequate electronic facilities being made available by the Company, affect the validity of the meeting or any business conducted at the meeting. If it appears to the Chairman of the meeting that the electronic facilities for the meeting have become inadequate for the purposes of holding the meeting then the Chairman of the meeting may, with or without the consent of the meeting, adjourn the meeting (before or after it has started). The Chairman of the meeting shall be present at, and the meeting shall be deemed to take place, at the place specified in the notice convening a meeting as the place of the meeting (the "**Specified Place**"). The powers of the Chairman of the meeting shall apply equally to the satellite locations. Under no circumstances will a failure (for any reason) of

communication equipment, or any other failure in the arrangements for participation in a general meeting at more than one place, affect the validity of such meeting at the Specified Place, or any business conducted at such meeting.

(2) If within thirty (30) minutes (or such longer time not exceeding one hour as the chairman of the meeting may determine to wait) after the time appointed for the meeting a quorum is not present, the meeting, if convened on the requisition of Members, shall be dissolved. In any other case it shall stand adjourned to the same day in the next week at the same time and place or to such time and place as the Board may determine. If at such adjourned meeting a quorum is not present within half an hour from the time appointed for holding the meeting, the meeting shall be dissolved.

(3) If the Specified Place is inadequate to accommodate all Members entitled to attend who wish to do so, then provided that the following requirements are satisfied the meeting shall be duly constituted and its proceedings valid. These requirements are that the chairman of the meeting is satisfied that adequate facilities are available to ensure that any Member who is unable to be accommodated in the Specified Place is nonetheless able to participate in the business for which the meeting has been convened, to hear all persons present who speak thereat (whether personally or by microphones or loudspeakers or otherwise) whether in the Specified Place itself or elsewhere, and to be in like manner heard himself by all other Members present.

(4) If the Specified Place is inadequate to accommodate all Members entitled to attend and who wish to do so then the chairman may, in his absolute discretion, adjourn the meeting and the chairman of the meeting shall have power to specify some other place for holding the meeting, notwithstanding that by reason of such adjournment some Members may be unable to be present at such adjourned meeting. Any such person may nevertheless execute a form of proxy for the adjourned meeting and if he shall do so and shall deliver the same to the chairman of the meeting or to the Secretary or to a Member of the auditors, such proxy shall be valid notwithstanding that it is given at less notice than would otherwise be required under these Articles.

66. The chairman of the Company or if there is more than one chairman, any one of them as may be agreed amongst themselves or failing such agreement, any one of them elected by all the Directors present shall preside as chairman at a general meeting. If at any meeting no chairman, is present within fifteen (15) minutes after the time appointed for holding the meeting, or no-one is willing to act as chairman, the deputy chairman of the Company or if there is more than one deputy chairman, any one of them as may be agreed amongst themselves or failing such agreement, any one of them elected by all the Directors present shall preside as chairman. If no chairman or deputy chairman is present or is willing to act as chairman of the meeting, the Directors present shall choose one of their number to act, or if one Director only is present he shall preside as chairman if willing to act. If no Director is present, or if each of the Directors present declines to take the chair, or if the chairman chosen shall retire from the chair, the Members present in person or (in the case of a Member being a corporation) by its duly authorised representative or by proxy and entitled to vote shall elect one of their number to be chairman of the meeting.

67. The chairman may, with the consent of any meeting at which a quorum is present (and shall if so directed by the meeting), adjourn the meeting from time to time and from place to place as the meeting shall determine, but no business shall be transacted at any adjourned meeting other than the business which might lawfully have been transacted at the meeting had the adjournment not taken place. When a meeting is adjourned for fourteen (14) days or more, at least seven (7) clear days' notice of the adjourned meeting shall be given specifying the time and place of the adjourned meeting but it shall not be necessary to specify in such notice the nature of the business to be transacted at the adjourned meeting and the

general nature of the business to be transacted. Save as aforesaid, it shall be unnecessary to give notice of an adjournment. The Chairman of a general meeting shall, for the purpose of conducting the meeting in an orderly manner, have power to take all such steps and actions as he deems appropriate to maintain order during the meeting.

68. If an amendment is proposed to any resolution under consideration but is in good faith ruled out of order by the chairman of the meeting, the proceedings on the substantive resolution shall not be invalidated by any error in such ruling. In the case of a resolution duly proposed as a special resolution, no amendment thereto (other than a mere clerical amendment to correct a patent error) may in any event be considered or voted upon.

VOTING

69. (1) Subject to any special rights or restrictions as to voting for the time being attached to any shares by or in accordance with these Articles, at any general meeting on a poll every Member present in person or by proxy or, in the case of a Member being a corporation, by its duly authorised representative shall have one vote for every fully paid share of which he is the holder but no amount paid up or credited as paid up on a share in advance of calls or instalments is treated for the foregoing purposes as paid up on the share; and where a show of hands is allowed, every Member present in person or by proxy (or, in the case of a Member being a corporation, by its duly authorised representative) shall have one vote.

(2) A resolution put to the vote of a meeting shall be decided by way of a show of hands or, where required by the rules of any Designated Stock Exchange, by way of a poll, save that the chairman of the meeting may in good faith, allow a resolution which relates purely to a procedural or administrative matter to be voted on by a show of hands in which case every Member present in person (or being a corporation, is present by a duly authorized representative), or by proxy(ies) shall have one vote provided that where more than one proxy is appointed by a Member which is a clearing house (or its nominee(s)), each such proxy shall have one vote on a show of hands. For purposes of this Article, procedural and administrative matters are those that (i) are not on the agenda of the general meeting or in any supplementary circular that may be issued by the Company to its Members; and (ii) relate to the chairman's duties to maintain the orderly conduct of the meeting and/or allow the business of the meeting to be properly and effectively dealt with, whilst allowing all Members a reasonable opportunity to express their views.

(3) Where a show of hands is allowed, before or on the declaration of the result of the show of hands, a poll may be demanded:

(a) by the chairman of such meeting; or

(b) by at least five (5) Members present in person or in the case of a Member being a corporation by its duly authorised representative or by proxy for the time being entitled to vote at the meeting; or

(c) by a Member or Members present in person or in the case of a Member being a corporation by its duly authorised representative or by proxy and representing not less than one-tenth of the total voting rights of all Members having the right to vote at the meeting; or

(d) by a Member or Members present in person or in the case of a Member being a corporation by its duly authorised representative or by proxy and holding shares in the Company conferring a right to vote at the meeting being shares on which an

aggregate sum has been paid up equal to not less than one-tenth of the total sum paid up on all shares conferring that right.

A demand by a person as proxy for a Member or in the case of a Member being a corporation by its duly authorised representative shall be deemed to be the same as a demand by the Member.

70. Where a resolution is voted on by a show of hands, a declaration by the chairman that a resolution has been carried, or carried unanimously, or by a particular majority, or not carried by a particular majority, or lost, and an entry to that effect made in the minute book of the Company, shall be conclusive evidence of the facts without proof of the number or proportion of the votes recorded for or against the resolution. The result of the poll shall be deemed to be the resolution of the meeting. The Company shall only be required to disclose the voting figures on a poll if such disclosure is required by the rules of the Designated Stock Exchange.

71. A poll demanded on the election of a chairman, or on a question of adjournment, shall be taken forthwith. A poll demanded on any other question shall be taken in such manner (including the use of ballot or voting papers or tickets) and either forthwith or at such time (being not later than thirty (30) days after the date of the demand) and place as the chairman directs. It shall not be necessary (unless the chairman otherwise directs) for notice to be given of a poll not taken immediately.

72. The demand for a poll shall not prevent the continuance of a meeting or the transaction of any business other than the question on which the poll has been demanded, and, with the consent of the chairman, it may be withdrawn at any time before the close of the meeting or the taking of the poll, whichever is the earlier.

73. On a poll votes may be given either personally or by proxy.

74. A person entitled to more than one vote on a poll need not use all his votes or cast all the votes he uses in the same way.

75. All questions submitted to a meeting shall be decided by a simple majority of votes except where a greater majority is required by these Articles or by the Law. In the case of an equality of votes, whether on a show of hands or on a poll, the chairman of such meeting shall be entitled to a second or casting vote in addition to any other vote he may have.

76. Where there are joint holders of any share any one of such joint holder may vote, either in person or by proxy, in respect of such share as if he were solely entitled thereto, but if more than one of such joint holders be present at any meeting the vote of the senior who tenders a vote, whether in person or by proxy, shall be accepted to the exclusion of the votes of the other joint holders, and for this purpose seniority shall be determined by the order in which the names stand in the Register in respect of the joint holding. Several executors or administrators of a deceased Member in whose name any share stands shall for the purposes of this Article be deemed joint holders thereof.

77. (1) A Member who is a patient for any purpose relating to mental health or in respect of whom an order has been made by any court having jurisdiction for the protection or management of the affairs of persons incapable of managing their own affairs may vote, whether on a show of hands or on a poll, by his receiver, committee, curator bonis or other person in the nature of a receiver, committee or curator bonis appointed by such court, and such receiver, committee, curator bonis or other person may vote on a poll by proxy, and may otherwise act and be treated as if he were the registered holder of such shares for the purposes of general meetings, provided that such evidence as the Board may require of the authority of the person claiming to vote shall have been deposited at the Office, head office or Registration Office,

as appropriate, not less than forty-eight (48) hours before the time appointed for holding the meeting, or adjourned meeting or poll, as the case may be.

(2) Any person entitled under Article 56 to be registered as the holder of any shares may vote at any general meeting in respect thereof in the same manner as if he were the registered holder of such shares, provided that forty-eight (48) hours at least before the time of the holding of the meeting or adjourned meeting, as the case may be, at which he proposes to vote, he shall satisfy the Board of his entitlement to such shares, or the Board shall have previously admitted his right to vote at such meeting in respect thereof.

78. (1) No Member shall, unless the Board otherwise determines, be entitled to attend and vote and to be reckoned in a quorum at any general meeting unless he is duly registered and all calls or other sums presently payable by him in respect of shares in the Company have been paid, and prior to commencement of the general meeting to which it relates a Direction Notice (as defined in Article 79) shall have been served and not withdrawn.

(2) Where the Company has knowledge that any Member is, under the rules of the Designated Stock Exchange, required to abstain from voting on any particular resolution of the Company or restricted to voting only for or only against any particular resolution of the Company, any votes cast by or on behalf of such Member in contravention of such requirement or restriction shall not be counted.

79. (1) If any Member, or any other person appearing to be interested in shares held by such Member, has been duly served with a notice referred to in Section 793 of the English Act and is in default for the prescribed period referred to in this Article in supplying to the Company the information thereby required, then the Directors may in their absolute discretion at any time thereafter serve a notice (a "Direction Notice") upon such Member as follows:

(a) a Direction Notice may direct that, in respect of the shares in relation to which the default occurred (the "Default Shares") (which expression shall include any further shares which are issued in respect of such shares), the Member shall not be entitled to be present or to vote at any General Meeting either personally or by proxy or to exercise any other rights conferred by membership in relation to meetings of the Company; and

(b) where the Default Shares represent at least 0.25 per cent of the share capital of the Company, then the Direction Notice may additionally direct that:

(i) in respect of the Default Shares, any dividend or other money which would otherwise be payable on such shares shall be retained by the Company without any liability to pay interest thereon when such money is finally paid to the Member; and/or

(ii) no transfer of any of the Default Shares held by such Member shall be registered unless:

(a) the Member is not himself in default as regards supplying the information required; and

(b) the transfer is of part only of the Member's holding and when presented for registration is accompanied by a certificate of the Member in a form satisfactory to the Directors to that effect that

after due and careful enquiry the Directors are satisfied that no person in default as regards supplying such information is interested in any of the shares the subject of the transfer.

(c) The Company shall send to each other person appearing to be interested in the shares the subject of any Direction Notice a copy of the Direction Notice, but the failure or omission by the Company to do so shall not invalidate such Direction Notice. Neither the Company nor the Directors shall in any event be liable to any person as a result of the Directors having imposed any restrictions pursuant to this Article if the Directors have acted in good faith.

(d) Any Direction Notice shall have effect in accordance with its terms for so long as the default in respect of which it was issued continues. Any Direction Notice shall cease to have effect in relation to any shares which are transferred by such Member by means of an approved transfer. The Directors may at any time give notice cancelling a Direction Notice, in whole or in part, or suspending, in whole or part, the imposition of any restrictions contained in the Direction Notice for a given period.

(e) For the purposes of this Article:

(i) a person shall be treated as appearing to be interested in any shares if the Member holding such shares has given to the Company a notification referred to in Section 793 of the English Act which either (a) names such person as being so interested or (b) fails to establish the identities of those interested in the shares and (after taking into account the said notification) the Company knows or has reasonable cause to believe that the person in question is or may be interested in the shares;

(ii) the prescribed period in respect of any particular Member is twenty-eight

(28) days from the date of service of the said notice, except where the Default Shares represent at least 0.25 per cent of the share capital of the Company, in which case such period shall be reduced to fourteen (14) days; and

(iii) a transfer of shares is an approved transfer if, but only if:

(a) it is a transfer of shares to an offeror by way or in pursuant of acceptance of a takeover offer for a Company; or

(b) the Directors are satisfied that the transfer is made pursuant to a bona fide sale of the whole of the beneficial ownership of the shares to a party unconnected with a Member and any other persons appearing to be interested in such shares and the transfer results from a sale made through a recognised investment exchange (as defined in the Financial Services and Markets Act 2000 of the United Kingdom) or any stock exchange outside the United Kingdom on which the Company's shares are normally traded (apart from any sale resulting from matching bargains) through the relevant market.

(f) Reference to a person being in default in supplying to the Company the information required by a Direction Notice includes:

(i) reference to his having failed or refused to give all or any part of it; and

(ii) reference to his having given information which he knows to be false in a material particular or having recklessly given information which is false in a material particular.

(2) Where the Company has knowledge that any Member is, under the rules of any Designated Stock Exchange, required to abstain from voting on any particular resolution of the Company or restricted to voting only for or only against any particular resolution of the Company, any votes cast by or on behalf of such Member in contravention of such requirement or restriction shall not be counted.

80. If:

(a) any objection shall be raised to the qualification of any voter; or

(b) any votes have been counted which ought not to have been counted or which might have been rejected; or

(c) any votes are not counted which ought to have been counted;

the objection or error shall not vitiate the decision of the meeting or adjourned meeting on any resolution unless the same is raised or pointed out at the meeting or, as the case may be, the adjourned meeting at which the vote objected to is given or tendered or at which the error occurs. Any objection or error shall be referred to the chairman of the meeting and shall only vitiate the decision of the meeting on any resolution if the chairman decides that the same may have affected the decision of the meeting. The decision of the chairman on such matters shall be final and conclusive.

PROXIES

81. Any Member entitled to attend and vote at a meeting of the Company shall be entitled to appoint another person as his proxy to attend and vote instead of him. A Member who is the holder of two or more shares may appoint more than one proxy to represent him and vote on his behalf at a general meeting of the Company or at a class meeting. A proxy need not be a Member. In addition, a proxy or proxies representing either a Member who is an individual or a Member which is a corporation shall be entitled to exercise the same powers on behalf of the Member which he or they represent as such Member could exercise.

82. (1) The instrument appointing a proxy shall be in writing under the hand of the appointor or of his attorney duly authorised in writing or, if the appointor is a corporation, either under its seal or under the hand of an officer, attorney or other person authorised to sign the same. In the case of an instrument of proxy purporting to be signed on behalf of a corporation by an officer thereof it shall be assumed, unless the contrary appears, that such officer was duly authorised to sign such instrument of proxy on behalf of the corporation without further evidence of the facts.

(2) The Company may, at its absolute discretion, designate from time to time an electronic address for the receipt of any document or information relating to proxies for a meeting (including any instrument of proxy or invitation to appoint a proxy, any document necessary to show the validity of, or

otherwise relating to, an appointment of proxy and notice of termination of the authority of a proxy). If any document or information required to be sent to the Company under this Article is sent to the Company by electronic means, such document or information is not treated as validly delivered to or deposited with the Company if the same is not received by the Company at its designated electronic address in accordance with this Article or if no electronic address is so designated by the Company for the receipt of such document or information.

83. (1) The instrument appointing a proxy and (if required by the Board) the power of attorney or other authority (if any) under which it is signed, or a certified copy of such power or authority, shall (i) in the case of an appointment of proxy in hard copy form, be delivered to such place or one of such places (if any) as may be specified for that purpose in or by way of note to or in the form of proxy or any other document accompanying the notice convening the meeting (or, if no place is so specified at the Registration Office or the Office, as may be appropriate) not less than forty-eight (48) hours before the time appointed for holding the meeting or adjourned meeting at which the person named in the instrument proposes to vote or, (ii) in the case of an appointment of proxy in electronic form, be received at the electronic address as may be specified for that purpose in or by way of note to or in the form of proxy or any other document accompanying the notice convening the meeting not less than forty-eight (48) hours before the time appointed for holding the meeting or adjourned meeting at which the person named in the instrument proposes to vote, or (iii) in the case of a poll taken subsequently to the date of a meeting or adjourned meeting, not less than twenty-four (24) hours before the time appointed for the taking of the poll and in default the instrument of proxy shall not be treated as valid.

(2) No instrument appointing a proxy shall be valid after the expiration of twelve (12) months from the date named in it as the date of its execution, except at an adjourned meeting or on a poll demanded at a meeting or an adjourned meeting in cases where the meeting was originally held within twelve (12) months from such date. Delivery of an instrument appointing a proxy shall not preclude a Member from attending and voting in person at the meeting convened and in such event, the instrument appointing a proxy shall be deemed to be revoked.

84. Instruments of proxy shall be in any common form or in such other form as the Board may approve (provided that this shall not preclude the use of the two-way form) and the Board may, if it thinks fit, send out with the notice of any meeting forms of instrument of proxy for use at the meeting. The instrument of proxy shall be deemed to confer authority to demand or join in demanding a poll and to vote on any amendment of a resolution put to the meeting for which it is given as the proxy thinks fit. The instrument of proxy shall, unless the contrary is stated therein, be valid as well for any adjournment of the meeting as for the meeting to which it relates.

85. A vote given in accordance with the terms of an instrument of proxy shall be valid notwithstanding the previous death or insanity of the principal, or revocation of the instrument of proxy or of the authority under which it was executed, provided that no intimation in writing of such death, insanity or revocation shall have been received by the Company at the Office or the Registration Office (or such other place as may be specified for the delivery of instruments of proxy in the notice convening the meeting or other document sent therewith) forty-eight (48) hours at least before the commencement of the meeting or adjourned meeting, or the taking of the poll, at which the instrument of proxy is used.

86. Anything which under these Articles a Member may do by proxy he may likewise do by his duly appointed attorney and the provisions of these Articles relating to proxies and instruments appointing proxies shall apply mutatis mutandis in relation to any such attorney and the instrument under which such attorney is appointed.

CORPORATIONS ACTING BY REPRESENTATIVES

87. (1) Any corporation which is a Member may by resolution of its directors or other governing body authorise such person as it thinks fit to act as its representative at any meeting of the Company or at any meeting of any class of Members. The person so authorised shall be entitled to exercise the same powers on behalf of such corporation as the corporation could exercise if it were an individual Member and such corporation shall for the purposes of these Articles be deemed to be present in person at any such meeting if a person so authorised is present thereat.

(2) If a clearing house (or its nominee(s)), being a corporation, is a Member, it may authorise such persons as it thinks fit to act as its representatives at any meeting of the Company or at any meeting of any class of Members provided that, if more than one person is so authorised, the authorisation shall specify the number and class of shares in respect of which each such representative is so authorised. Each person so authorised under the provisions of this Article shall be deemed to have been duly authorised without further evidence of the facts and be entitled to exercise the same rights and powers on behalf of the clearing house (or its nominee(s)) as if such person was the registered holder of the shares of the Company held by the clearing house (or its nominee(s)) including, where a show of hands is allowed, the right to vote individually on a show of hands.

(3) Any reference in these Articles to a duly authorised representative of a Member being a corporation shall mean a representative authorised under the provisions of this Article.

WRITTEN RESOLUTIONS OF MEMBERS

88. A resolution in writing signed (in such manner as to indicate, expressly or impliedly, unconditional approval) by or on behalf of all persons for the time being entitled to receive notice of and to attend and vote at general meetings of the Company shall, for the purposes of these Articles, be treated as a resolution duly passed at a general meeting of the Company and, where relevant, as a special resolution so passed. Any such resolution shall be deemed to have been passed at a meeting held on the date on which it was signed by the last Member to sign, and where the resolution states a date as being the date of his signature thereof by any Member the statement shall be prima facie evidence that it was signed by him on that date. Such a resolution may consist of several documents in the like form, each signed by one or more relevant Members.

BOARD OF DIRECTORS

89. (1) Unless otherwise determined by the Company in general meeting, the number of Directors shall not be less than two (2). There shall be no maximum number of Directors unless otherwise determined from time to time by the Members in general meeting. The Directors shall be elected or appointed in the first place by the subscribers to the Memorandum or by a majority of them and thereafter in accordance with Article 90 called for such purpose and who shall hold office for such term as the Members may determine or, in the absence of such determination, in accordance with Article 90 or until their successors are elected or appointed or their office is otherwise vacated.

(2) Subject to the Articles and the Law, the Company may by ordinary resolution elect any person to be a Director either to fill a casual vacancy on the Board, or as an addition to the existing Board.

(3) The Directors shall have the power from time to time and at any time to appoint any person as a Director either to fill a casual vacancy on the Board or as an addition to the existing Board. Any Director so appointed by the Board shall hold office until either (i) the first general meeting of Members after his appointment (in the case of filling a casual vacancy) or (ii) the next following annual general meeting of the Company (in the case of an addition to the existing Board) and shall then be eligible for re-election at that meeting.

(4) Neither a Director nor an alternate Director shall be required to hold any shares of the Company by way of qualification and a Director or alternate Director (as the case may be) who is not a Member shall be entitled to receive notice of and to attend and speak at any general meeting of the Company and of all classes of shares of the Company.

(5) The Members may, at any general meeting convened and held in accordance with these Articles, by ordinary resolution remove a Director at any time before the expiration of his period of office notwithstanding anything to the contrary in these Articles or in any agreement between the Company and such Director (but without prejudice to any claim for damages under any such agreement).

(6) A vacancy on the Board created by the removal of a Director under the provisions of paragraph (5) above may be filled by the election or appointment by ordinary resolution of the Members at the meeting at which such Director is removed.

(7) The Company may from time to time in general meeting by ordinary resolution increase or reduce the number of Directors but so that the number of Directors shall never be less than two (2).

RETIREMENT OF DIRECTORS

90. (1) Notwithstanding any other provisions in the Articles, at each annual general meeting one- third of the Directors for the time being (or, if their number is not a multiple of three (3), the number nearest to but not less than one-third) shall retire from office by rotation provided that every Director shall be subject to retirement at an annual general meeting at least once every three (3) years.

(2) A retiring Director shall be eligible for re-election and shall continue to act as a Director throughout the meeting at which he retires. The Directors to retire by rotation shall include (so far as necessary to ascertain the number of directors to retire by rotation) any Director who wishes to retire and not to offer himself for re-election. Any further Directors so to retire shall be those of the other Directors subject to retirement by rotation who have been longest in office since their last re-election or appointment and so that as between persons who became or were last re-elected Directors on the same day those to retire shall (unless they otherwise agree among themselves) be determined by lot. Any Director appointed pursuant to Article 89(2), Article 89(3) or Article 89(6) shall not be taken into account in determining which particular Directors or the number of Directors who are to retire by rotation.

91. No person other than a Director retiring at the meeting shall, unless recommended by the Directors for election, be eligible for election as a Director at any general meeting unless a Notice signed by a Member (other than the person to be proposed) duly qualified to attend and vote at the meeting for which such notice is given of his intention to propose such person for election and also a Notice signed by the person to be proposed of his willingness to be elected shall have been lodged at the head office or at the Registration Office during the period as may from time to time be designated by the Company. Unless otherwise determined by the Directors and notified by the Company to the Members, the period for

lodgement of the above Notice(s) shall be a seven (7) day period commencing on the day after the despatch of the notice of the general meeting appointed for such election. If the Directors should so determine and notify the Members of a different period for lodgement of the said Notice(s), such period shall in any event be a period of not less than seven (7) days, commencing no earlier than the day after the despatch of the notice of the general meeting and ending no later than seven (7) days prior to the date of such general meeting.

DISQUALIFICATION OF DIRECTORS

92. The office of a Director shall be vacated if the Director:

(1) resigns his office by notice in writing delivered to the Company at the Office or tendered at a meeting of the Board;

(2) becomes of unsound mind or dies;

(3) without special leave of absence from the Board, is absent from meetings of the Board for six consecutive months, and his alternate Director, if any, shall not during such period have attended in his stead and the Board resolves that his office be vacated; or

(4) becomes bankrupt or has a receiving order made against him or suspends payment or compounds with his creditors;

(5) is prohibited by law from being a Director; or

(6) ceases to be a Director by virtue of any provision of the Statutes or is removed from office pursuant to these Articles.

EXECUTIVE DIRECTORS

93. The Board may from time to time appoint any one or more of its body to be a managing director, joint managing director or deputy managing director or to hold any other employment or executive office with the Company for such period (subject to their continuance as Directors) and upon such terms as the Board may determine and the Board may revoke or terminate any of such appointments. Any such revocation or termination as aforesaid shall be without prejudice to any claim for damages that such Director may have against the Company or the Company may have against such Director. A Director appointed to an office under this Article shall be subject to the same provisions as to removal as the other Directors of the Company, and he shall (subject to the provisions of any contract between him and the Company) ipso facto and immediately cease to hold such office if he shall cease to hold the office of Director for any cause.

94. Notwithstanding Articles 99, 100, 101 and 102, an executive director appointed to an office under Article 93 hereof shall receive such remuneration (whether by way of salary, commission, participation in on, or percentage of, operating revenue, profits or otherwise or by all or any of those modes) and such other benefits (including pension and/or gratuity and/or other benefits on retirement) and allowances as the Board may from time to time determine, and either in addition to or in lieu of his remuneration as a Director.

ALTERNATE DIRECTORS

95. Any Director may at any time by Notice delivered to the Office or head office or at a meeting of the Directors appoint any person (including another Director) to be his alternate Director. Any person so appointed shall have all the rights and powers of the Director or Directors for whom such person is appointed in the alternative provided that such person shall not be counted more than once in determining whether or not a quorum is present. An alternate Director may be removed at any time by the body which appointed him and, subject thereto, the office of alternate Director shall continue until the happening of any event which, if he were a Director, would cause him to vacate such office or if his appointer ceases for any reason to be a Director. Any appointment or removal of an alternate Director shall be effected by Notice signed by the appointer and delivered to the Office or head office or tendered at a meeting of the Board. An alternate Director may also be a Director in his own right and may act as alternate to more than one Director. An alternate Director shall, if his appointor so requests, be entitled to receive notices of meetings of the Board or of committees of the Board to the same extent as, but in lieu of, the Director appointing him and shall be entitled to such extent to attend and vote as a Director at any such meeting at which the Director appointing him is not personally present and generally at such meeting to exercise and discharge all the functions, powers and duties of his appointor as a Director and for the purposes of the proceedings at such meeting the provisions of these Articles shall apply as if he were a Director save that as an alternate for more than one Director his voting rights shall be cumulative.

96. An alternate Director shall only be a Director for the purposes of the Law and shall only be subject to the provisions of the Law insofar as they relate to the duties and obligations of a Director when performing the functions of the Director for whom he is appointed in the alternative and shall alone be responsible to the Company for his acts and defaults and shall not be deemed to be the agent of or for the Director appointing him. An alternate Director shall be entitled to contract and be interested in and benefit from contracts or arrangements or transactions and to be repaid expenses and to be indemnified by the Company to the same extent mutatis mutandis as if he were a Director but he shall not be entitled to receive from the Company any fee in his capacity as an alternate Director except only such part, if any, of the remuneration otherwise payable to his appointor as such appointor may by Notice to the Company from time to time direct.

97. Every person acting as an alternate Director shall have one vote for each Director for whom he acts as alternate (in addition to his own vote if he is also a Director). If his appointor is for the time being absent from Hong Kong or otherwise not available or unable to act, the signature of an alternate Director to any resolution in writing of the Board or a committee of the Board of which his appointor is a Member shall, unless the notice of his appointment provides to the contrary, be as effective as the signature of his appointor.

98. An alternate Director shall ipso facto cease to be an alternate Director if his appointor ceases for any reason to be a Director, however, such alternate Director or any other person may be re-appointed by the Directors to serve as an alternate Director PROVIDED always that, if at any meeting any Director retires but is re-elected at the same meeting, any appointment of such alternate Director pursuant to these Articles which was in force immediately before his retirement shall remain in force as though he had not retired.

DIRECTORS' FEES AND EXPENSES

99. Directors shall be paid out of the funds of the Company for their services subject to such limit (if any) as the Directors may from time to time determine. The Directors shall also receive by way of

additional fees for performing (in the view of the Directors or any committee of them so authorised) any special or extra services for the Company such further sums (if any) as the Company in General Meeting may from time to time determine. Such fees and additional fees shall be divided among the Directors in such proportion and manner as they may determine and in default of determination equally. Such remuneration shall be deemed to accrue from day to day. The provisions of this Article shall not apply to the remuneration of any Managing Director or executive Director which shall be determined pursuant to the other provisions of these Articles.

100. Each Director shall be entitled to be repaid or prepaid all travelling, hotel and incidental expenses reasonably incurred or expected to be incurred by him in attending meetings of the Board or committees of the Board or general meetings or separate meetings of any class of shares or of debentures of the Company or otherwise in connection with the discharge of his duties as a Director.

101. Any Director who, by request, goes or resides abroad for any purpose of the Company or who performs services which in the opinion of the Board go beyond the ordinary duties of a Director may be paid such extra remuneration (whether by way of salary, commission, participation in profits or otherwise) as the Board may determine and such extra remuneration shall be in addition to or in substitution for any ordinary remuneration provided for by or pursuant to any other Article.

102. (1) The remuneration of any Director holding executive office must, subject to the provisions of any contract between each of them and the Company, be fixed by the Directors, and must not be set as a commission on, or percentage of, operating revenue, profits or otherwise without the prior approval of the Members.

(2) The Board shall obtain the approval of the Company in general meeting before making any payment to any Director or past Director of the Company by way of compensation for loss of office, or as consideration for or in connection with his retirement from office (not being payment to which the Director is contractually entitled).

DIRECTORS' INTERESTS

103. A Director may:

(a) hold any other office or place of profit with the Company (except that of Auditor) in conjunction with his office of Director for such period and upon such terms as the Board may determine. Any remuneration (whether by way of salary, commission, participation in profits or otherwise) paid to any Director in respect of any such other office or place of profit shall be in addition to any remuneration provided for by or pursuant to any other Article;

(b) act by himself or his firm in a professional capacity for the Company (otherwise than as Auditor) and he or his firm may be remunerated for professional services as if he were not a Director;

(c) continue to be or become a director, managing director, joint managing director, deputy managing director, executive director, manager or other officer or member of any other company promoted by the Company or in which the Company may be interested as a vendor, Member or otherwise and (unless otherwise agreed) no such Director shall be accountable for any remuneration, profits or other benefits received by him as a director, managing director, joint managing director, deputy managing director, executive director, manager or other officer or member of or from his interests in any such other company. Subject as otherwise provided by these Articles the Directors may exercise or cause to be exercised the voting powers conferred by the shares in any other company held or owned by the Company,

or exercisable by them as Directors of such other company in such manner in all respects as they think fit (including the exercise thereof in favour of any resolution appointing themselves or any of them directors, managing directors, joint managing directors, deputy managing directors, executive directors, managers or other officers of such company) or voting or providing for the payment of remuneration to the director, managing director, joint managing director, deputy managing director, executive director, manager or other officers of such other company and any Director may vote in favour of the exercise of such voting rights in manner aforesaid notwithstanding that he may be, or about to be, appointed a director, managing director, joint managing director, deputy managing director, executive director, manager or other officer of such a company, and that as such he is or may become interested in the exercise of such voting rights in manner aforesaid.

104. Subject to the Law and to these Articles, no Director or proposed or intending Director shall be disqualified by his office from contracting with the Company, either with regard to his tenure of any office or place of profit or as vendor, purchaser or in any other manner whatever, nor shall any such contract or any other contract or arrangement in which any Director is in any way interested be liable to be avoided, nor shall any Director so contracting or being so interested be liable to account to the Company or the Members for any remuneration, profit or other benefits realised by any such contract or arrangement by reason of such Director holding that office or of the fiduciary relationship thereby established provided that such Director shall disclose the nature of his interest in any contract or arrangement in which he is interested in accordance with Article 105 herein.

105. (1) Subject to the Hong Kong Listing Rules and save as herein provided, a Director shall not vote on any resolution of the Board approving any contract, arrangement, transaction or any other proposal whatsoever in which he or any of his close associates is materially interested otherwise than by virtue of his interests in shares or debentures or other securities of or otherwise in or through the Company. A Director shall not be counted in the quorum at a meeting in relation to any resolution on which he is prohibited from voting.

(2) A Director shall (in the absence of some other material interest than is indicated below) be entitled to vote (and be counted in the quorum) in respect of any resolution including:

(a) any contract or arrangement for the giving to such Director or his close associate(s) any security or indemnity in respect of money lent by him or any of his close associate(s) or obligations incurred or undertaken by him or any of his close associate(s) at the request of or for the benefit of the Company or any of its subsidiaries;

(b) any contract or arrangement for the giving of any security or indemnity to a third party in respect of a debt or obligation of the Company or any of its subsidiaries for which the Director or his close associate(s) has himself/themselves assumed responsibility in whole or in part whether alone or jointly under a guarantee or indemnity or by the giving of security;

(c) any contract or arrangement concerning an offer of shares or debentures or other securities of or by the Company or any other company which the Company may promote or be interested in for subscription or purchase, where the Director or his close associate(s) is/are or is/are to be interested as a participant in the underwriting or sub-underwriting of the offer;

(d) any contract or arrangement in which the Director or his close associate(s) is/are interested in the same manner as other holders of shares or debentures or other securities of the Company by virtue only of his/their interest in shares or debentures or other securities of the Company;

(e) any contract, arrangement, transaction or other proposal concerning any other company in which he is interested, directly or indirectly and whether as an officer or Member or otherwise howsoever provided that he is not the holder of or beneficially interested in five (5) per cent or more of any class of the equity share capital of such company (or of a third company through which his interest is derived) or of the voting rights available to members of the relevant company (any such interest being deemed for the purpose of this Article to be a material interest in all circumstances);

(f) any contract, arrangement, transaction or other proposal concerning the adoption, modification or operation of a superannuation fund or retirement benefits scheme or employees' share scheme under which he may benefit and which either relates to both employees and Directors of the Company;

(g) any proposal or arrangement concerning the adoption, modification or operation of a share option scheme, a pension fund or retirement, death or disability benefits scheme or other arrangement which relates both to Directors or his close associate(s) and to employees of the Company or of any of its subsidiaries and does not provide in respect of any Director, or his close associate(s), as such any privilege or advantage not accorded generally to the class of persons to which such scheme or fund relates;

(h) any contract, arrangement, transaction or proposal concerning the adoption modification or operation of any scheme for enabling employees including full time executive Directors of the Company and/or any subsidiary to acquire shares of the Company or any arrangement for the benefit of employees of the Company or any of its subsidiaries under which the Director benefits in a similar manner to employees and which does not accord to any Director as such any privilege not accorded to the employees to whom the scheme relates; and

(i) any arrangement for purchasing or maintaining for any officer or auditor of the Company or any of its subsidiaries insurance against any liability which by virtue of any rule of law would otherwise attach to him in respect of any negligence, breach of duty or breach of trust for which he may be guilty in relation to the Company or any of its subsidiaries of which he is a director, officer or auditor.

(3) A Director shall not vote or be counted in the quorum on any resolution concerning his own appointment as the holder of any office or place of profit with the Company or any Company in which the Company is interested including fixing or varying the terms of his appointment or the termination thereof.

(4) If any question shall arise at any meeting of the Board as to the materiality of the interest of a Director (other than the chairman of the meeting) or as to the entitlement of any Director (other than such chairman) to vote and such question is not resolved by his voluntarily agreeing to abstain from voting, such question shall be referred to the chairman of the meeting and his ruling in relation to such other Director shall be final and conclusive except in a case where the nature or extent of the interest of the Director concerned as known to such Director has not been fairly disclosed to the Board. If any question as aforesaid shall arise in respect of the chairman of the meeting such question shall be decided

by a resolution of the Board (for which purpose such chairman shall not vote thereon) and such resolution shall be final and conclusive except in a case where the nature or extent of the interest of such chairman as known to such chairman has not been fairly disclosed to the Board.

(5) A Director who to his knowledge is, or whose close associate is, in any way, whether directly or indirectly, interested in a contract or arrangement or proposed contract or arrangement with the Company shall declare the nature of his or his close associate's interest at the meeting of the Board at which the question of entering into the contract or arrangement is first considered, if he knows his or his close associate's interest then exists, or in any other case at the first meeting of the Board after he knows that he or his close associate is or has become so interested. For the purposes of this Article, a general Notice to the Board by a Director to the effect that:

(a) he or his close associate is a member or officer of a specified company or firm and is to be regarded as interested in any contract or arrangement which may after the date of the Notice be made with that company or firm; or

(b) he or his close associate is to be regarded as interested in any contract or arrangement which may after the date of the Notice be made with a specified person who is connected with him;

shall be deemed to be a sufficient declaration of interest under this Article in relation to any such contract or arrangement, provided that no such Notice shall be effective unless either it is (i) given in writing at a meeting of the Board or the Director takes reasonable steps to secure that it is brought up and read at the next Board meeting after it is given, in which case it shall take effect on the date of the meeting of the Board or the next Board Meeting (as the case maybe); or (ii) in writing and sent to the Company in which case it shall take effect on the twenty-first day after the day on which it is sent, and the Company must send such general notice to the other Directors within fifteen days after the day it receives that notice.

106. The Directors may exercise the voting power conferred by the shares in any other company held or owned by the Company or exercisable by them as directors of such other company in such manner and in all respects as they think fit (including the exercise thereof in favour of any resolution appointing themselves or any of them directors or other officers or servants of such company or voting or providing for the payment of remuneration to such officers or servants).

106A. (1) If at any time the Company shall have a class of shares admitted to trading on AIM, a market operated by the London Stock Exchange, the provisions of chapter 5 of the Disclosure Guidance and Transparency Rules (as amended from time to time) of the UK Financial Conduct Authority Handbook ("DTR") shall be deemed to be incorporated by reference into these Articles and accordingly the vote holder and issuer notification rules as set out in the DTR shall apply to the Company and each Member of the Company as if the Company were an "issuer" (as defined in the DTR).

(2) Pursuant to Article 106A(l) above, for the purpose of the application of the DTR to the Company and each Member of the Company and for the purposes of this Article 106A only:

(a) the Company shall be deemed to be an "issuer" as defined in chapter 5 of the DTR (and not a "non-UK issuer");) ; and

(b) "shares" shall mean any class of shares in the Company admitted to trading on AIM, a market operated by the London Stock Exchange.

(3) For the avoidance of doubt, rules 5.9, 5.10 and 5.11 of chapter 5 of the DTR shall not apply to the Company or the Company's Members, as the case may be.

GENERAL POWERS OF THE DIRECTORS

107. (1) The business of the Company shall be managed and conducted by the Board, which may pay all expenses incurred in forming and registering the Company and may exercise all powers of the Company (whether relating to the management of the business of the Company or otherwise) which are not by the Statutes or by these Articles required to be exercised by the Company in general meeting, subject nevertheless to the provisions of the Statutes and of these Articles and to such regulations being not inconsistent with such provisions, as may be prescribed by the Company in general meeting, but no regulations made by the Company in general meeting shall invalidate any prior act of the Board which would have been valid if such regulations had not been made. The general powers given by this Article shall not be limited or restricted by any special authority or power given to the Board by any other Article.

(2) Any person contracting or dealing with the Company in the ordinary course of business shall be entitled to rely on any written or oral contract or agreement or deed, document or instrument entered into or executed as the case may be by any two of the Directors acting jointly on behalf of the Company and the same shall be deemed to be validly entered into or executed by the Company as the case may be and shall, subject to any rule of law, be binding on the Company.

(3) Without prejudice to the general powers conferred by these Articles it is hereby expressly declared that the Board shall have the following powers:

(a) To give to any person the right or option of requiring at a future date that an allotment shall be made to him of any share at par or at such premium as may be agreed.

(b) To give to any Directors, officers or servants of the Company an interest in any particular business or transaction or participation in the profits thereof or in the general profits of the Company either in addition to or in substitution for a salary or other remuneration.

(c) To resolve that the Company be deregistered in the Cayman Islands and continued in a named jurisdiction outside the Cayman Islands subject to the provisions of the Law.

(4) Except as permitted under the Law, the Company shall not directly or indirectly:

(i) make a loan to a Director or a director of any holding company of the Company or to any of their respective associates (as defined by the rules, where applicable, of the Designated Stock Exchange);

(ii) enter into any guarantee or provide any security in connection with a loan made by any person to a Director or such a director;

(iii) if any one or more of the Directors hold (jointly or severally or directly or indirectly) a controlling interest in another company, make a loan to that other company or enter into any guarantee or provide any security in connection with a loan made by any person to that other company; or

(iv) make any loan, directly or indirectly, to a Director or his close associate(s) if and to the extent it would be prohibited by the Companies Ordinance (Chapter 622 of the laws of Hong Kong) as if the Company were a company incorporated in Hong Kong.

Article 107(4)(iv) shall only have effect for so long as the shares of the Company are listed on the Hong Kong Stock Exchange.

108. The Board may establish any regional or local boards or agencies for managing any of the affairs of the Company in any place, and may appoint any persons to be members of such local boards, or any managers or agents, and may fix their remuneration (either by way of salary or by commission or by conferring the right to participation in the profits of the Company or by a combination of two or more of these modes) and pay the working expenses of any staff employed by them upon the business of the Company. The Board may delegate to any regional or local board, manager or agent any of the powers, authorities and discretions vested in or exercisable by the Board (other than its powers to make calls and forfeit shares), with power to sub-delegate, and may authorise the members of any of them to fill any vacancies therein and to act notwithstanding vacancies. Any such appointment or delegation may be made upon such terms and subject to such conditions as the Board may think fit, and the Board may remove any person appointed as aforesaid, and may revoke or vary such delegation, but no person dealing in good faith and without notice of any such revocation or variation shall be affected thereby.

109. The Board may by power of attorney appoint under the Seal any company, firm or person or any fluctuating body of persons, whether nominated directly or indirectly by the Board, to be the attorney or attorneys of the Company for such purposes and with such powers, authorities and discretions (not exceeding those vested in or exercisable by the Board under these Articles) and for such period and subject to such conditions as it may think fit, and any such power of attorney may contain such provisions for the protection and convenience of persons dealing with any such attorney as the Board may think fit, and may also authorise any such attorney to sub-delegate all or any of the powers, authorities and discretions vested in him. Such attorney or attorneys may, if so authorised under the Seal of the Company, execute any deed or instrument under their personal seal with the same effect as the affixation of the Company's Seal.

110. The Board may entrust to and confer upon a managing director, joint managing director, deputy managing director, an executive director or any Director any of the powers exercisable by it upon such terms and conditions and with such restrictions as it thinks fit, and either collaterally with, or to the exclusion of, its own powers, and may from time to time revoke or vary all or any of such powers but no person dealing in good faith and without notice of such revocation or variation shall be affected thereby.

111. All cheques, promissory notes, drafts, bills of exchange and other instruments, whether negotiable or transferable or not, and all receipts for moneys paid to the Company shall be signed, drawn, accepted, endorsed or otherwise executed, as the case may be, in such manner as the Board shall from time to time by resolution determine. The Company's banking accounts shall be kept with such banker or bankers as the Board shall from time to time determine.

112. (1) The Board may establish or concur or join with other companies (being subsidiary companies of the Company or companies with which it is associated in business) in establishing and making contributions out of the Company's moneys to any schemes or funds for providing pensions, sickness or compassionate allowances, life assurance or other benefits for employees (which expression as used in this and the following paragraph shall include any Director or ex-Director who may hold or have held any executive office or any office of profit under the Company or any of its subsidiary

companies) and ex-employees of the Company and their dependants or any class or classes of such person.

(2) The Board may pay, enter into agreements to pay or make grants of revocable or irrevocable, and either subject or not subject to any terms or conditions, pensions or other benefits to employees and ex-employees and their dependants, or to any of such persons, including pensions or benefits additional to those, if any, to which such employees or ex-employees or their dependants are or may become entitled under any such scheme or fund as mentioned in the last preceding paragraph. Any such pension or benefit may, as the Board considers desirable, be granted to an employee either before and in anticipation of or upon or at any time after his actual retirement.

(3) The Board may establish, maintain, support and subscribe to and contribute to all kinds of trusts, funds and schemes including but without prejudice to the generality of the foregoing share option, profit sharing and share incentive schemes and enter into any other arrangement permitted by law for the benefit of such persons referred to in Article 108 or any of them or any class of them and so that any Director shall be entitled to receive and retain any benefit under any such trust, fund, scheme, or arrangement.

BORROWING POWERS

113. The Board may exercise all the powers of the Company to raise or borrow money and to mortgage or charge all or any part of the undertaking, property and assets (present and future) and uncalled capital of the Company and, subject to the Law, to issue debentures, bonds and other securities, whether outright or as collateral security for any debt, liability or obligation of the Company or of any third party.

114. Debentures, bonds and other securities may be made assignable free from any equities between the Company and the person to whom the same may be issued.

115. Any debentures, bonds or other securities may be issued at a discount (other than shares), premium or otherwise and with any special privileges as to redemption, surrender, drawings, allotment of shares, attending and voting at general meetings of the Company, appointment of Directors and otherwise.

116. (1) Where any uncalled capital of the Company is charged, all persons taking any subsequent charge thereon shall take the same subject to such prior charge, and shall not be entitled, by notice to the Members or otherwise, to obtain priority over such prior charge.

(2) The Board shall cause a proper register to be kept, in accordance with the provisions of the Law, of all charges specifically affecting the property of the Company and of any series of debentures issued by the Company and shall duly comply with the requirements of the Law in regard to the registration of charges and debentures therein specified and otherwise.

PROCEEDINGS OF THE DIRECTORS

117. The Board may meet for the despatch of business, adjourn and otherwise regulate its meetings as it considers appropriate. Questions arising at any meeting shall be determined by a majority of votes. In the case of any equality of votes the chairman of the meeting shall have an additional or casting vote.

118. A meeting of the Board may be convened by the Secretary on request of a Director or by any Director. The Secretary shall convene a meeting of the Board whenever he shall be required so to do by any Director. Notice of a meeting of the Board shall be deemed to be duly given to a Director if it is given to such Director in writing or verbally (including in person or by telephone) or via electronic mail or in such other manner as the Board may from time to time determine.

119. (1) The quorum necessary for the transaction of the business of the Board may be fixed by the Board and, unless so fixed at any other number, shall be two (2). An alternate Director shall be counted in a quorum in the case of the absence of a Director for whom he is the alternate provided that he shall not be counted more than once for the purpose of determining whether or not a quorum is present.

(2) Directors may participate in any meeting of the Board by means of a conference telephone, electronic or other communications equipment through which all persons participating in the meeting can communicate with each other simultaneously and instantaneously and, for the purpose of counting a quorum, such participation shall constitute presence at a meeting as if those participating were present in person.

(3) Any Director who ceases to be a Director at a Board meeting may continue to be present and to act as a Director and be counted in the quorum until the termination of such Board meeting if no other Director objects and if otherwise a quorum of Directors would not be present.

120. The continuing Directors or a sole continuing Director may act notwithstanding any vacancy in the Board but, if and so long as the number of Directors is reduced below the minimum number fixed by or in accordance with these Articles, the continuing Directors or Director, notwithstanding that the number of Directors is below the number fixed by or in accordance with these Articles as the quorum or that there is only one continuing Director, may act for the purpose of filling vacancies in the Board or of summoning general meetings of the Company but not for any other purpose.

121. The Board may elect one or more chairman and one or more deputy chairman of its meetings and determine the period for which they are respectively to hold such office. If no chairman or deputy chairman is elected, or if at any meeting neither the chairman nor any deputy chairman is present within five (5) minutes after the time appointed for holding the same, the Directors present may choose one of their number to be chairman of the meeting.

122. A meeting of the Board at which a quorum is present shall be competent to exercise all the powers, authorities and discretions for the time being vested in or exercisable by the Board.

123. (1) The Board may delegate any of its powers, authorities and discretions to committees, consisting of such Director or Directors and other persons as it thinks fit, and they may, from time to time, revoke such delegation or revoke the appointment of and discharge any such committees either wholly or in part, and either as to persons or purposes. Any committee so formed shall, in the exercise of the powers, authorities and discretions so delegated, conform to any regulations which may be imposed on it by the Board.

(2) All acts done by any such committee in conformity with such regulations, and in fulfilment of the purposes for which it was appointed, but not otherwise, shall have like force and effect as if done by the Board, and the Board shall have power, with the consent of the Company in general meeting, to remunerate the members of any such committee, and charge such remuneration to the current expenses of the Company.

124. The meetings and proceedings of any committee consisting of two or more Members shall be governed by the provisions contained in these Articles for regulating the meetings and proceedings of the Board so far as the same are applicable and are not superseded by any regulations imposed by the Board under the last preceding Article.

125. (1) A resolution in writing signed by not less than two-thirds of the Board for the time being except such as are temporarily unable to act through ill-health or disability, and all the alternate Directors, if appropriate, whose appointors are temporarily unable to act as aforesaid shall (provided that such number is sufficient to constitute a quorum and further provided that a copy of such resolution has been given or the contents thereof communicated to all the Directors for the time being entitled to receive notices of Board meetings in the same manner as notices of meetings are required to be given by these Articles) be as valid and effectual as if a resolution had been passed at a meeting of the Board duly convened and held. Such resolution may be contained in one document or in several documents in like form each signed by one or more of the Directors or alternate Directors and for this purpose a facsimile signature of a Director or an alternate Director shall be treated as valid.

(2) Without prejudice to the provision of Article 125(1), a Director (or his alternate Director) may sign or otherwise signify agreement to resolution in writing of Directors. A Director (or his alternate Director) signifies agreement to a written resolution of Directors when the Company receives from that Director (or from his alternate Director) a document or notification in hard copy form or in electronic form as authenticated by that Director or by his alternate Director in a manner previously agreed between that Director and the Company:

(a) identifying the resolution to which it relates; and

(b) indicating that Director's agreement to the resolution.

Notwithstanding any contrary provisions contained in these Articles and subject to any applicable laws, rules and regulations:

(i) any signature of the Director or alternate Director to any such resolution in writing may be made electronically, and any such resolution bearing the electronic signature of any Director or alternate Director shall be as valid and effectual as if it were bearing the handwritten signature of the relevant Director or alternate Director. Any such resolution in writing may consist of several documents in like form each signed (whether in handwritten form or in electronic form as aforesaid) by one or more of the Directors or alternate Directors; and

(ii) any signification of agreement to resolution in writing of Directors authenticated as aforesaid shall be as valid and effectual as if the resolution had been signed by such Director or alternate Director, and a certificate by a Director or the Company Secretary of such signification and authentication shall be sufficient evidence without further proof thereof.

126. All acts bona fide done by the Board or by any committee or by any person acting as a Director or members of a committee, shall, notwithstanding that it is afterwards discovered that there was some defect in the appointment of any member of the Board or such committee or person acting as aforesaid or that they or any of them were disqualified or had vacated office, be as valid as if every such person had been duly appointed and was qualified and had continued to be a Director or member of such committee.

MANAGERS

127. The Board may from time to time appoint a general manager, a manager or managers of the Company and may fix his or their remuneration either by way of salary or commission or by conferring the right to participation in the profits of the Company or by a combination of two or more of these modes and pay the working expenses of any of the staff of the general manager, manager or managers who may be employed by him or them upon the business of the Company.

128. The appointment of such general manager, manager or managers may be for such period as the Board may decide, and the Board may confer upon him or them all or any of the powers of the Board as they may think fit.

129. The Board may enter into such agreement or agreements with any such general manager, manager or managers upon such terms and conditions in all respects as the Board may in their absolute discretion think fit, including a power for such general manager, manager or managers to appoint an assistant manager or managers or other employees whatsoever under them for the purpose of carrying on the business of the Company.

OFFICERS

130. (1) The officers of the Company shall consist of at least one chairman, the Directors and Secretary and such additional officers (who may or may not be Directors) as the Board may from time to time determine, all of whom shall be deemed to be officers for the purposes of the Law and these Articles.

(2) The Directors shall, as soon as may be after each appointment or election of Directors, elect amongst the Directors a chairman and if more than one (1) Director is proposed for this office, the Directors may elect more than one chairman in such manner as the Directors may determine.

(3) The officers shall receive such remuneration as the Directors may from time to time determine.

131. (1) The Secretary and additional officers, if any, shall be appointed by the Board and shall hold office on such terms and for such period as the Board may determine. If thought fit, two (2) or more persons may be appointed as joint Secretaries. The Board may also appoint from time to time on such terms as it thinks fit one or more assistant or deputy Secretaries.

(2) The Secretary or deputy or assistant Secretary shall attend all meetings of the Members and shall keep correct minutes of such meetings and enter the same in the proper books provided for the purpose. He shall perform such other duties as are prescribed by the Law or these Articles or as may be prescribed by the Board.

132. The officers of the Company shall have such powers and perform such duties in the management, business and affairs of the Company as may be delegated to them by the Directors from time to time.

133. A provision of the Law or of these Articles requiring or authorising a thing to be done by or to a Director and the Secretary shall not be satisfied by its being done by or to the same person acting both as Director and as or in place of the Secretary.

REGISTER OF DIRECTORS AND OFFICERS

134. (1) The Company shall cause to be kept in one or more books at its Office a Register of Directors and Officers in which there shall be entered the full names and addresses of the Directors and Officers and such other particulars as required by the Law or as the Directors may determine. The Company shall send to the Registrar of Companies in the Cayman Islands a copy of such register, and shall from time to time notify to the said Registrar of any change that takes place in relation to such Directors and Officers as required by the Law.

MINUTES

135. (1) The Board shall cause minutes to be duly entered in books provided for the purpose:

(a) of all elections and appointments of officers;

(b) of the names of the Directors present at each meeting of the Directors and of any committee of the Directors;

(c) of all resolutions and proceedings of each general meeting of the Members, meetings of the Board and meetings of committees of the Board and where there are managers, of all proceedings of meetings of the managers.

(2) Minutes shall be kept by the Secretary at the head office.

SEAL

136. (1) The Company shall have one or more Seals, as the Board may determine. For the purpose of sealing documents creating or evidencing securities issued by the Company, the Company may have a securities seal which is a facsimile of the Seal of the Company with the addition of the word "Securities" on its face or in such other form as the Board may approve. The Board shall provide for the custody of each Seal and no Seal shall be used without the authority of the Board or of a committee of the Board authorised by the Board in that behalf. Subject as otherwise provided in these Articles, any instrument to which a Seal is affixed shall be signed autographically by one Director and the Secretary or by two Directors or by such other person (including a Director) or persons as the Board may appoint, either generally or in any particular case, save that as regards any certificates for shares or debentures or other securities of the Company the Board may by resolution determine that such signatures or either of them shall be dispensed with or affixed by some method or system of mechanical signature. Every instrument executed in manner provided by this Article shall be deemed to be sealed and executed with the authority of the Board previously given.

(2) Where the Company has a Seal for use abroad, the Board may by writing under the Seal appoint any agent or committee abroad to be the duly authorised agent of the Company for the purpose of affixing and using such Seal and the Board may impose restrictions on the use thereof as may be thought fit. Wherever in these Articles reference is made to the Seal, the reference shall, when and so far as may be applicable, be deemed to include any such other Seal as aforesaid.

AUTHENTICATION OF DOCUMENTS

137. Any Director or the Secretary or any person appointed by the Board for the purpose may authenticate any documents affecting the constitution of the Company and any resolution passed by the Company or the Board or any committee, and any books, records, documents and accounts relating to the business of the Company, and to certify copies thereof or extracts therefrom as true copies or extracts, and if any books, records, documents or accounts are elsewhere than at the Office or the head office the local manager or other officer of the Company having the custody thereof shall be deemed to be a person so appointed by the Board. A document purporting to be a copy of a resolution, or an extract from the minutes of a meeting, of the Company or of the Board or any committee which is so certified shall be conclusive evidence in favour of all persons dealing with the Company upon the faith thereof that such resolution has been duly passed or, as the case may be, that such minutes or extract is a true and accurate record of proceedings at a duly constituted meeting.

DESTRUCTION OF DOCUMENTS

138. (1) The Company shall be entitled to destroy the following documents at the following times:

(a) any share certificate which has been cancelled at any time after the expiry of one (1) year from the date of such cancellation;

(b) any dividend mandate or any variation or cancellation thereof or any notification of change of name or address at any time after the expiry of two (2) years from the date such mandate variation cancellation or notification was recorded by the Company;

(c) any instrument of transfer of shares which has been registered at any time after the expiry of seven (7) years from the date of registration;

(d) any allotment letters after the expiry of seven (7) years from the date of issue thereof; and

(e) copies of powers of attorney, grants of probate and letters of administration at any time after the expiry of seven (7) years after the account to which the relevant power of attorney, grant of probate or letters of administration related has been closed;

and it shall conclusively be presumed in favour of the Company that every entry in the Register purporting to be made on the basis of any such documents so destroyed was duly and properly made and every share certificate so destroyed was a valid certificate duly and properly cancelled and that every instrument of transfer so destroyed was a valid and effective instrument duly and properly registered and that every other document destroyed hereunder was a valid and effective document in accordance with the recorded particulars thereof in the books or records of the Company. Provided always that: (1) the foregoing provisions of this Article shall apply only to the destruction of a document in good faith and without express notice to the Company that the preservation of such document was relevant to a claim; (2) nothing contained in this Article shall be construed as imposing upon the Company any liability in respect of the destruction of any such document earlier than as aforesaid or in any case where the conditions of proviso (1) above are not fulfilled; and (3) references in this Article to the destruction of any document include references to its disposal in any manner.

(2) Notwithstanding any provision contained in these Articles, the Directors may, if permitted by applicable law, authorise the destruction of documents set out in sub-paragraphs (a) to (e) of paragraph (1) of this Article and any other documents in relation to share registration which have been microfilmed or electronically stored by the Company or by the share registrar on its behalf provided always that this Article shall apply only to the destruction of a document in good faith and without express notice to the Company and its share registrar that the preservation of such document was relevant to a claim.

DIVIDENDS AND OTHER PAYMENTS

139. Subject to the Law, the Company in general meeting may from time to time declare final dividends in any currency to be paid to the Members but no final dividend shall be declared in excess of the amount recommended by the Board.

140. Dividends may be declared and paid out of the profits of the Company, realised or unrealised, or from any reserve set aside from profits which the Directors determine is no longer needed. With the sanction of an ordinary resolution dividends may also be declared and paid out of share premium account or any other fund or account which can be authorised for this purpose in accordance with the Law.

141. Except in so far as the rights attaching to, or the terms of issue of, any share otherwise provide:

(a) all dividends shall be declared and paid according to the amounts paid up on the shares in respect of which the dividend is paid, but no amount paid up on a share in advance of calls shall be treated for the purposes of this Article as paid up on the share; and

(b) all dividends shall be apportioned and paid pro rata according to the amounts paid up on the shares during any portion or portions of the period in respect of which the dividend is paid.

142. The Board may from time to time pay to the Members such interim dividends as appear to the Board to be justified by the profits of the Company and in particular (but without prejudice to the generality of the foregoing) if at any time the share capital of the Company is divided into different classes, the Board may pay such interim dividends in respect of those shares in the capital of the Company which confer on the holders thereof deferred or non-preferential rights as well as in respect of those shares which confer on the holders thereof preferential rights with regard to dividend and provided that the Board acts bona fide the Board shall not incur any responsibility to the holders of shares conferring any preference for any damage that they may suffer by reason of the payment of an interim dividend on any shares having deferred or non-preferential rights and may also pay any fixed dividend which is payable on any shares of the Company half yearly or on any other dates, whenever such profits, in the opinion of the Board, justifies such payment.

143. The Board may deduct from any dividend or other moneys payable to a Member by the Company on or in respect of any shares all sums of money (if any) presently payable by him to the Company on account of calls or otherwise.

144. No dividend or other moneys payable by the Company on or in respect of any share shall bear interest against the Company.

145. Any dividend, interest or other sum payable in cash to the holder of shares may be paid by cheque or warrant sent through the post addressed to the holder at his registered address or, in the case of joint holders, addressed to the holder whose name stands first in the Register in respect of the shares at his

address as appearing in the Register or addressed to such person and at such address as the holder or joint holders may in writing direct. Every such cheque or warrant shall, unless the holder or joint holders otherwise direct, be made payable to the order of the holder or, in the case of joint holders, to the order of the holder whose name stands first on the Register in respect of such shares, and shall be sent at his or their risk and payment of the cheque or warrant by the bank on which it is drawn shall constitute a good discharge to the Company notwithstanding that it may subsequently appear that the same has been stolen or that any endorsement thereon has been forged. Any one of two or more joint holders may give effectual receipts for any dividends or other moneys payable or property distributable in respect of the shares held by such joint holders.

146. All dividends or bonuses unclaimed for one (1) year after having been declared may be invested or otherwise made use of by the Board for the benefit of the Company until claimed. Any dividend or bonuses unclaimed after a period of six (6) years from the date of declaration shall be forfeited and shall revert to the Company. The payment by the Board of any unclaimed dividend or other sums payable on or in respect of a share into a separate account shall not constitute the Company a trustee in respect thereof.

147. Whenever the Board or the Company in general meeting has resolved that a dividend be paid or declared, the Board may further resolve that such dividend be satisfied wholly or in part by the distribution of specific assets of any kind and in particular of paid up shares, debentures or warrants to subscribe securities of the Company or any other company, or in any one or more of such ways, and where any difficulty arises in regard to the distribution the Board may settle the same as it thinks expedient, and in particular may issue certificates in respect of fractions of shares, disregard fractional entitlements or round the same up or down, and may fix the value for distribution of such specific assets, or any part thereof, and may determine that cash payments shall be made to any Members upon the footing of the value so fixed in order to adjust the rights of all parties, and may vest any such specific assets in trustees as may seem expedient to the Board and may appoint any person to sign any requisite instruments of transfer and other documents on behalf of the persons entitled to the dividend, and such appointment shall be effective and binding on the Members. The Board may resolve that no such assets shall be made available to Members with registered addresses in any particular territory or territories where, in the absence of a registration statement or other special formalities, such distribution of assets would or might, in the opinion of the Board, be unlawful or impracticable and in such event the only entitlement of the Members aforesaid shall be to receive cash payments as aforesaid. Members affected as a result of the foregoing sentence shall not be or be deemed to be a separate class of Members for any purpose whatsoever.

148. (1) Whenever the Board or the Company in general meeting has resolved that a dividend be paid or declared on any class of the share capital of the Company, the Board may further resolve either:

(a) that such dividend be satisfied wholly or in part in the form of an allotment of shares credited as fully paid up, provided that the Members entitled thereto will be entitled to elect to receive such dividend (or part thereof if the Board so determines) in cash in lieu of such allotment. In such case, the following provisions shall apply:

(i) the basis of any such allotment shall be determined by the Board;

(ii) the Board, after determining the basis of allotment, shall give not less than two (2) weeks' Notice to the holders of the relevant shares of the right of election accorded to them and shall send with such notice forms of election and specify the procedure to be followed and the place at which and the latest date and time by which duly completed forms of election must be lodged in order to be effective;

(iii) the right of election may be exercised in respect of the whole or part of that portion of the dividend in respect of which the right of election has been accorded; and

(iv) the dividend (or that part of the dividend to be satisfied by the allotment of shares as aforesaid) shall not be payable in cash on shares in respect whereof the cash election has not been duly exercised ("the non-elected shares") and in satisfaction thereof shares of the relevant class shall be allotted credited as fully paid up to the holders of the non-elected shares on the basis of allotment determined as aforesaid and for such purpose the Board shall capitalise and apply out of any part of the undivided profits of the Company (including profits carried and standing to the credit of any reserves or other special account, share premium account, capital redemption reserve other than the Subscription Rights Reserve) as the Board may determine, such sum as may be required to pay up in full the appropriate number of shares of the relevant class for allotment and distribution to and amongst the holders of the non-elected shares on such basis; or

(b) that the Members entitled to such dividend shall be entitled to elect to receive an allotment of shares credited as fully paid up in lieu of the whole or such part of the dividend as the Board may think fit. In such case, the following provisions shall apply:

(i) the basis of any such allotment shall be determined by the Board;

(ii) the Board, after determining the basis of allotment, shall give not less than two (2) weeks' Notice to the holders of the relevant shares of the right of election accorded to them and shall send with such notice forms of election and specify the procedure to be followed and the place at which and the latest date and time by which duly completed forms of election must be lodged in order to be effective;

(iii) the right of election may be exercised in respect of the whole or part of that portion of the dividend in respect of which the right of election has been accorded; and

(iv) the dividend (or that part of the dividend in respect of which a right of election has been accorded) shall not be payable in cash on shares in respect whereof the share election has been duly exercised ("the elected shares") and in lieu thereof shares of the relevant class shall be allotted credited as fully paid up to the holders of the elected shares on the basis of allotment determined as aforesaid and for such purpose the Board shall capitalise and apply out of any part of the undivided profits of the Company (including profits carried and standing to the credit of any reserves or other special account, share premium account, capital redemption reserve other than the Subscription Rights Reserve) as the Board may determine, such sum as may be required to pay up in full the appropriate number of shares of the relevant class for allotment and distribution to and amongst the holders of the elected shares on such basis.

(2) (a) The shares allotted pursuant to the provisions of paragraph (1) of this Article shall rank pari passu in all respects with shares of the same class (if any) then in issue save only as regards participation in the relevant dividend or in any other distributions, bonuses or rights paid, made, declared or announced prior to or contemporaneously with the payment or declaration of the relevant dividend unless, contemporaneously with the announcement by the Board of their proposal to apply the provisions of sub-paragraph (a) or (b) of paragraph (2) of this Article in relation to the relevant dividend or contemporaneously with their announcement of the distribution, bonus or rights in question, the Board shall specify that the shares to be allotted pursuant to the provisions of paragraph (1) of this Article shall rank for participation in such distribution, bonus or rights.

(b) The Board may do all acts and things considered necessary or expedient to give effect to any capitalisation pursuant to the provisions of paragraph (1) of this Article, with full power to the Board to make such provisions as it thinks fit in the case of shares becoming distributable in fractions (including provisions whereby, in whole or in part, fractional entitlements are aggregated and sold and the net proceeds distributed to those entitled, or are disregarded or rounded up or down or whereby the benefit of fractional entitlements accrues to the Company rather than to the Members concerned). The Board may authorise any person to enter into on behalf of all Members interested, an agreement with the Company providing for such capitalisation and matters incidental thereto and any agreement made pursuant to such authority shall be effective and binding on all concerned.

(3) The Company may upon the recommendation of the Board by ordinary resolution resolve in respect of any one particular dividend of the Company that notwithstanding the provisions of paragraph (1) of this Article a dividend may be satisfied wholly in the form of an allotment of shares credited as fully paid up without offering any right to Members to elect to receive such dividend in cash in lieu of such allotment.

(4) The Board may on any occasion determine that rights of election and the allotment of shares under paragraph (1) of this Article shall not be made available or made to any Members with registered addresses in any territory where, in the absence of a registration statement or other special formalities, the circulation of an offer of such rights of election or the allotment of shares would or might, in the opinion of the Board, be unlawful or impracticable, and in such event the provisions aforesaid shall be read and construed subject to such determination. Members affected as a result of the foregoing sentence shall not be or be deemed to be a separate class of Members for any purpose whatsoever.

(5) Any resolution declaring a dividend on shares of any class, whether a resolution of the Company in general meeting or a resolution of the Board, may specify that the same shall be payable or distributable to the persons registered as the holders of such shares at the close of business on a particular date, notwithstanding that it may be a date prior to that on which the resolution is passed, and thereupon the dividend shall be payable or distributable to them in accordance with their respective holdings so registered, but without prejudice to the rights inter se in respect of such dividend of transferors and transferees of any such shares. The provisions of this Article shall mutatis mutandis apply to bonuses, capitalisation issues, distributions of realised capital profits or offers or grants made by the Company to the Members.

RESERVES

149. (1) The Board shall establish an account to be called the share premium account and shall carry to the credit of such account from time to time a sum equal to the amount or value of the premium paid on the issue of any share in the Company. Unless otherwise provided by the provisions of these Articles, the Board may apply the share premium account in any manner permitted by the Law. The Company shall at all times comply with the provisions of the Law in relation to the share premium account.

(2) Before recommending any dividend, the Board may set aside out of the profits of the Company such sums as it determines as reserves which shall, at the discretion of the Board, be applicable for any purpose to which the profits of the Company may be properly applied and pending such application may, also at such discretion, either be employed in the business of the Company or be invested in such investments as the Board may from time to time think fit and so that it shall not be necessary to keep any investments constituting the reserve or reserves separate or distinct from any other investments of the Company. The Board may also without placing the same to reserve carry forward any profits which it may think prudent not to distribute.

CAPITALISATION

150. The Company may, upon the recommendation of the Board, at any time and from time to time pass an ordinary resolution to the effect that it is desirable to capitalise all or any part of any amount for the time being standing to the credit of any reserve or fund (including a share premium account and capital redemption reserve and the profit and loss account) whether or not the same is available for distribution and accordingly that such amount be set free for distribution among the Members or any class of Members who would be entitled thereto if it were distributed by way of dividend and in the same proportions, on the footing that the same is not paid in cash but is applied either in or towards paying up the amounts for the time being unpaid on any shares in the Company held by such Members respectively or in paying up in full unissued shares, debentures or other obligations of the Company, to be allotted and distributed credited as fully paid up among such Members, or partly in one way and partly in the other, and the Board shall give effect to such resolution provided that, for the purposes of this Article, a share premium account and any capital redemption reserve or fund representing unrealised profits, may be applied only in paying up in full unissued shares of the Company to be allotted to such Members credited as fully paid.

151. Notwithstanding any provisions in these Articles, the Board may resolve to capitalise all or any part of any amount for the time being standing to the credit of any reserve or fund (including a share premium account and the profit and loss account) whether or not the same is available for distribution by applying such sum in paying up unissued shares to be allotted to (i) employees (including directors) of the Company and/or its affiliates (meaning any individual, corporation, partnership, association, joint-stock company, trust, unincorporated association or other entity (other than the Company) that directly, or indirectly through one or more intermediaries, controls, is controlled by or is under common control with, the Company) upon exercise or vesting of any options or awards granted under any share incentive scheme or employee benefit scheme or other arrangement which relates to such persons that has been adopted or approved by the Members at a general meeting, or (ii) any trustee of any trust to whom shares are to be allotted and issued by the Company in connection with the operation of any share incentive scheme or employee benefit scheme or other arrangement which relates to such persons that has been adopted or approved by the Members at a general meeting.

152. The Board may settle, as it considers appropriate, any difficulty arising in regard to any distribution under the last preceding Article and in particular may issue certificates in respect of fractions of shares or authorise any person to sell and transfer any fractions or may resolve that the distribution should be as nearly as may be practicable in the correct proportion but not exactly so or may ignore fractions altogether, and may determine that cash payments shall be made to any Members in order to adjust the rights of all parties, as may seem expedient to the Board. The Board may appoint any person to sign on behalf of the persons entitled to participate in the distribution any contract necessary or desirable for giving effect thereto and such appointment shall be effective and binding upon the Members.

SECURITY ARRANGEMENTS, ORDERLY CONDUCT AND CONFIDENTIAL INFORMATION

153. (1) The Directors can put in place arrangement, both before and during any general meeting, which they consider to be appropriate for the proper and orderly conduct of the general meeting and the safety of people attending it. This authority includes power to refuse entry to, or remove from meetings, people who fail to comply with the arrangements.

(2) The Chairman of a meeting can take any action he considers appropriate for proper and orderly conduct at a general meeting. The Chairman's decision on points of order, matters of procedure or on matters that arise incidentally from the business of a meeting is final, as is the Chairman's decision on whether a point or matter is of this nature.

(3) No Member at a general meeting is entitled to require disclosure of or any information about any detail of the Company's trading, or any matter that is or may be in the nature of a trade secret, commercial secret or secret process, or that may relate to the conduct of the business of the Company, if the directors decide it would be inexpedient in the interests of the company to make that information public.

SUBSCRIPTION RIGHTS RESERVE

154. The following provisions shall have effect to the extent that they are not prohibited by and are in compliance with the Law:

(1) If, so long as any of the rights attached to any warrants issued by the Company to subscribe for shares of the Company shall remain exercisable, the Company does any act or engages in any transaction which, as a result of any adjustments to the subscription price in accordance with the provisions of the conditions of the warrants, would reduce the subscription price to below the par value of a share, then the following provisions shall apply:

(a) as from the date of such act or transaction the Company shall establish and thereafter (subject as provided in this Article) maintain in accordance with the provisions of this Article a reserve (the "Subscription Rights Reserve") the amount of which shall at no time be less than the sum which for the time being would be required to be capitalised and applied in paying up in full the nominal amount of the additional shares required to be issued and allotted credited as fully paid pursuant to sub-paragraph (c) below on the exercise in full of all the subscription rights outstanding and shall apply the Subscription Rights Reserve in paying up such additional shares in full as and when the same are allotted;

(b) the Subscription Rights Reserve shall not be used for any purpose other than that specified above unless all other reserves of the Company (other than share premium account) have been extinguished and will then only be used to make good losses of the Company if and so far as is required by law;

(c) upon the exercise of all or any of the subscription rights represented by any warrant, the relevant subscription rights shall be exercisable in respect of a nominal amount of shares equal to the amount in cash which the holder of such warrant is required to pay on exercise of the subscription rights represented thereby (or, as the case may be the relevant portion thereof in the event of a partial exercise of the subscription rights) and, in addition, there shall be allotted in respect of such subscription rights to the exercising warrantholder, credited as fully paid, such additional nominal amount of shares as is equal to the difference between:

(i) the said amount in cash which the holder of such warrant is required to pay on exercise of the subscription rights represented thereby (or, as the case may be, the relevant portion thereof in the event of a partial exercise of the subscription rights); and

(ii) the nominal amount of shares in respect of which such subscription rights would have been exercisable having regard to the provisions of the conditions of the warrants, had it been possible for such subscription rights to represent the right to subscribe for shares at less than par and immediately upon such exercise so much of the sum standing to the credit of the Subscription Rights Reserve as is required to pay up in full such additional nominal amount of shares shall be capitalised and applied in paying up in full such additional nominal amount of shares which shall forthwith be allotted credited as fully paid to the exercising warrantholders; and

(d) if, upon the exercise of the subscription rights represented by any warrant, the amount standing to the credit of the Subscription Rights Reserve is not sufficient to pay up in full such additional nominal amount of shares equal to such difference as aforesaid to which the exercising warrantholder is entitled, the Board shall apply any profits or reserves then or thereafter becoming available (including, to the extent permitted by law, share premium account) for such purpose until such additional nominal amount of shares is paid up and allotted as aforesaid and until then no dividend or other distribution shall be paid or made on the fully paid shares of the Company then in issue. Pending such payment and allotment, the exercising warrantholder shall be issued by the Company with a certificate evidencing his right to the allotment of such additional nominal amount of shares. The rights represented by any such certificate shall be in registered form and shall be transferable in whole or in part in units of one share in the like manner as the shares for the time being are transferable, and the Company shall make such arrangements in relation to the maintenance of a register therefor and other matters in relation thereto as the Board may think fit and adequate particulars thereof shall be made known to each relevant exercising warrantholder upon the issue of such certificate.

(2) Shares allotted pursuant to the provisions of this Article shall rank pari passu in all respects with the other shares allotted on the relevant exercise of the subscription rights represented by the warrant concerned. Notwithstanding anything contained in paragraph (1) of this Article, no fraction of any share shall be allotted on exercise of the subscription rights.

(3) The provision of this Article as to the establishment and maintenance of the Subscription Rights Reserve shall not be altered or added to in any way which would vary or abrogate, or which would have the effect of varying or abrogating the provisions for the benefit of any warrantholder or class of warrantholders under this Article without the sanction of a special resolution of such warrantholders or class of warrantholders.

(4) A certificate or report by the auditors for the time being of the Company as to whether or not the Subscription Rights Reserve is required to be established and maintained and if so the amount thereof so required to be established and maintained, as to the purposes for which the Subscription Rights Reserve has been used, as to the extent to which it has been used to make good losses of the Company, as to the additional nominal amount of shares required to be allotted to exercising warrantholders credited as fully paid, and as to any other matter concerning the Subscription Rights Reserve shall (in the absence of manifest error) be conclusive and binding upon the Company and all warrantholders and Members.

ACCOUNTING RECORDS

155. The Board shall cause true accounts to be kept of the sums of money received and expended by the Company, and the matters in respect of which such receipt and expenditure take place, and of the property, assets, credits and liabilities of the Company and of all other matters required by the Law or necessary to give a true and fair view of the Company's affairs and to explain its transactions.

156. The accounting records shall be kept at the Office or, at such other place or places as the Board decides and shall always be open to inspection by the Directors. No Member (other than a Director) shall have any right of inspecting any accounting record or book or document of the Company except as conferred by law or authorised by the Board or the Company in general meeting.

157. Subject to Article 158, a printed copy of the Directors' report, accompanied by the balance sheet and profit and loss account, including every document required by law to be annexed thereto, made up to the end of the applicable financial year and containing a summary of the assets and liabilities of the Company under convenient heads and a statement of income and expenditure, together with a copy of the Auditors' report, shall be sent to each person entitled thereto at least twenty-one (21) days before the date of the general meeting and at the same time as the notice of annual general meeting and laid before the Company at the annual general meeting held in accordance with Article 62 provided that this Article shall not require a copy of those documents to be sent to any person whose address the Company is not aware or to more than one of the joint holders of any shares or debentures.

158. Subject to due compliance with all applicable Statutes, rules and regulations, including, without limitation, the rules of any Designated Stock Exchange, and to obtaining all necessary consents, if any, required thereunder, the requirements of Article 157 shall be deemed satisfied in relation to any person by sending to the person in any manner not prohibited by the Statutes, a summary financial statement derived from the Company's annual accounts and the directors' report which shall be in the form and containing the information required by applicable laws and regulations, provided that any person who is otherwise entitled to the annual financial statements of the Company and the directors' report thereon may, if he so requires by notice in writing served on the Company, demand that the Company sends to him, in addition to a summary financial statement, a complete printed copy of the Company's annual financial statement and the directors' report thereon.

159. The requirement to send to a person referred to in Article 157 the documents referred to in that article or a summary financial report in accordance with Article 158 shall be deemed satisfied where, in accordance with all applicable Statutes, rules and regulations, including, without limitation, the rules of any Designated Stock Exchange, the Company publishes copies of the documents referred to in Article 157 and, if applicable, a summary financial report complying with Article 158, on the Company's computer network or in any other permitted manner (including by sending any form of electronic

communication), and that person has agreed or is deemed to have agreed to treat the publication or receipt of such documents in such manner as discharging the Company's obligation to send to him a copy of such documents.

AUDIT

160. (1) At the annual general meeting or at a subsequent extraordinary general meeting in each year, the Members shall appoint an auditor to audit the accounts of the Company and such auditor shall hold office until the next annual general meeting. Such auditor may be a Member but no Director or officer or employee of the Company shall, during his continuance in office, be eligible to act as an auditor of the Company.

(2) The Members may, at any general meeting convened and held in accordance with these Articles, by special resolution remove the Auditor at any time before the expiration of his term of office and shall by ordinary resolution at that meeting appoint another Auditor in his stead for the remainder of his term.

161. Subject to the Law the accounts of the Company shall be audited at least once in every year.

162. The remuneration of the Auditor shall be fixed by the Company in general meeting or in such manner as the Members may determine.

163. If the office of auditor becomes vacant by the resignation or death of the Auditor, or by his becoming incapable of acting by reason of illness or other disability at a time when his services are required, the Directors shall fill the vacancy and fix the remuneration of the Auditor so appointed.

164. The Auditor shall at all reasonable times have access to all books kept by the Company and to all accounts and vouchers relating thereto; and he may call on the Directors or officers of the Company for any information in their possession relating to the books or affairs of the Company.

165. The statement of income and expenditure and the balance sheet provided for by these Articles shall be examined by the Auditor and compared by him with the books, accounts and vouchers relating thereto; and he shall make a written report thereon stating whether such statement and balance sheet are drawn up so as to present fairly the financial position of the Company and the results of its operations for the period under review and, in case information shall have been called for from Directors or officers of the Company, whether the same has been furnished and has been satisfactory. The financial statements of the Company shall be audited by the Auditor in accordance with generally accepted auditing standards. The Auditor shall make a written report thereon in accordance with generally accepted auditing standards and the report of the Auditor shall be submitted to the Members in general meeting. The generally accepted auditing standards referred to herein may be those of a country or jurisdiction other than the Cayman Islands. If so, the financial statements and the report of the Auditor should disclose this act and name such country or jurisdiction.

NOTICES

166. Any Notice or document (including any "corporate communication" within the meaning ascribed thereto under the rules of any Designated Stock Exchange), whether or not, to be given or issued under these Articles from the Company to a Member shall be in writing or by cable, telex or facsimile transmission message or other form of electronic transmission or communication and any such Notice and document may be served or delivered by the Company on or to any Member either personally or by sending it through the post in a prepaid envelope addressed to such Member at his registered address as

appearing in the Register or at any other address supplied by him to the Company for the purpose or, as the case may be, by transmitting it to any such address or transmitting it to any telex or facsimile transmission number or electronic number or address or website supplied by him to the Company for the giving of Notice to him or which the person transmitting the notice reasonably and bona fide believes at the relevant time will result in the Notice being duly received by the Member or may also be served by advertisement in appropriate newspapers in accordance with the requirements of the Designated Stock Exchange or, to the extent permitted by the applicable laws, by placing it on the Company's website or the website of any Designated Stock Exchange (as appropriate), and giving to the Member a Notice stating that the Notice or other document is available there (a "notice of availability"). The notice of availability may be given to the Member by any of the means set out above other than by posting it on a website. In the case of joint holders of a share all Notices shall be given to that one of the joint holders whose name stands first in the Register and Notice so given shall be deemed a sufficient service on or delivery to all the joint holders.

167. Any Notice or other document:

(a) if served or delivered by post, shall where appropriate be sent by airmail and shall be deemed to have been served or delivered on the day following that on which the envelope containing the same, properly prepaid and addressed, is put into the post; in proving such service or delivery it shall be sufficient to prove that the envelope or wrapper containing the Notice or document was properly addressed and put into the post and a certificate in writing signed by the Secretary or other officer of the Company or other person appointed by the Board that the envelope or wrapper containing the Notice or other document was so addressed and put into the post shall be conclusive evidence thereof;

(b) if sent by electronic communication, shall be deemed to be given on the day on which it is transmitted from the server of the Company or its agent. A Notice placed on the Company's website or the website of any Designated Stock Exchange (as appropriate), is deemed given by the Company to a Member on the day following that on which a notice of availability is deemed served on the Member;

(c) if served or delivered in any other manner contemplated by these Articles, shall be deemed to have been served or delivered at the time of personal service or delivery or, as the case may be, at the time of the relevant despatch, transmission or publication; and in proving such service or delivery a certificate in writing signed by the Secretary or other officer of the Company or other person appointed by the Board as to the act and time of such service, delivery, despatch, transmission or publication shall be conclusive evidence thereof; and

(d) may be given to a Member either in the English language or the Chinese language, subject to due compliance with all applicable Statutes, rules and regulations.

168. (1) Any Notice or other document delivered or sent by post to or left at the registered address of any Member in pursuance of these Articles shall, notwithstanding that such Member is then dead or bankrupt or that any other event has occurred, and whether or not the Company has notice of the death or bankruptcy or other event, be deemed to have been duly served or delivered in respect of any share registered in the name of such Member as sole or joint holder unless his name shall, at the time of the service or delivery of the notice or document, have been removed from the Register as the holder of the share, and such service or delivery shall for all purposes be deemed a sufficient service or delivery of such Notice or document on all persons interested (whether jointly with or as claiming through or under him) in the share.

(2) A notice may be given by the Company to the person entitled to a share in consequence of the death, mental disorder or bankruptcy of a Member by sending it through the post in a prepaid letter, envelope or wrapper addressed to him by name, or by the title of representative of the deceased, or trustee of the bankrupt, or by any like description, at the address, if any, supplied for the purpose by the person claiming to be so entitled, or (until such an address has been so supplied) by giving the notice in any manner in which the same might have been given if the death, mental disorder or bankruptcy had not occurred.

(3) Any person who by operation of law, transfer or other means whatsoever shall become entitled to any share shall be bound by every notice in respect of such share which prior to his name and address being entered on the Register shall have been duly given to the person from whom he derives his title to such share.

SIGNATURES

169. For the purposes of these Articles, a cable or telex or facsimile or electronic transmission message purporting to come from a holder of shares or, as the case may be, a Director or alternate Director, or, in the case of a corporation which is a holder of shares from a director or the secretary thereof or a duly appointed attorney or duly authorised representative thereof for it and on its behalf, shall in the absence of express evidence to the contrary available to the person relying thereon at the relevant time be deemed to be a document or instrument in writing signed by such holder or Director or alternate Director in the terms in which it is received.

WINDING UP

170. (l) The Board shall have power in the name and on behalf of the Company to present a petition to the court for the Company to be wound up.

(2) A resolution that the Company be wound up by the court or be wound up voluntarily shall be a special resolution.

171. (1) Subject to any special rights, privileges or restrictions as to the distribution of available surplus assets on liquidation for the time being attached to any class or classes of shares (i) if the Company shall be wound up and the assets available for distribution amongst the Members of the Company shall be more than sufficient to repay the whole of the capital paid up at the commencement of the winding up, the excess shall be distributed pari passu amongst such members in proportion to the amount paid up on the shares held by them respectively and (ii) if the Company shall be wound up and the assets available for distribution amongst the Members as such shall be insufficient to repay the whole of the paid-up capital such assets shall be distributed so that, as nearly as may be, the losses shall be borne by the Members in proportion to the capital paid up, or which ought to have been paid up, at the commencement of the winding up on the shares held by them respectively.

(2) If the Company shall be wound up (whether the liquidation is voluntary or by the court) the liquidator may, with the authority of a special resolution and any other sanction required by the Law, divide among the Members in specie or kind the whole or any part of the assets of the Company and whether or not the assets shall consist of properties of one kind or shall consist of properties to be divided as aforesaid of different kinds, and may for such purpose set such value as he deems fair upon any one or more class or classes of property and may determine how such division shall be carried out as between the Members or

different classes of Members. The liquidator may, with the like authority, vest any part of the assets in trustees upon such trusts for the benefit of the Members as the liquidator with the like authority shall think fit, and the liquidation of the Company may be closed and the Company dissolved, but so that no contributory shall be compelled to accept any shares or other property in respect of which there is a liability.

INDEMNITY

172. (1) The Directors, Secretary and other officers and every Auditor of the Company at any time, whether at present or in the past, and the liquidator or trustees (if any) acting or who have acted in relation to any of the affairs of the Company and every one of them, and every one of their heirs, executors and administrators, shall be indemnified and secured harmless out of the assets and profits of the Company from and against all actions, costs, charges, losses, damages and expenses which they or any of them, their or any of their heirs, executors or administrators, shall or may incur or sustain by or by reason of any act done, concurred in or omitted in or about the execution of their duty, or supposed duty, in their respective offices or trusts; and none of them shall be answerable for the acts, receipts, neglects or defaults of the other or others of them or for joining in any receipts for the sake of conformity, or for any bankers or other persons with whom any moneys or effects belonging to the Company shall or may be lodged or deposited for safe custody, or for insufficiency or deficiency of any security upon which any moneys of or belonging to the Company shall be placed out on or invested, or for any other loss, misfortune or damage which may happen in the execution of their respective offices or trusts, or in relation thereto; PROVIDED THAT this indemnity shall not extend to any matter in respect of any fraud or dishonesty which may attach to any of said persons.

(2) Each Member agrees to waive any claim or right of action he might have, whether individually or by or in the right of the Company, against any Director on account of any action taken by such Director, or the failure of such Director to take any action in the performance of his duties with or for the Company; PROVIDED THAT such waiver shall not extend to any matter in respect of any fraud or dishonesty which may attach to such Director.

AMENDMENT TO MEMORANDUM AND ARTICLES OF ASSOCIATION AND NAME OF COMPANY

173. No Article shall be rescinded, altered or amended and no new Article shall be made until the same has been approved by a special resolution of the Members. A special resolution shall be required to alter the provisions of the Memorandum or to change the name of the Company.

INFORMATION

174. No Member shall be entitled to require discovery of or any information respecting any detail of the Company's trading or any matter which is or may be in the nature of a trade secret or secret process which may relate to the conduct of the business of the Company and which in the opinion of the Directors it will be inexpedient in the interests of the Members to communicate to the public.

Exhibit 2.4

Description of Ordinary Shares

The following are summaries of material provisions of our currently effective amended and restated memorandum and articles of association and the Cayman Islands Companies Act (2022 Revision), or the Companies Act, insofar as they relate to the material terms of our ordinary shares. You should read this summary together with our amended and restated memorandum and articles of association which have been filed with the Securities and Exchange Commission, or SEC, as exhibit 1.1 to our annual report on Form 20-F for the year ended December 31, 2021.

General

All of our outstanding shares are fully paid and non-assessable. Our ordinary shares are issued in registered form and are issued when registered in our register of members. Our shareholders who are non-residents of the Cayman Islands may freely hold and vote their ordinary shares. Each ordinary share has US$0.10 par value.

Dividends

Under our amended and restated memorandum and articles of association, our company in general meeting may from time to time declare final dividends in any currency to be paid to the members but no final dividend shall be declared in excess of the amount recommended by our board of directors. Dividends may be declared and paid out of the profits of our company, realized or unrealized, or from any reserve set aside from profits which our directors determine is no longer needed. With the sanction of an ordinary resolution, dividends may also be declared and paid out of share premium account or any other fund or account which can be authorized for this purpose in accordance with the Companies Act. Except in so far as the rights attaching to, or the terms of issue of, any share otherwise provide: (a) all dividends shall be declared and paid according to the amounts paid up on the shares in respect of which the dividend is paid, but no amount paid up on a share in advance of calls shall be treated for this purpose as paid up on that share; and (b) all dividends shall be apportioned and paid pro rata according to the amounts paid up on the shares during any portion or portions of the period in respect of which the dividend is paid.

Our board of directors may from time to time pay to the members such interim dividends as appear to the board of directors to be justified by the profits of our company, whenever such profits, in the opinion of our board of directors, justifies such payment.

Our board of directors may deduct from any dividend or other moneys payable to a member by our company on or in respect of any shares all sums of money (if any) presently payable by such shareholder to our company on account of calls or otherwise.

No dividend or other moneys payable by our company on or in respect of any share shall bear interest against our company.

Any dividend, interest or other sum payable in cash to the holder of shares may be paid by check or warrant sent through the post addressed to the holder at his or her registered address or, in the case of joint holders, addressed to the holder whose name stands first in the register of members in respect of the shares at his or her address as appearing in the register of members or addressed to such person and at such address as the holder or joint holders may in writing direct. Every such check or warrant shall, unless the holder or joint holders otherwise direct, be made payable to the order of the holder or, in the case of joint holders, to the order of the holder whose name stands first on the register of members in respect of such shares, and shall be sent at his, her or their risk and payment of the check or warrant by the bank on which it is drawn shall constitute a good discharge to our company.

All dividends or bonuses unclaimed for one year after having been declared may be invested or otherwise made use of by our board of directors for the benefit of our company until claimed. Any dividend or bonuses unclaimed after a period of six years from the date of declaration shall be forfeited and shall revert to our company.

Whenever our board of directors or our company in general meeting has resolved that a dividend be paid or declared, our board of directors may further resolve that such dividend be satisfied wholly or in part by the distribution of specific assets of any kind and in particular of paid up shares, debentures or warrants to subscribe securities of our company or any other company, or in any one or more of such ways, and where any difficulty arises in regard to the distribution the board of directors may settle the same as it thinks expedient, and in particular may issue certificates in respect of fractions of shares, disregard fractional entitlements or round the same up or down, and may fix the value for distribution of such specific assets, or any part thereof, and may determine that cash payments

shall be made to any of our members upon the footing of the value so fixed in order to adjust the rights of all parties, and may vest any such specific assets in trustees as may seem expedient to our board of directors and may appoint any person to sign any requisite instruments of transfer and other documents on behalf of the persons entitled to the dividend, and such appointment shall be effective and binding on our members.

Whenever our board of directors or our company in general meeting has resolved that a dividend be paid or declared on any class of the share capital of our company, our board of directors may further resolve either: (a) that such dividend be satisfied wholly or in part in the form of an allotment of shares credited as fully paid up, provided that our members entitled thereto will be entitled to elect to receive such dividend (or part thereof if our board of directors so determines) in cash in lieu of such allotment; or (b) that the members entitled to such dividend shall be entitled to elect to receive an allotment of shares credited as fully paid up in lieu of the whole or such part of the dividend as our board of directors may think fit. We may upon the recommendation of our board of directors by ordinary resolution resolve in respect of any one particular dividend of our company that notwithstanding the provisions as set out in our amended and restated memorandum and articles of association in respect of the foregoing, a dividend may be satisfied wholly in the form of an allotment of shares credited as fully paid up without offering any right to members to elect to receive such dividend in cash in lieu of such allotment.

Voting Rights

Under our amended and restated memorandum and articles of association, subject to any special rights or restrictions as to voting for the time being attached to any shares by or in accordance with the articles of the association of our company, at any general meeting on a poll every member present in person or by proxy or, in the case of a member being a corporation, by its duly authorized representative shall have one vote for every fully paid share of which he is the holder but no amount paid up or credited as paid up on a share in advance of calls or installments is treated for the foregoing purposes as paid up on the share; and where a show of hands is allowed, every member present in person or by proxy (or, in the case of a member being a corporation, by its duly authorized representative) shall have one vote. A resolution put to the vote of a meeting shall be decided by way of a show of hands or, where required by the rules of any designated stock exchange, by way of a poll, save that the chairman of the meeting may in good faith, allow a resolution which relates purely to a procedural or administrative matter to be voted on by a show of hands in which case every member present in person (or being a corporation, is present by a duly authorized representative), or by proxy(ies) shall have one vote provided that where more than one proxy is appointed by a member which is a clearing house (or its nominee(s)), each such proxy shall have one vote on a show of hands. For purposes of the articles of association of our company, procedural and administrative matters are those that (i) are not on the agenda of the general meeting or in any supplementary circular that may be issued by our company to its members; and (ii) relate to the chairman's duties to maintain the orderly conduct of the meeting and/or allow the business of the meeting to be properly and effectively dealt with, whilst allowing all members a reasonable opportunity to express their views.

Where a show of hands is allowed, before or on the declaration of the result of the show of hands, a poll may be demanded (a) by the chairman of such meeting, or (b) by at least five members present in person or in the case of a member being a corporation by its duly authorized representative or by proxy for the time being entitled to vote at the meeting, or (c) by a member or members present in person or in the case of a member being a corporation by its duly authorized representative or by proxy and representing not less than one-tenth of the total voting rights of all members having the right to vote at the meeting, or (d) by a member or members present in person or in the case of a member being a corporation by its duly authorized representative or by proxy and holding shares in our company conferring a right to vote at the meeting being shares on which an aggregate sum has been paid up equal to not less than one-tenth of the total sum paid up on all shares conferring that right.

No member shall, unless our board of directors otherwise determines, be entitled to attend and vote and to be reckoned in a quorum at any general meeting unless he or she is duly registered and all calls or other sums presently payable by him or her in respect of shares in our company have been paid. Where our company has knowledge that any member is, under the rules of the designated stock exchange, required to abstain from voting on any particular resolution of our company or restricted to voting only for or only against any particular resolution of our company, any votes cast by or on behalf of such member in contravention of such requirement or restriction shall not be counted. Furthermore, our amended and restated memorandum and articles of association provide that if any member, or any other person appearing to be interested in shares held by such member, has been duly served with a notice issued by or on behalf of our company requiring disclosure of interests in shares pursuant to Section 793 of the Companies Act 2006 of England and Wales and is in default for the prescribed period referred to in the article of association of our company in supplying to our company the information thereby required, then the directors of our company may in their absolute discretion at any time thereafter serve a notice, called a Direction Notice, upon such member in

accordance with the articles of association of our company, pursuant to which such member may be precluded from attending, voting or being reckoned in a quorum at any general meeting. The Direction Notice may direct that such member shall not be entitled to vote or exercise any right conferred by membership in relation to meetings of our company in respect of the shares to which the notice relates. Where the holding represents at least 0.25% of the share capital of our company, then the Direction Notice may additionally direct that (i) in respect of such shares, any dividends or other money which would otherwise be payable on such shares shall be retained by our company without any liability to pay interest thereon when such money is finally paid to the member; and/or (ii) no transfer of any of the shares held by such member shall be registered unless: (a) the member is not himself in default as regards supplying the information required and (b) the transfer is of part only of the member's holding and when presented for registration is accompanied by a certificate of the member in a form satisfactory to the directors of our company to that effect that after due and careful enquiry the directors of our company are satisfied that no person in default as regards supplying such information is interested in any of the shares which are the subject of the transfer.

Under our amended and restated memorandum and articles of association, a resolution shall be an ordinary resolution when it has been passed at a meeting by a simple majority of votes cast by such members as, being entitled so to do, vote in person or, in the case of any member being a corporation, by its duly authorized representative or, where proxies are allowed, by proxy at a general meeting of which notice has been duly given in accordance with the articles of association of our company, while a resolution shall be a special resolution when it has been passed by a majority of not less than three-fourths of votes cast by such members as, being entitled so to do, vote in person or, in the case of any member being a corporation, by its duly authorized representative or, where proxies are allowed, by proxy at a general meeting of which notice has been duly given in accordance with the articles of association of our company. Both ordinary resolutions and special resolutions may also be passed by a unanimous written resolution signed by all the shareholders of our company, as permitted by the Companies Act and our amended and restated memorandum and articles of association. A special resolution will be required for important matters such as a change of name or making changes to our amended and restated memorandum and articles of association. Holders of the ordinary shares may, among other things, divide or consolidate their shares by ordinary resolution.

Subject to the provisions set forth below, any of our shareholders may transfer all or any of his or her ordinary shares by an instrument of transfer in the usual or common form or in a form prescribed by the designated stock exchange or in in any other form approved by our board of directors and may be under hand or, if the transferor or transferee is a clearing house or its nominee(s), by hand or by machine imprinted signature or by such other manner of execution as our board of directors may approve from time to time. Notwithstanding the above, for so long as any shares are listed on the designated stock exchange, title to such listed shares may be evidenced and transferred in accordance with the laws applicable to and the rules and regulations of the designated stock exchange that are or shall be applicable to such listed shares. The register of members of our company in respect of its listed shares (whether the principal register or a branch register) may be kept by recording the particulars required by Section 40 of the Companies Act in a form otherwise than legible if such recording otherwise complies with the laws applicable to and the rules and regulations of the designated stock exchange that are or shall be applicable to such listed shares.

Our board of directors may, in its absolute discretion, and without giving any reason therefor, refuse to register a transfer of any share (not being a fully paid up share) to a person whom it does not approve, or any share issued under any share incentive scheme for employees upon which a restriction on transfer imposed thereby still subsists, and it may also, without prejudice to the foregoing generality, refuse to register a transfer of any share to more than four joint holders or a transfer of any share (not being a fully paid up share) on which our company has a lien. Our board of directors may decline to recognize any instrument of transfer unless:

- a fee of such maximum sum as the rules of any designated stock exchange may determine to be payable or such lesser sum as our board of directors may from time to time require is paid to our company in respect thereof;
- the instrument of transfer is in respect of only one class of share;
- the instrument of transfer is lodged at the registered office of our company or such other place at which the register of members is kept in accordance with the Companies Act or the registration office (as the case may be) accompanied by the relevant share certificate(s) and such other evidence as our board of directors may reasonably require to show the right of the transferor to make the transfer (and, if the instrument of transfer is executed by some other person on his or her behalf, the authority of that person so to do); and

- if applicable, the instrument of transfer is duly and properly stamped.

If our board of directors refuses to register a transfer of any share, it shall, within two months after the date on which the transfer was lodged with our company, send to each of the transferor and the transferee notice of such refusal.

Notwithstanding above, our board of directors may permit shares of any class to be held in uncertificated form to be transferred without an instrument of transfer by means of a relevant system, including (without limitation) CREST, an electronic settlement system for U.K. and Irish securities operated by Euroclear UK & Ireland Limited for the paperless settlement of securities in uncertificated form.

Where any class of shares is a participating security and our company is entitled under the Companies Act, our articles of association or any applicable regulations to sell, transfer, dispose of, forfeit, re-allot, accept the surrender of or otherwise enforce a lien over a share held in uncertificated form without an instrument of transfer, our company shall be entitled, subject to the Companies Act, our articles of association, any applicable regulations and the facilities and requirements of the relevant system:

- to require the holder of that uncertificated share by notice to change that share into certificated form within the period specified in the notice and to hold that share in certificated form so long as required by our company;

- to require the holder of that uncertificated share by notice to give any instructions necessary to transfer title to that share by means of the relevant system within the period specified in the notice;

- to require the holder of that uncertificated share by notice to appoint any person to take any step, including without limitation the giving of any instructions by means of the relevant system, necessary to transfer that share within the period specified in the notice; and

- to take any action that our board of directors considers appropriate to achieve the sale, transfer, disposal of, forfeiture, re-allotment or surrender of that share or otherwise to enforce a lien in respect of it.

The registration of transfers of shares or of any class of shares may, after notice has been given by advertisement in any newspapers or by any other means in accordance with the requirements of any designated stock exchange to that effect, be suspended and the register closed at such times and for such periods (not exceeding in the whole thirty (30) days in any year or such longer period as our members may by ordinary resolution determine, provided that such period shall not be extended beyond sixty (60) days in any year) as our board may determine.

Liquidation

Under our amended and restated memorandum and articles of association, subject to any special rights, privileges or restrictions as to the distribution of available surplus assets on liquidation for the time being attached to any class or classes of shares (i) if our company shall be wound up and the assets available for distribution amongst the members of our company shall be more than sufficient to repay the whole of the capital paid up at the commencement of the winding up, the excess shall be distributed pari passu amongst such members in proportion to the amount paid up on the shares held by them respectively and (ii) if our company shall be wound up and the assets available for distribution amongst the members as such shall be insufficient to repay the whole of the paid-up capital such assets shall be distributed so that, as nearly as may be, the losses shall be borne by the members in proportion to the capital paid up, or which ought to have been paid up, at the commencement of the winding up on the shares held by them respectively.

If our company shall be wound up (whether the liquidation is voluntary or by the court) the liquidator may, with the authority of a special resolution and any other sanction required by the Companies Act, divide among the members in specie or kind the whole or any part of the assets of our company and whether or not the assets shall consist of properties of one kind or shall consist of properties to be divided as aforesaid of different kinds, and may for such purpose set such value as he or she deems fair upon any one or more class or classes of property and may determine how such division shall be carried out as between the members or different classes of members. The liquidator may, with the like authority, vest any part of the assets in trustees upon

such trusts for the benefit of the members as the liquidator with the like authority shall think fit, and the liquidation of our company may be closed and our company dissolved, but so that no contributory shall be compelled to accept any shares or other property in respect of which there is a liability.

Calls on Shares and Forfeiture of Shares

Our board of directors may from time to time make calls upon members in respect of any moneys unpaid on their shares, and each member shall (subject to being given at least 14 clear days' notice specifying the time and place of payment) pay to our company as required by such notice the amount called on such shares. The shares that have been called upon and remain unpaid are subject to forfeiture. Notwithstanding any such forfeiture described above, our board of directors may at any time, before any shares so forfeited shall have been sold, re-allotted or otherwise disposed of, permit the forfeited shares to be bought back upon the terms of payment of all calls and interest due upon, and expenses incurred in respect of, the shares and upon further terms (if any) as it thinks fit. The forfeiture of a share shall not prejudice the right of our company to any call already made, or installment payable, thereon.

Redemption, Repurchase and Surrender of Ordinary Shares

Under our amended and restated memorandum and articles of association, subject to the Companies Act, our amended and restated memorandum and articles of association and the rules of any designated stock exchange and/or any competent regulatory authority, any power of our company to purchase or otherwise acquire its own shares shall be exercisable by our board of directors in such manner, upon such terms and subject to such conditions as it thinks fit. Furthermore, under the Companies Act, the redemption or repurchase of any share may be paid out of our company's profits or out of the share premium account or out of the proceeds of a fresh issue of shares made for the purpose of such redemption or repurchase, or out of capital if our company is able to, immediately following such payment, pay its debts as they fall due in the ordinary course of business. In addition, under the Companies Act no such share may be redeemed or repurchased (a) unless it is fully paid, (b) if as a result of the redemption or repurchase would result in there being no issued shares of our company other than shares held as treasury shares. Under our amended and restated memorandum and articles of association, our board of directors may accept the surrender of any share liable to be forfeited hereunder and, in such case, references in our amended and restated memorandum and articles of association to forfeiture will include surrender.

Variations of Rights of Shares

According to our articles of association and without prejudice to our amended and restated memorandum and articles of association, all or any of the special rights for the time being attached to the shares or any class of shares may, unless otherwise provided by the terms of issue of the shares of that class, from time to time, whether or not our company is being wound up, be varied, modified or abrogated either with the consent in writing of the holders of not less than three-fourths in nominal value of the issued shares of that class or with the sanction of a special resolution passed at a separate general meeting of the holders of the shares of that class. The special rights conferred upon the holders of any shares or class of shares shall not, unless otherwise expressly provided in the rights attaching to or the terms of issue of such shares, be deemed to be varied, modified or abrogated by the creation or issue of further shares ranking pari passu with such existing class of shares.

Issuance of Additional Shares and Pre-emptive Rights

Our amended and restated memorandum and articles of association authorizes our board of directors to issue additional ordinary shares from time to time as our board of directors shall determine, to the extent of available authorized but unissued shares. Our amended and restated memorandum and articles of association provides that, unless our company by special resolution directed otherwise, any new ordinary shares will be offered by our directors for subscription to the holders of the ordinary shares in such proportions as equal (as nearly as possible) the proportion of ordinary shares held by them respectively at that time.

Our amended and restated memorandum and articles of association also provides that, subject to the provisions of the Companies Act and our amended and restated memorandum and articles of association and to any special rights conferred on the holders of any shares or class of shares, any share in our company (whether forming part of the present capital or not) may be issued with or have attached thereto such rights or restrictions whether in regard to dividend, voting, return of capital or otherwise as our company may by ordinary resolution determine or, if there has not been any such determination or so far as the same shall not make specific provision, as our board of directors may determine.

Subject to the provisions of the Companies Act, the rules of any designated stock exchange and our amended and restated memorandum and

articles of association, and to any special rights conferred on the holders of any shares or attaching to any class of shares, shares may be issued on the terms that they may be, or at the option of our company or the holder are, liable to be redeemed on such terms and in such manner, including out of capital, as our board of directors may deem fit.

Subject to the Companies Act, any preference shares may be issued or converted into shares that, at a determinable date or at the option of our company or the holder if so authorized by our amended and restated memorandum and articles of association, are liable to be redeemed on such terms and in such manner as our company before the issue or conversion may be ordinary resolution of the members determine.

Where our company purchases for redemption a redeemable share, purchases not made through the market or by tender shall be limited to a maximum price as may from time to time be determined by our company in general meeting, either generally or with regard to specific purchases. If purchases are by tender, tenders shall be available to all members alike.

Inspection of Books and Records

Our shareholders do not have a general right under the Companies Act to inspect or obtain copies of our list of shareholders or our corporate records. They will, however, have such rights as may be set out in our company's articles of association.

Anti-Takeover Provisions

Some provisions of our amended and restated memorandum and articles of association may discourage, delay or prevent a change of control of our company or management that shareholders may consider favorable, including provisions that limit the ability of shareholders to requisition and convene general meetings of shareholders. However, under Cayman Islands law, our directors may only exercise the rights and powers granted to them under our amended and restated memorandum and articles of association for a proper purpose and for what they believe in good faith to be in the best interests of our company.

General Meetings of Shareholders and Shareholder Proposals

Our shareholders' general meetings may be held in such time and place within or outside the Cayman Islands as our board of directors considers appropriate.

As a Cayman Islands exempted company, we are not obliged by the Companies Act to call shareholders' annual general meetings. Our amended and restated memorandum and articles of association provide that we shall in each year hold a general meeting as our annual general meeting. Our board of directors may whenever it thinks fit call extraordinary general meetings.

Cayman Islands law does not provide shareholders with an express right to put any proposal before a general meeting. However, these rights may be provided in a company's articles of association. Our amended and restated memorandum and articles of association allow our shareholders holding shares representing in aggregate not less than one-tenth of the paid up capital of our company carrying the right of voting at general meetings of our company shall at all times have the right, by written requisition to our board of directors or the secretary of our company, to require an extraordinary general meeting to be called by the board of directors for the transaction of any business specified in such requisition; however, our amended and restated memorandum and articles of association do not provide our shareholders with any right to put any proposals before annual general meetings or extraordinary general meetings not called by such shareholders.

Exempted Company

We are an exempted company with limited liability under the Companies Act. Any company that is registered in the Cayman Islands and the objects of which are to be carried out mainly outside of the Cayman Islands may apply to be registered as an exempted company.

Register of Members

Under the Companies Act, our company must keep a register of members and there should be entered therein:

- the names and addresses of the members, the number and class of shares held by each member, the amount paid or agreed to be considered as paid, on such shares, and whether for each relevant category of

shares held by a member carries voting rights under the articles of association of the company, and if so, whether such voting rights are conditional; and

- the date on which the name of any person was entered on the register as a member; and the date on which any person ceased to be a member.

In accordance with Section 48 of the Companies Act, the register of members is prima facie evidence of the registered holder or member of shares of a company. Therefore, a person becomes a registered holder or member of shares of our company only upon entry being made in the register of members.

If the name of any person is, without sufficient cause, entered in or omitted from our register of members, or if default is made or unnecessary delay takes place in entering on the register the fact of any person having ceased to be a member of our company, the person or member aggrieved (or any member of our company or our company itself) may apply to the Cayman Islands Grand Court for an order that the register be rectified, and the Court may either refuse such application or it may, if satisfied of the justice of the case, make an order for the rectification of the register.

Differences in Corporate Law

The Companies Act is derived, to a large extent, from the older Companies Acts of England but does not follow recent U.K. statutory enactments, and accordingly there are significant differences between the Companies Act and the current Companies Act of England and Wales. In addition, the Companies Act differs from laws applicable to U.S. corporations and their shareholders. Set forth below is a summary of the significant differences between the provisions of the Companies Act applicable to our company and the laws applicable to companies incorporated in the United States and their shareholders.

Mergers and Similar Arrangements

The Companies Act permits mergers and consolidations between Cayman Islands companies and between Cayman Islands companies and non-Cayman Islands companies. For these purposes, (a) "merger" means the merging of two or more constituent companies and the vesting of their undertaking, property and liabilities in one of such companies as the surviving company and (b) a "consolidation" means the combination of two or more constituent companies into a consolidated company and the vesting of the undertaking, property and liabilities of such companies in the consolidated company. A merger of two or more constituent companies under Cayman Islands law requires a plan of merger or consolidation to be approved by the directors of each constituent company and (a) authorization by a special resolution of the members of each constituent company and (b) such other authorization, if any, as may be specified in such constituent company's articles of association.

A merger between a Cayman Islands parent company and its Cayman Islands subsidiary or subsidiaries does not require authorization by a resolution of shareholders if a copy of the plan of merger is given to every member of each subsidiary company to be merged unless that member agrees otherwise. For this purpose, a subsidiary is a company of which at least 90% of the votes represented by issued shares of the subsidiary company are held by the parent company.

The consent of each holder of a fixed or floating security interest over a constituent company is required unless this requirement is waived by a court in the Cayman Islands.

Save in certain circumstances, a dissident shareholder of a Cayman Islands constituent company is entitled to payment of the fair value of his shares upon dissenting to a merger or consolidation. The exercise of appraisal rights will preclude the exercise of any other rights save for the right to seek relief on the grounds that the merger or consolidation is void or unlawful.

In addition, there are statutory provisions that facilitate the reconstruction and amalgamation of companies, provided that the scheme of arrangement is approved by a majority in number of each class of shareholders or creditors (representing 75% by value) with whom the arrangement is to be made, as the case may be, that are present and voting either in person or by proxy at a meeting, or meetings, convened for that purpose. The convening of the meetings and subsequently the arrangement must be sanctioned by the Grand Court of the Cayman Islands. While a dissenting shareholder has the right to express to the court the view that the transaction ought not to be approved, the Grand Court can be expected to approve the arrangement if it determines that:

- the statutory provisions as to the required majority vote have been met;

- the shareholders have been fairly represented at the meeting in question and the statutory majority are acting bona fide without coercion of the minority to promote interests adverse to those of the class;

- the arrangement is such that may be reasonably approved by an intelligent and honest man of that class acting in respect of his interest; and

- the arrangement is not one that would more properly be sanctioned under some other provision of the Companies Act.

When a takeover offer is made and accepted by holders of 90% in value of the shares affected within four months, the offeror may, within a two-month period commencing on the expiration of such four month period, require the holders of the remaining shares to transfer such shares on the terms of the offer. An objection can be made to the Grand Court of the Cayman Islands but this is unlikely to succeed in the case of an offer which has been so approved unless there is evidence of fraud or bad faith.

Shareholders' Suits

The Cayman Islands Grand Court Rules allow shareholders to seek leave to continue derivative actions in the name of the company against wrongdoers. In principle, we will normally be the proper plaintiff and a derivative action may not be brought by a minority shareholder. However, based on English authorities, which would in all likelihood be of persuasive authority in the Cayman Islands, exceptions to the foregoing principle apply in circumstances in which:

- a company is acting or proposing to act illegally or beyond the scope of its authority;

- the act complained of, although not beyond the scope of the company's authority, could be effected if authorized by more than a simple majority vote which has not been obtained; or

- those who control the company are perpetrating a "fraud on the minority."

Indemnification of Directors and Executive Officers and Limitation of Liability

Cayman Islands law does not limit the extent to which a company's memorandum and articles of association may provide for indemnification of officers and directors, except to the extent any such provision may be held by the Cayman Islands courts to be contrary to public policy, such as to provide indemnification against civil fraud or the consequences of committing a crime. Our amended and restated memorandum and articles of association require us to indemnify our officers and directors for losses, damages, costs and expenses incurred in their capacities as such unless such losses or damages arise from dishonesty or fraud of such directors or officers. This standard of conduct is generally the same as permitted under the Delaware General Corporation Law for a Delaware corporation.

In addition, we have entered into indemnification agreements with our directors and executive officers that provide such persons with additional indemnification beyond that provided in our amended and restated memorandum and articles of association to the fullest extent permitted by applicable law.

Insofar as indemnification for liabilities arising under the Securities Act of 1933, as amended, or the Securities Act may be permitted to our directors, officers or persons controlling us under the foregoing provisions, we have been informed that in the opinion of the SEC, such indemnification is against public policy as expressed in the Securities Act and is therefore unenforceable.

Duties of Directors

Under Cayman Islands law, our directors have a fiduciary duty to act honestly, in good faith, with skill and care and with a view to our best interests. Our directors also have a duty to exercise skills they actually possess and such care and diligence that a reasonably prudent person would exercise in comparable circumstances. In fulfilling their duty of care to us, our directors must ensure compliance with our amended and restated memorandum and articles of association, as amended and restated from time to time. Our company has the right to seek damages if a duty owed by our directors is breached. Our board of directors has all the powers necessary for

managing, and for directing and supervising, our business affairs. The functions and powers of our board of directors include, among others:

- convening shareholders' annual general meetings and reporting its work to shareholders at such meetings; declaring dividends and distributions;
- appointing officers and determining the term of office of the officers;
- exercising the borrowing powers of our company and mortgaging the property of our company; and approving the transfer of shares in our company, including the registration of such shares in our share register.

A director who is in any way, whether directly or indirectly, interested in a contract or proposed contract with our company shall declare the nature of his or her interest at a meeting of the directors in accordance with the Companies Act and our articles of association. Subject to the Hong Kong Listing Rules and save as provided in the amended and restated memorandum and articles of association of our company, a director shall not vote on any resolution of our board approving any contract, arrangement, transaction or any other proposal whatsoever in which he or any of his or her close associates is materially interested otherwise than by virtue of his or her interests in shares or debentures or other securities of or otherwise in or through our company. A director of our company may not be counted in the quorum at a meeting in relation to any resolution on which that director is prohibited from voting. Our directors may exercise all the powers of our company to borrow money, mortgage our undertaking, property and uncalled capital and issue debentures or other securities whether outright or as collateral security for any debt, liability or obligation of our company or of any third party.

Under Delaware corporate law, a director of a Delaware corporation has a fiduciary duty to the corporation and its shareholders. This duty has two components: the duty of care and the duty of loyalty. The duty of care requires that a director act in good faith, with the care that an ordinarily prudent person would exercise under similar circumstances. Under this duty, a director must inform himself of, and disclose to shareholders, all material information reasonably available regarding a significant transaction. The duty of loyalty requires that a director acts in a manner he reasonably believes to be in the best interests of the corporation. He must not use his corporate position for personal gain or advantage. This duty prohibits self-dealing by a director and mandates that the best interest of the corporation and its shareholders take precedence over any interest possessed by a director, officer or controlling shareholder and not shared by the shareholders generally. In general, actions of a director are presumed to have been made on an informed basis, in good faith and in the honest belief that the action taken was in the best interests of the corporation. However, this presumption may be rebutted by evidence of a breach of one of the fiduciary duties. Should such evidence be presented concerning a transaction by a director, the director must prove the procedural fairness of the transaction, and that the transaction was of fair value to the corporation.

Cayman Islands laws do not restrict transactions with directors but a director of a Cayman Islands company is in the position of a fiduciary with respect to the company and a director is required to exercise a duty of care, a duty to act bona fide in the best interests of the company, a duty not to make a profit based on his or her position as director (unless the company permits him to do so) and a duty not to put himself in a position where the interests of the company conflict with his or her personal interest or his or her duty to a third party. A director of a Cayman Islands company also owes to the company a duty to act with skill and care.

Shareholder Action by Written Consent

Under the Delaware General Corporation Law, a corporation may eliminate the right of shareholders to act by written consent by amendment to its certificate of incorporation. Cayman Islands laws and our articles of association provide that shareholders may approve corporate matters by way of a unanimous written resolution signed by or on behalf of each shareholder who would have been entitled to vote on such matter at a general meeting without a meeting being held.

Shareholder Proposals

The Delaware General Corporation Law does not provide shareholders an express right to put any proposal before the annual meeting of shareholders, but in keeping with common law, Delaware corporations generally afford shareholders an opportunity to make proposals and nominations provided that they comply with the notice provisions in the certificate of incorporation or bylaws. The Companies Act does not provide shareholders with an express right to put forth any proposal before

the annual general meeting of the shareholders. However, depending on what is stipulated in a company's articles of association, shareholders in an exempted Cayman Islands company may make proposals in accordance with the relevant shareholder requisition provisions. For shares that are represented by ADSs, the depositary in many cases may be the only shareholder. In such cases, only the depositary has the direct right to requisition a shareholders' meeting. However, unless otherwise provided in the deposit agreement, the holders of the ADSs generally do not have the right to petition the depositary to requisition a shareholders' meeting or to put forth shareholder proposals through the depositary.

Cumulative Voting

Under the Delaware General Corporation Law, cumulative voting for elections of directors is not permitted unless the corporation's certificate of incorporation specifically provides for it. Cumulative voting potentially facilitates the representation of minority shareholders on a board of directors since it permits the minority shareholder to cast all the votes to which the shareholder is entitled on a single director, which increases the shareholder's voting power with respect to electing such director. There are no prohibitions in relation to cumulative voting under the laws of the Cayman Islands, but our articles of association do not provide for cumulative voting. As a result, our shareholders are not afforded any less protections or rights on this issue than shareholders of a Delaware corporation.

Removal of Directors

Under the Delaware General Corporation Law, a director of a corporation with a classified board may be removed only for cause with the approval of a majority of the outstanding shares entitled to vote, unless the certificate of incorporation provides otherwise. Under our amended and restated memorandum and articles of association, directors may be removed by ordinary resolution of our shareholders.

Transactions with Interested Shareholders

The Delaware General Corporation Law contains a business combination statute applicable to Delaware corporations whereby, unless the corporation has specifically elected not to be governed by such statute by amendment to its certificate of incorporation, it is prohibited from engaging in certain business combinations with an "interested shareholder" for three years following the date that such person becomes an interested shareholder. An interested shareholder generally is a person or a group who or which owns or owned 15% or more of the target's outstanding voting share within the past three years. This has the effect of limiting the ability of a potential acquirer to make a two-tiered bid for the target in which all shareholders would not be treated equally. The statute does not apply if, among other things, prior to the date on which such shareholder becomes an interested shareholder, the board of directors approves either the business combination or the transaction which resulted in the person becoming an interested shareholder. This encourages any potential acquirer of a Delaware corporation to negotiate the terms of any acquisition transaction with the target's board of directors.

Cayman Islands law has no comparable statute. As a result, we cannot avail ourselves of the types of protections afforded by the Delaware business combination statute.

Dissolution; Winding up

Under the Delaware General Corporation Law, unless the board of directors approves the proposal to dissolve, dissolution must be approved by shareholders holding 100% of the total voting power of the corporation. Only if the dissolution is initiated by the board of directors may it be approved by a simple majority of the corporation's outstanding shares. Delaware law allows a Delaware corporation to include in its certificate of incorporation a supermajority voting requirement in connection with dissolutions initiated by the board.

A Cayman Islands company may be wound up compulsorily by order of the Court of the Cayman Islands, voluntarily or under supervision of the Court of the Cayman Islands. The Court of the Cayman Islands has authority to order winding up in a number of specified circumstances including where it is, in the opinion of the Court, just and equitable to do so.

A company may be wound up voluntarily when the members so resolve in general meeting by special resolution, or, in the case of a limited duration company, when the period fixed for the duration of the company by its memorandum expires, or the event occurs on the occurrence of which the memorandum provides that the company is to be dissolved, or, the company does not commence business for a year from its incorporation (or suspends its business for a year), or, the company is unable to pay its

debts. In the case of a voluntary winding up, such company is obliged to cease to carry on its business from the time of passing the resolution for voluntary winding up or upon the expiry of the period or the occurrence of the event referred to above.

Variation of Rights of Shares

Under the Delaware General Corporation Law, a corporation may vary the rights of a class of shares with the approval of a majority of the outstanding shares of such class, unless the certificate of incorporation provides otherwise. Cayman Islands law has no comparable statute.

Amendment of Governing Documents

Under the Delaware General Corporation Law, a corporation's governing documents may be amended with the approval of a majority of the outstanding shares entitled to vote, unless the certificate of incorporation provides otherwise. Under Cayman Islands law, our amended and restated memorandum and articles of association may only be amended with a special resolution of our shareholders.

Exhibit 4.2
EXECUTION VERSION
CONFIDENTIAL

AMENDMENT TO THE AMENDED AND RESTATED LICENSE AND COLLABORATION AGREEMENT

This Amendment (the "**Amendment**") to the Amended and Restated License and Collaboration Agreement dated December 7th, 2020 (collectively, the "**Agreement**") and made by and between:

(1) **AstraZeneca AB (publ)**, a company incorporated in Sweden under no. 556011-7482 with its registered office at SE-151 85 Södertälje, Sweden and with offices at SE-431 83, Mölndal, Sweden ("**AstraZeneca**"); and

(2) **Hutchison MediPharma Limited 和记黄埔医药（上海）有限公司**, a company organised under the laws of the People's Republic of China, having its place of business at Building 4,720 Cailun Road, Zhangjiang Hi-Tech Park, and Shanghai 201203, P.R. China ("**Hutchison**" and, collectively with AstraZeneca, the "**Parties**" and each, a "**Party**")).

is made as of 29 November 2021.

Recitals

WHEREAS, the Parties have entered into the Agreement and have implemented the Development Plan.

WHEREAS, Hutchison wishes to carry out a Phase III Clinical Trial to be conducted in China for the Collaboration Product in combination with osimertinib, an AstraZeneca proprietary product, in NSCLC (the "**SANOVO Phase III Trial**");

WHEREAS, the Parties wish to amend, modify and restate certain terms and conditions of the Agreement to address the Parties' respective rights and obligations regarding the SANOVO Phase III Trial, the SACHI Study and commercialization of Collaboration Products in SE Asian Markets (as defined below), and certain other matters.

NOW THEREFORE, in consideration of the mutual covenants contained in this Amendment, and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Parties, intending to be legally bound, agree as follows:

1. Definitions

Any capitalized term not separately defined in this Amendment shall have the meaning ascribed to it in the Agreement.

2. General Modifications to the Agreement.

a. Section 4.1.2 of the Agreement - Development Activities shall be deleted and replaced by the following:

> Each Party shall use Commercially Reasonable Efforts to implement and conduct the Development activities assigned to it under the Development Plan, in accordance with the Development Budget and the timelines set forth in the Development Plan, and to cooperate with and provide reasonable support to the other Party in such other Party's conduct of activities under the Development Plan. Each Party will undertake its respective Development activities in accordance with

GLP, GCP, GMP, as appropriate, and with all Applicable Laws. Except for the specific responsibilities allocated to Hutchison as set forth in the Development Plan with respect to Development activities intended to support obtaining Regulatory Approval for Collaboration Products or Diagnostic Products in China (which responsibilities shall include being sponsor of registrational trials in China, including any trials required by the China Health Authority for conditional approval, and which responsibilities shall include, for the avoidance of doubt, the China Life Cycle Indications and the SANOVO Phase III Study) (collectively, "**Hutchison China Development Activities**"), AstraZeneca will be responsible for performing all Development activities, including global studies with a China component, for the purpose of obtaining Regulatory Approval for Collaboration Product and Diagnostic Products in the ROW Territory. The Parties shall share costs and expenses under this Section 4.1.2 in accordance with the allocations set forth in Section 5.7 or as otherwise provided in the Agreement and this Amendment. All Clinical Trials initiated after the Effective Date and performed by a Third Party will be conducted by agents both Parties agree have sufficient capability to ensure all Clinical Trials performed by such Third Party are conducted and reported, and can be audited to show they have been conducted and reported, to comply with standards of GCP acceptable to Regulatory Authorities globally.

b. Subsection (b) of Section 4.1.6 of the Agreement - Life Cycle Indications of China shall be deleted and replaced by the following:

(b) Hutchison shall consult with AstraZeneca through the Joint Development Committee in planning the Development activities with respect to the China Life Cycle Indications; provided that, subject to this Section 4.1.6, Hutchison shall have the final and determinative decision making authority for the Development activities for the China Life Cycle Indications under Section 3.3.1. Development activities under this Section 4.1.6 shall be set forth and subject to the Development Plan. Notwithstanding anything in this Agreement to the contrary, subject to Section 8.c of this Amendment, AstraZeneca shall, at Hutchison's reasonable request, and in a timely manner as necessary to conduct the Development activities for the China Life Cycle Indications: (1) provide sufficient quantities of osimertinib and durvalumab at no cost to Hutchison for a period of up to 6 months, and thereafter sell osimertinib and durvalumab to Hutchison at a price equivalent to AstraZeneca's fully absorbed cost of goods (to the extent reasonably incurred), and (2) provide reasonable technical support in connection with the supply of osimertinib and durvalumab, which obligations shall survive any termination of this Agreement by AstraZeneca under Section 10.2 (but only for the duration stated here).

3. **Modifications to the Agreement related to SANOVO Phase III Trial.** Notwithstanding anything to the contrary in the Agreement, including Sections 4.3.1(c) and 5.7.2(a) of the Agreement,

a. The Parties agree and acknowledge that, by execution of this Amendment, the Development Plan contains the SANOVO Phase III Study and the China Life Cycle Indications, and the Development Plan incorporating the SANOVO Phase III Study and the China Life Cycle Indications as of the Amendment Effective Date is attached hereto as Exhibit A.

b. Hutchison shall consult with AstraZeneca through the Joint Development Committee in planning the Development activities with respect to the SANOVO Phase III Trial; provided that, subject to this Section 2.b, Hutchison shall have the final and determinative decision making authority for the Development activities for SANOVO Phase III Trial under Section 3.3.1 of the Agreement. Hutchison shall also provide reports on the Development activities for SANOVO Phase III Trial consistent with Section 4.1.3 of the Agreement.

c. Hutchison shall be responsible for all regulatory matters related to the SANOVO Phase III Trial and shall be the Regulatory Submission Party for the AZ Proprietary Combination Product that is the subject of the SANOVO Phase III Trial in China.

d. Notwithstanding anything to the contrary in the Agreement, [**].

e. As additional consideration for the rights granted to AstraZeneca under the Agreement, AstraZeneca will pay Hutchison, upon receipt of an invoice, the following non-creditable, non-refundable (except as set forth in Section 9.3 of the Agreement) amounts, within thirty (30) days after the first occurrence of each of the following Development Milestones in the table below. For the avoidance of doubt, each Development Milestone in Table 1 below of this Amendment shall be paid only once during the Term, regardless of the number of Collaboration Compounds or Collaboration Products that achieve the corresponding Milestone Event:

TABLE 1: DEVELOPMENT MILESTONES RELATED TO SANOVO PHASE III TRIAL

Development Milestone	**In China**	**In the US, European Union or Japan**
1. SANOVO Phase III Trial primary endpoint data mPFS by investigator in *EGFRm+, MET+ NSCLC IHC3+ subgroup* is used as the primary efficacy data set for obtaining a Regulatory Approval or expanded label for a Collaboration Product	To the extent not already paid under Row 2 below, [**]	$[**]
2. SANOVO Phase III Trial primary endpoint data mPFS by investigator in EGFRm+ MET+ NSCLC ITT population (incl. IHC2+ & IHC3+) is used as the primary efficacy data set for obtaining a Regulatory Approval or expanded label for a Collaboration Product	To the extent not already paid under Row 1 above, [**]	$[**]

4. **Modifications to the Agreement Related to the Commercialization of Collaboration Products in SE Asian Markets.** Notwithstanding anything to the contrary in the Agreement, including Section 4.5 of the Agreement,

a. Following Regulatory Approval of a Collaboration Product in the People's Republic of China (excluding Hong Kong and Macau) in which data from any of the Hutchison China Development Activities was used as the primary efficacy data set for obtaining such Regulatory Approval, and following AstraZeneca's review and approval of Hutchison's applicable protocols(such approval not to be unreasonably withheld, conditioned or delayed), Hutchison shall have the ability to conduct certain lawful initial commercialization activities related to such Collaboration Product in the SE Asian Markets subject to Hutchison's protocols (such activities, the "**Initial Commercialization Activities**"). The Initial Commercialization Activities in the SE Asian Markets shall include compassionate use and named-patient programs (which may include charging the HCP/HCOs for the cost of the Collaboration Product). Additionally, with respect to Hong Kong and Macau only, the Initial Commercialization Activities shall include seeking and maintaining only those Regulatory Approvals in which data from any of the Hutchison China Development Activities serves as the primary efficacy data set for such Regulatory Approval (with any regulatory submissions to be provided to AstraZeneca for review and approval prior to submission, such approval not to be unreasonably withheld, conditioned or delayed). In no event will Initial Commercialization Activities constitute a First Commercial Sale or yield a Net Sale under the Agreement, and for the avoidance of doubt, no Milestone Payments shall be triggered in connection with these activities.

b. In the event Hutchison obtains Regulatory Approval for the Collaboration Product in Hong Kong and/or Macau in accordance with section 3.a, Hutchison shall have the ability to additionally carry out all lawful Commercialization activities in respect of such approved markets and be able to book the sales of such Collaboration Product but in no event will such activities constitute a First Commercial Sale or yield a Net Sale under the Agreement (such activities, the "**Additional Commercialization Activities**"). The Initial Commercialization Activities and Additional Commercialization Activities conducted by Hutchison shall be at Hutchison's expense and Hutchison will book all sales and revenue made or received in the conduct of such activities.

c. Upon written notice by AstraZeneca to Hutchison that AstraZeneca intends to commercialize a Collaboration Product in a country or region in which Hutchison is conducting Initial Commercialization Activities and/or Additional Commercial Activities, Hutchison shall transfer all Commercialization activities to AstraZeneca, and use Commercially Reasonable Efforts to effectuate any legal or regulatory instruments required to transfer all rights to Commercialization activities to AstraZeneca, within nine (9) months of receipt of the written notice by AstraZeneca, or by another deadline as agreed by the Parties in writing (the "**Commercialization Transition Deadline**").

d. Under the Agreement, Hutchison hereby retains all rights necessary from the licenses and other rights granted by Hutchison and its Affiliates to AstraZeneca under the Agreement for Hutchison and its Affiliates to conduct the Initial Commercialization Activities in the SE Asian Markets and the Additional Commercialization Activities in Hong Kong and/or Macau with respect to a Collaboration Product, and AstraZeneca hereby grants to Hutchison a co-exclusive, sublicensable (solely to subcontractors and Affiliates), royalty-

free license under the AstraZeneca Technology and AstraZeneca's right, title and interest under the Joint Technology solely to conduct such Initial Commercialization Activities in the SE Asian Markets and the Additional Commercialization Activities in Hong Kong and/or Macau with respect to a Collaboration Product; *provided* that such license and retained rights shall terminate with respect to a Collaboration Product in a country or region on the Commercialization Transition Deadline.

e. For the purposes of this Agreement, "**SE Asian Markets**" shall mean Hong Kong, Macau, Singapore, the Philippines, and any other market the Parties mutually agree to designate as a "SE Asian Market" under the Agreement.

4 Indemnity.

In addition to the indemnification obligations set forth in Section 11.1 of the Agreement, Hutchison shall indemnify, defend and hold harmless any AstraZeneca Indemnified Party from and against any and all Liabilities that the AstraZeneca Indemnified Party may be required to pay to one or more Third Parties to the extent resulting from or arising out of Hutchison's or its Affiliates' Commercialization in SE Asian Markets of a Collaboration Compound, except in each case, to the extent caused by the gross negligence or willful misconduct of AstraZeneca or any AstraZeneca Indemnified Party, or by breach of the Agreement by AstraZeneca.

5 Agreement to Proceed with SAFFRON Phase III Trial. This Amendment will become effective upon approval by AstraZeneca's Late Stage Project Committee to proceed to completion with the SAFFRON global Phase III Clinical Trial for the Collaboration Product as outlined in Exhibit B (which may be modified by the mutual written agreement of the Parties) (the "**Amendment Effective Date**".)

6 Modifications to the Agreement related to SACHI Study.

a. Section 5.7.2(f)(ii) of the Agreement is hereby amended to add the following proviso at the end of the sentence "; *provided* that, with respect to the SACHI Study, Hutchison shall be responsible for [**].

b. Notwithstanding anything to the contrary in the Agreement, as additional consideration for the rights granted to AstraZeneca under the Agreement, AstraZeneca will pay Hutchison, upon receipt of an invoice, the following non-creditable, non-refundable (except as set forth in Section 9.3 of the Agreement) amounts, within thirty (30) days after the first occurrence of each of the following Development Milestones in the table below with respect to the SACHI Study. For the avoidance of doubt, each Development Milestone in Table 2 below of this Amendment shall be paid only once during the Term, regardless of the number of Collaboration Compounds or Collaboration Products that achieve the corresponding Milestone Event:

TABLE 2: DEVELOPMENT MILESTONES RELATED TO SACHI STUDY

Development Milestone	Amount
1. SACHI Study used as the basis for applying for Regulatory Approval or expanded label for a	$[**]

	Collaboration Product in People's Republic of China	
2.	SACHI Study used as the basis for obtaining a Regulatory Approval or expanded label for a Collaboration Product in People's Republic of China	$[**]

Notwithstanding anything to the contrary, the Development Milestone # 1 above (for applying for Regulatory Approval or expanded label (i.e., $6 million)) will not be payable to Hutchison if AstraZeneca achieves both Breakthrough Therapy Designation from the FDA and conditional Regulatory Approval in the U.S. for the Tagrisso plus savolitinib combination product on or before September 30, 2023, in each case based on the data from such SAVANNAH Clinical Trial.

7 Supply

a. AstraZeneca shall, at its sole expense and at no cost to Hutchison, manufacture or have manufactured and supply to Hutchison sufficient supply of osimertinib for the conduct of the SANOVO Phase III Trial and SACHI Study on the timelines set forth in the Development Plan under the Drug Supply Agreement between AstraZeneca UK Limited and Hutchison (as amended from time to time in accordance with its terms, the "**Supply Agreement**"), and such supply obligation shall survive any termination of the Agreement, *provided that* in the event of a termination of the Agreement under Section 10.2 or 10.3, other than a termination by Hutchison for a material breach of the Agreement by AstraZeneca pursuant to Section 10.3.1, and subject to Section 8(d) of this Amendment, AstraZeneca shall instead sell osimertinib to Hutchison for the conduct of the SANOVO Phase III Trial and SACHI Study at a price equivalent to AstraZeneca's fully absorbed cost of goods (to the extent reasonably incurred). AstraZeneca hereby agrees and acknowledges that, upon any delivery of osimertinib by or on behalf of AstraZeneca or its Affiliate to Hutchison or its Affiliate, such osimertinib will not have a Significant Deviation (as defined in the Supply Agreement) or fail to meet Specification (as defined in the Supply Agreement).

b. AstraZeneca hereby grants to Hutchison a co-exclusive, sublicensable (solely to subcontractors and Affiliates), royalty-free license under Know-How or Patent Rights Controlled by AstraZeneca or its Affiliates, including AstraZeneca's right, title and interest under the Collaboration Technology, solely to use osimertinib in the performance of Development Activities to be conducted by or on behalf of Hutchison under and in accordance with the Development Plan, including, for clarity, the SANOVO Phase III Trial and the SACHI Study.

c. In the event of a termination of the Agreement (i) by AstraZeneca for convenience under Section 10.2, or (ii) by Hutchison for a material breach of the Agreement by AstraZeneca pursuant to Section 10.3.1, and subject to Section 8(d) of this Amendment, AstraZeneca shall provide durvalumab to Hutchison for the conduct of the SAMETA Trial at no cost to Hutchison.

d. AstraZeneca's obligations under this Section 8 of the Amendment to supply osimertinib and durvalumab to Hutchison shall be effective as of the date of this Amendment's execution by the last Party to so execute and shall not be terminated, modified or delayed by any decision by AstraZeneca to not proceed or initiate the SAFFRON global Phase III Clinical Trial.

e. Notwithstanding anything to the contrary in the Agreement or this Amendment, AZ may terminate supply of osimertinib or durvalumab for a Clinical Trial by written notice to Hutchison if:

    i. Hutchison commits a material breach of this Agreement, and such material breach continues for thirty (30) days after receipt of written notice thereof from AstraZeneca; provided that if such material breach cannot reasonably be cured within thirty (30) days, Hutchison shall be given a reasonable period of time to cure such breach; provided further, that if such material breach is incapable of cure, then AstraZeneca may terminate supply effective after the expiration of such thirty (30) day period;

ii. A Regulatory Authority determines that such Clinical Trial may unreasonably affect patient safety, whereby termination of supply shall be immediate upon such notice from AstraZeneca;

iii. any Regulatory Authority takes any action, or raises any objection, that prevents AstraZeneca from supplying osimertinib or durvalumab, or AstraZeneca determines in its sole discretion to withdraw any applicable regulatory approval for osimertinib or durvalumab or cease commercialization of osimeritinib or durvalumab, whereby termination of supply of the osimertinib or durvalumab (as relevant) shall be immediate upon such notice from AstraZeneca; or

iv. AstraZeneca determines in good faith that the Clinical Trial may unreasonably affect patient safety, whereby termination of supply shall be immediate upon such notice from AstraZeneca.

8 Counterparts

This Amendment may be executed in two or more counterparts, each of which shall be deemed an original and all of which shall together be deemed to constitute one agreement. The Parties agree that execution of this Amendment by industry standard electronic signature software or by exchanging PDF signatures shall have the same legal force and effect as the exchange of original signatures, and that in any proceeding arising under or relating to this Amendment, each Party hereby waives any right to raise any defense or waiver based upon execution of this Amendment by means of such electronic signatures or maintenance of the executed Amendment electronically.

9 Entire Agreement

This Amendment, together with the Agreement, as amended, constitutes the entire agreement between the Parties with respect to the subject matter of the Agreement. The Agreement together with this Amendment supersedes all prior agreements, whether written or oral, with respect to the subject matter of the Agreement, as amended. The Parties hereby agree that subject to the modifications specifically stated in this Amendment, all terms and conditions of the Agreement, as amended, shall remain in full force and effect.

[*Remainder of page intentionally left blank. Signatures follow.*]

Each Party is signing this Amendment as of the Amendment Effective Date.

AstraZeneca AB (publ)	**Hutchison MediPharma Limited** **和记黄埔医药（上海）有限公司**
By: /s/ Martin Sundblad	By: /s/ Christian Hogg
Name: Martin Sundblad	Name: Christian Hogg
Title: Authorised signatory	Title: Director
Date:	Date: November 29, 2021

Exhibit A

Development Plan incorporating the SANOVO Phase III Study as of Amendment Effective Date

[**]

Exhibit B

Outline of the SAFFRON Global Phase III Clinical Trial

[**]

Exhibit 4.15

Certain identified information has been excluded from the exhibit because it is both (i) not material and (ii) is the type of information that the registrant treats as private or confidential. Double asterisks denote omissions.

Execution Version

LICENSE AGREEMENT

THIS LICENSE AGREEMENT (this "**Agreement**") is made and entered into as of August 7, 2021 ("**Effective Date**") between Epizyme, Inc., a corporation organized and existing under the laws of the State of Delaware, with a principal place of business at 400 Technology Square, Cambridge, Massachusetts 02139 U.S. ("**Epizyme**"), and Hutchison China MediTech Investment Limited, a company organized and existing under the laws of the British Virgin Islands, with company number 2031179 and its registered office being Vistra Corporate Services Centre, Wickhams Cay II, Road Town, Tortola, VG1110, British Virgin Islands ("**Hutchmed**"). Epizyme and Hutchmed may be referred to herein individually as a "**Party**" and collectively as the "**Parties**."

RECITALS

WHEREAS, Epizyme is Developing and Commercializing Licensed Products (as defined below);

WHEREAS, Hutchmed has expertise in the development of biopharmaceutical products and has regulatory and commercial capabilities in the Territory, and is interested in obtaining a co-exclusive (with the Epizyme Entities) license to Develop, an exclusive license to Commercialize, and a co-exclusive license to Manufacture (following Manufacturing Technology Transfer), the Licensed Products in the Territory (each as defined below); and

WHEREAS, the Parties desire to collaborate to Develop, Manufacture, and Commercialize the Licensed Products in the Territory.

NOW THEREFORE, in consideration of the premises and the mutual promises and conditions hereinafter set forth, and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Parties agree as follows:

ARTICLE 1. DEFINITIONS

1.1 "**101 Trial**" means the Phase 1/2 open-label multicenter study of monotherapy Tazemetostat identified on clinicaltrials.gov as NCT01897571.

1.2 "**202 Trial**" means the Phase 2 open-label multicenter study of monotherapy Tazemetostat identified on clinicaltrials.gov as NCT02601950.

1.3 "**301 Global Trial**" means the global confirmatory clinical trial testing Tazemetostat in combination with doxorubicin versus doxorubicin alone in subjects with advanced ES (clinicaltrials.gov identifier NCT04204941).

1.4 "**302 Global Trial**" means the global confirmatory clinical trial testing Tazemetostat in combination with rituximab and lenalidomide versus rituximab and lenalidomide alone in subjects with relapsed/refractory FL (clinicaltrials.gov identifier NCT04224493).

1.5 "**AAA**" means the American Arbitration Association.

1.6 "**Accounting Standards**" means the then-current United States Generally Accepted Accounting Principles, as consistently applied.

1.7 "**Acquired Party**" has the meaning set forth in Section 16.2.

1.8 "**Acquirer**" has the meaning set forth in Section 16.2.

1.9 "**Additional Indication**" has the meaning set forth in Section 4.3(a).

1.10 "**Affiliate**" means, with respect to an entity, any corporation, or other business entity controlled by, controlling, or under common control with such entity, with "control" meaning (a) direct or indirect beneficial ownership of at least fifty percent (50%) of the voting stock of, or at least a fifty percent (50%) interest in the income of, the applicable entity (or such lesser percentage that is the maximum allowed to be owned by a foreign entity in a particular jurisdiction and is sufficient to grant the holder of such voting stock or interest the power to direct the management and policies of such entity) or (b) possession, directly or indirectly, of the power to direct the management and policies of an entity, whether through ownership of voting securities, by contract relating to voting rights or corporate governance or otherwise.

1.11 "**Alliance Manager**" has the meaning set forth in Section 3.13.

1.12 "**Anti-Corruption Laws**" has the meaning set forth in Section 12.7(c)(i).

1.13 "**Applicable Law**" means any applicable law, statute, rule, regulation, order, judgment, standard, or ordinance of any Governmental Authority that may be in effect from time to time, including disclosure obligations required by any stock exchange or securities commission having authority over a Party and any applicable rules, regulations, guidances, or other requirements of any Governmental Authority, including any Regulatory Authority, that may be in effect from time to time.

1.14 "**Authorized Regulatory Agent**" means (a) a local entity authorized by Hutchmed or any of its Affiliates, if Hutchmed or its Affiliate is the CTA holder or license holder of imported Drug Product or (b) Hutchmed or its Affiliate, if Hutchmed or its Affiliate is not the CTA holder or license holder of imported Drug Product, in either case ((a) or (b)), where such entity, Hutchmed, or Hutchmed Affiliate, as applicable, manages the work associated with obtaining and maintaining any Regulatory Approval or product registration in the Territory and which possesses and maintains valid licenses or permits in the Territory if such licenses or permits are required for such local entity to engage in the relevant activities in the Territory.

1.15 "**Business Day**" means a day other than (a) a Saturday or a Sunday or (b) a day on which banking institutions in Boston, Massachusetts, U.S., or in Hong Kong, are authorized or required by Applicable Law to remain closed.

1.16 "**Buy-In Right Payment**" has the meaning set forth in Section 9.3(d).

1.17 "**Calendar Quarter**" means the respective periods of three (3) consecutive calendar months ending on March 31st, June 30th, September 30th, or December 31st in any Calendar Year; provided that the first Calendar Quarter of the Term will begin on the Effective Date and end on the first to occur of March 31st, June 30th, September 30th, or December 31st, and the last Calendar Quarter of the Term will end on the last day of the Term.

1.18 "**Calendar Year**" means any calendar year beginning on January 1st and ending on December 31st; provided that the first Calendar Year of the Term will begin on the Effective Date and end on December 31, and the last Calendar Year of the Term will end on the last day of the Term.

1.19 "**Change in Control**" means, as to a Party, the (a) consolidation or merger of such Party with or into any Third Party as a result of which the beneficial owners of the outstanding voting securities or other ownership interests of such Party immediately prior to such transaction have beneficial ownership of fifty percent (50%) or less of the outstanding voting securities or other ownership interests of the surviving person or entity or the parent entity of such surviving person or entity immediately following such transaction, or (b) sale, transfer or other disposition of all or substantially all of the assets of such Party related to this Agreement to any Third Party, or group of Third Parties acting in concert, or (c) acquisition by any Third Party, or group of Third Parties acting in concert, of beneficial ownership of more than fifty percent (50%) percent of the outstanding voting securities or other ownership interests of such Party or the power, directly or indirectly, to elect a majority of the members of such Party's board of directors or similar governing body. No initial or subsequent offering by a Party of securities for sale on a public securities exchange shall be considered to be or to involve a Change in Control of such Party unless such offering meets the requirements of clause (c) of the preceding sentence; provided, however, that an acquisition of voting securities by an underwriter in an underwritten public offering for the purpose of effecting a wider distribution of such voting securities shall be deemed not to meet the requirements of clause (c) of the preceding sentence.

1.20 "**Clinical Development Plan**" or "**CDP**" means the plan, as further described in Sections 4.2 and 4.3, setting out activities to be undertaken by Hutchmed in Developing the Licensed Products (whether as monotherapies or Combination Therapies) in the Field in the Territory, together with timelines and budgets for such activities, including proposed bridging studies, Local Trials, Joint Global Trials, registry studies, investigator sponsored studies, Pre-Clinical Research, and regulatory plans, as well as outlining the key elements involved in obtaining Regulatory Approval of the Licensed Products in the Field in the Territory and plans to address Medical Affairs matters (taking into consideration in good faith the Global Medical Affairs Strategy), and the quality plan to verify GxP compliance, each as applicable. The Clinical Development Plan may be amended from time to time in accordance with Section 4.3 and approved by the JDC in accordance with Article 3. The approved Clinical Development Plan as of the Effective Date for the Development of the Licensed Products in each Initial Indication is attached hereto as Exhibit A.

1.21 "**Clinical Supply Agreement**" has the meaning set forth in Section 7.1.

1.22 "**Clinical Supply Price**" means, with respect to any quantity of Licensed Compound or Licensed Product (including Drug Substance or Drug Product) for use in Development in the Territory, the Fully-Burdened Cost of such quantity.

1.23 "**Combination Product**" has the meaning set forth in Section 1.139.

1.24 "**Combination Therapy**" means, subject to Section 3.10(b)(ii), any therapeutic or palliative regimen consisting of the separate but concurrent administration of (a) a Licensed Product, and (b) one or more other active pharmaceutical ingredients or drugs for the treatment of Hematological Indications or Solid Tumor Indications (each, an "**Other Combination Drug**") (whether or not co-packaged with the Licensed Product), and consists of either:

(i) the use of both (A) a Licensed Product and (B) one or more Other Combination Drugs where at least one of the Other Combination Drugs is a Hutchmed Compound (a "**Joint Combination Therapy**"); or

(ii) the use of both (A) a Licensed Product and (B) one or more Other Combination Drugs other than as described in subsection (i)(B) above (an "**Epizyme Combination Therapy**"). Without limiting the foregoing, an example of an Epizyme Combination Therapy could include the

use of both a Licensed Product and one or more Other Combination Drugs proprietary to, or Controlled by, Epizyme or Other Combination Drugs commercially available from a Third Party.

In no event shall the Other Combination Drugs of a Combination Therapy be co-packaged or co-formulated with Licensed Product in the Territory unless the Parties mutually agree.

1.25 "**Commercial Supply Agreement**" has the meaning set forth in Section 7.3.

1.26 "**Commercial Supply Price**" means, with respect to any quantity of Licensed Product (including Drug Substance or Drug Product) for Commercialization in the Territory, the Fully-Burdened Cost of such quantity plus [**] percent ([**]%).

1.27 "**Commercialization**" means, with respect to a pharmaceutical product (whether in monotherapy or as part of a Combination Therapy), any and all activities directed to the marketing, promotion, importation, distribution, pricing, Reimbursement Approval, offering for sale, or sale of such pharmaceutical product, and interacting with Regulatory Authorities regarding the foregoing. Commercialization shall exclude Development and Manufacturing. "**Commercialize**," "**Commercializing**," and "**Commercialized**" will be construed accordingly.

1.28 "**Commercialization Plan**" means the [**] plan for the Commercialization of Licensed Products in the Field in the Territory and the activities to be conducted by or on behalf of the Hutchmed Entities relating thereto, including (a) the Launch Plan, and (b) reasonably detailed plans for sales and marketing after launch, a high-level [**] sales and marketing budget (for informational purposes only), estimated sales forecasts, market access plans, and reimbursement plans and strategies.

1.29 "**Commercially Reasonable Efforts**" means, with respect to the performing Party under this Agreement, the carrying out of obligations of such Party with efforts and resources that are consistent with the efforts and resources typically used by biopharmaceutical companies of similar size and resources as such Party with respect to the Development, Manufacture or Commercialization of products of market potential, profit potential and strategic value and of a stage in Development or product life comparable to that of Licensed Product(s), based on conditions then prevailing and taking into account issues of safety and efficacy, product profile, difficulty in Developing such Licensed Product, competitiveness of alternative Third Party products in the marketplace, the patent or other proprietary position of such Licensed Product, the regulatory structure involved, the potential profitability of such Licensed Product and other relevant factors, as applicable, but without regard for any payment obligations under this Agreement. Commercially Reasonable Efforts shall be determined on a Jurisdiction-by-Jurisdiction basis and, with respect to Hutchmed, without regard to any activities to Develop or Commercialize Hutchmed Dual Inhibitor Products in the Territory.

1.30 "**Comparable Third Party Product**" means, with respect to a particular Licensed Product in the Territory, any pharmaceutical product sold by a Third Party in the Territory not authorized by or on behalf of Hutchmed or any other Hutchmed Entity that (a) contains, as an active pharmaceutical ingredient, the same compound as the Licensed Compound contained in the applicable Licensed Product, and (b) has received Regulatory Approval from the relevant Regulatory Authority in the Territory for the same indication as such Licensed Product.

1.31 "**Comparable Third Party Product Competition**" means, with respect to a specific Licensed Product in the Territory in a given Calendar Quarter, that during such Calendar Quarter: (a) one (1) or more Comparable Third Party Product(s) are commercially available in the Territory; and (b) such Comparable Third Party Product(s) have a market share of [**] percent ([**]%) or more of the aggregate market in the Territory of such Licensed Product and such Comparable Third Party Product(s) collectively (based on

sales of units of such Licensed Product and Comparable Third Party Product(s), as reported by IQVIA, or if such data is not available, such other reliable data source as reasonably determined by the Parties). As used herein, a "unit" of a product means the equivalent amount of product used for an equivalent treatment cycle of such product.

1.32 "**Competing Product**" means any compound or product that, as its primary intended therapeutic mechanism of action, directly or indirectly inhibits or modulates the activity of, or degrades, one or more of EZH2, EZH1, or any other member of the polycomb repressive complex 2 ("**PRC2**"), including the EED protein.

1.33 "**Compulsory Third Party Product**" has the meaning set forth in Section 9.6(b)(ii).

1.34 "**Confidential Information**" means, subject to Section 10.2, Know-How and any technical, scientific, trade, research, manufacturing, business, financial, compliance, marketing, product, supplier, intellectual property or other information that may be disclosed by one Party or any of its Representatives ("**Discloser**") to the other Party or any of its Representatives ("**Recipient**"); provided that, if such information is (a) in tangible form, it is labelled in writing as proprietary or confidential, (b) in oral or visual form, is identified as proprietary or confidential at the time of disclosure or within [**] thereafter, or (c) is disclosed in writing, orally, electronically or visually to a Recipient and would be apparent to a reasonable person familiar with the life sciences industry, to be of a confidential or proprietary nature. Notwithstanding the foregoing, subject to Section 10.2, all information that (i) was disclosed prior to the Effective Date by or on behalf of either Party or any of its Affiliates under, and subject to, the Mutual Non-Disclosure Agreement dated [**] between Hutchison MediPharma Limited and Epizyme ("**Confidentiality Agreement**") and (ii) is "Confidential Information" as defined in the Confidentiality Agreement, shall be deemed "Confidential Information" hereunder.

1.35 "**Controlled**" means, subject to Section 2.7 and Section 16.2, with respect to a Party, and any Know-How, Patent Right, Regulatory Documents or other intellectual property right, that such Party or any of its Affiliates has the ability (other than pursuant to a license granted to such Party under this Agreement) to grant to the other Party (in the applicable country) a license or sublicense to, or other right with respect to, such Know-How, Patent Right, Regulatory Documents or other intellectual property right without violating the terms of any pre-existing agreement or other pre-existing arrangement with any Third Party.

1.36 "**Covered**" means, with respect to a product, composition, technology, process or method and a Patent Right, that, in the absence of ownership of, or a license granted under, a Valid Claim in such Patent Right, the manufacture, use, offer for sale, sale or importation of such product or composition or the practice of such technology, process or method would infringe such Valid Claim (or, in the case of a claim of a pending patent application, would infringe such claim if it were to issue as a claim of an issued patent). "Cover" and "Covering" will be construed accordingly.

1.37 "**CTA**" means a clinical trial application filed with a Regulatory Authority in the Territory pursuant to the Drug Administration Law and other relevant regulations and rules governing drug clinical trials in the Territory.

1.38 "**CTA Data**" means (a) the data in the CTAs for the 302 Global Trial which were filed by Epizyme in Mainland China and Taiwan, and (b) all information regarding the Licensed Product in Epizyme's Control that was generated by or on behalf of Epizyme as of the Effective Date to the extent necessary or reasonably useful for the CTA filing for the 301 Global Trial in the Territory.

1.39 "**Development**" means Pre-Clinical Research and clinical development activities, including (i) clinical trials of a pharmaceutical compound or product, investigator sponsored trials and registry studies

(whether in monotherapy or as part of a combination therapy) and (ii) the preparation, submission, review, and development of data or information for the purpose of submission to a Regulatory Authority to obtain authorization to conduct clinical trials or to obtain Regulatory Approval of a pharmaceutical product. Development shall include clinical trials initiated prior to or following receipt of Regulatory Approval, but shall exclude Manufacturing and Commercialization. "Develop," "Developing," and "Developed" will be construed accordingly.

1.40 "**Discloser**" has the meaning set forth in Section 1.34.

1.41 "**Dispute**" has the meaning set forth in Section 15.1.

1.42 "**DLBCL**" means diffuse large B-cell lymphoma.

1.43 "**Dollars**" or "**$**" means the legal tender of the U.S.

1.44 "**Dosage Form Change**" has the meaning set forth in Section 7.4(b).

1.45 "**Drug Approval Application**" means a New Drug Application as defined in the FD&C Act, or an equivalent application filed with any Regulatory Authority in any country other than the United States, including any new drug application filed with the NMPA in Mainland China or other Regulatory Authorities pursuant to the Drug Administration Law, the Administrative Regulations on Drug Registration and other Applicable Laws in the Territory.

1.46 "**Drug Class**" means the class of all active pharmaceutical ingredients and compounds that have the same mechanism of action and physiologic effect.

1.47 "**Drug Product**" or "**DP**" means oral solid dose tablets in finished form (bulk packaged) that contain Drug Substance as set forth in the applicable specifications provided by Epizyme.

1.48 "**Drug Substance**" or "**DS**" means Licensed Compound in bulk form manufactured for use as an active pharmaceutical ingredient in a Licensed Product, as set forth in the applicable specifications provided by Epizyme.

1.49 "**Eisai Agreement**" means that certain Amended and Restated Collaboration and License Agreement dated as of March 12, 2015 by and between Eisai Co., Ltd. ("**Eisai**") and Epizyme.

1.50 "**Epizyme Basket Trial**" means any Phase 1b/2 basket clinical trial of Licensed Product that includes cohorts of patients who are being treated for different disease indications within the same trial and that is conducted by Epizyme outside the Territory. For clarity, an Epizyme Basket Trial is not a Joint Global Trial or a Rejected Global Trial.

1.51 "**Epizyme Combination Therapy**" has the meaning set forth in Section 1.24.

1.52 "**Epizyme Combination Therapy IP**" means Epizyme Combination Therapy Know-How and Epizyme Combination Therapy Patent Rights.

1.53 "**Epizyme Combination Therapy Know-How**" means any and all Know-How including any invention (whether or not patentable and whether or not claimed in any Patent Right) that:

(a) comprises or encompasses, either generically or specifically, or is necessary or reasonably useful for the Development or Commercialization of, any Licensed Product used with Other Combination Drug(s) as an Epizyme Combination Therapy in the Field, and

(b) (i) is Controlled by Epizyme or any of its Affiliates as of the Effective Date or during the Term, including Know-How that is conceived, identified, discovered, authored, developed, or reduced to practice solely by or on behalf any Epizyme Entity during the Term in the performance of any activity conducted under this Agreement (including any Local Trial or, subject to Section 9.3(e), Joint Global Trial, or subject to Section 9.3(d), Rejected Global Trial), or (ii) solely to the extent such Know-How specifically relates to the Development or Commercialization of any Licensed Product used with Other Combination Drug(s) as an Epizyme Combination Therapy in the Field, is conceived, identified, discovered, authored, developed, or reduced to practice solely by or on behalf any Hutchmed Entity or jointly by or on behalf of any Hutchmed Entity and Epizyme, in each case, during the Term in the performance of any activity conducted under this Agreement (including any Local Trial or, subject to Section 9.3(e), Joint Global Trial), or (iii) consists of safety data to the extent pertaining to an Epizyme Combination Therapy from any patient treated under this Agreement or outside of this Agreement provided under the Safety Data Exchange Agreement;

provided that in no event shall Epizyme Combination Therapy Know-How include any Epizyme Know-How, Epizyme Manufacturing Know-How, Joint Know-How, or Joint Combination Therapy Know-How. For clarity, Epizyme Combination Therapy Know-How includes any inventions assigned or licensed by Hutchmed to Epizyme pursuant to Section 11.1(b).

1.54 "**Epizyme Combination Therapy Patent Rights**" means any and all Patent Rights (a) Covering Epizyme Combination Therapy Know-How, and (b) Controlled by Epizyme or any of its Affiliates as of the Effective Date or during the Term, including any such Patent Rights assigned or licensed by Hutchmed to Epizyme pursuant to Section 11.1(b) and any such Patent Rights licensed to Epizyme pursuant to an Epizyme In-License Agreement. The Epizyme Combination Therapy Patent Rights as of the Effective Date are included on Exhibit B, which shall be updated periodically during the Term upon the request of Hutchmed.

1.55 "**Epizyme CRO**" has the meaning set forth in Section 4.5(b).

1.56 "**Epizyme Entity**" means, as applicable, (a) Epizyme, (b) any of Epizyme's Affiliates, or (c) any direct or indirect licensee, sublicensee or contractor of Epizyme or any of Epizyme's Affiliates with respect to Licensed Compound or any Licensed Product (other than any Hutchmed Entity).

1.57 "**Epizyme In-License Agreement**" means (a) the Eisai Agreement, and (b) any agreement entered into between Epizyme or any of its Affiliates, on the one hand, and one or more Third Parties, on the other hand, pursuant to which Epizyme or any of its Affiliates acquires Control of any Know-How necessary or reasonably useful for, or Patent Right that Covers, the Development or Commercialization of any Licensed Product in the Field in the Territory, or the Manufacture of Licensed Compound or Licensed Products that is entered into after the Effective Date and accepted by Hutchmed under Section 2.7(a) (each, an "**Epizyme New In-License Agreement**").

1.58 "**Epizyme IP**" means Epizyme Know-How and Epizyme Patent Rights.

1.59 "**Epizyme Know-How**" means any and all Know-How including any invention (whether or not patentable and whether or not claimed in any Patent Right) that:

(a) comprises or encompasses, either generically or specifically, or is necessary or reasonably useful for the Development or Commercialization of, any Licensed Product in the Field (other than a Licensed

Product used with Other Combination Drug(s) as an Epizyme Combination Therapy in the Field), including any Know-How relating to biomarkers, genetic mutations, or the identification or selection of patients, in each case related to any Licensed Product in the Field, and

(b) (i) is Controlled by Epizyme or any of its Affiliates as of the Effective Date or during the Term, including Know-How that is conceived, identified, discovered, authored, developed, or reduced to practice solely by or on behalf any Epizyme Entity during the Term in the performance of any activity conducted under this Agreement (including any Local Trial or, subject to Section 9.3(e), Joint Global Trial, or subject to Section 9.3(d), any Rejected Global Trial), or (ii) solely to the extent such Know-How specifically relates to the Development or Commercialization of any Licensed Product in the Field, is conceived, identified, discovered, authored, developed, or reduced to practice solely by or on behalf any Hutchmed Entity or jointly by or on behalf of any Hutchmed Entity and Epizyme, in each case, during the Term in the performance of any activity conducted under this Agreement (including any Local Trial or, subject to Section 9.3(e), Joint Global Trial), or (iii) consists of safety data pertaining to any Licensed Product from any patient treated under this Agreement or outside of this Agreement provided under the Safety Data Exchange Agreement;

provided that in no event shall Epizyme Know-How include any Epizyme Combination Therapy Know-How, Epizyme Manufacturing Know-How, Joint Know-How, or Joint Combination Therapy Know-How. For clarity, Epizyme Know-How includes any inventions assigned or licensed by Hutchmed to Epizyme pursuant to Section 11.1(b).

1.60 "**Epizyme Manufacturing IP**" means Epizyme Manufacturing Know-How and Epizyme Manufacturing Patent Rights.

1.61 "**Epizyme Manufacturing Know-How**" means any and all Know-How including any invention (whether or not patentable and whether or not claimed in any Patent Right) that:

(a) is necessary or reasonably useful for the Manufacture of any Licensed Product in the Field and

(b) (i) is Controlled by Epizyme or any of its Affiliates as of the Effective Date or (ii) is conceived, identified, discovered, authored, developed, or reduced to practice (A) by or on behalf of any Epizyme Entity during the Term in the performance of any activity conducted under this Agreement, (B) solely by or on behalf of any Hutchmed Entity or jointly by or on behalf of Epizyme and any Hutchmed Entity, in each case, during the Term in the performance of any activity conducted under this Agreement but only to the extent such Know-How specifically relates to the Manufacture of any Licensed Product, or (C) by or on behalf of Epizyme or any of its Affiliates during the Term outside this Agreement;

provided that in no event shall Epizyme Manufacturing Know-How include any Epizyme Combination Therapy Know-How, Epizyme Know-How, Joint Know-How, or Joint Combination Therapy Know-How. For clarity, Epizyme Manufacturing Know-How shall include any inventions assigned or licensed by Hutchmed to Epizyme pursuant to Section 11.1(b).

1.62 "**Epizyme Manufacturing Patent Rights**" means any and all Patent Rights (a) Covering Epizyme Manufacturing Know-How and (b) Controlled by Epizyme as of the Effective Date or during the Term, including any such Patent Rights assigned or licensed by Hutchmed to Epizyme pursuant to Section 11.1(b) and any such Patent Rights licensed to Epizyme pursuant to an Epizyme In-License Agreement. The Epizyme Manufacturing Patent Rights as of the Effective Date are included on Exhibit B, which shall be updated periodically during the Term upon the request of Hutchmed.

1.63 "**Epizyme Patent Rights**" means any and all Patent Rights (a) Covering Epizyme Know-How and (b) Controlled by Epizyme as of the Effective Date or during the Term, including any such Patent Rights assigned or licensed by Hutchmed to Epizyme pursuant to Section 11.1(b) and any such Patent Rights licensed to Epizyme pursuant to an Epizyme In-License Agreement. The Epizyme Patent Rights as of the Effective Date are included on Exhibit B which shall be updated periodically during the Term upon the request of Hutchmed.

1.64 "**Epizyme Product Data**" has the meaning set forth in Section 2.6(a).

1.65 "**Epizyme Product Filing Data**" has the meaning set forth in Section 2.6(a)

1.66 "**Epizyme Regulatory Documents**" means Regulatory Documents Controlled by Epizyme or its Affiliates as of the Effective Date or at any time during the Term that relate to Licensed Compound or a Licensed Product. For clarity, Epizyme Regulatory Documents includes any Regulatory Documents that Epizyme Controls through the Eisai Agreement.

1.67 "**Epizyme Trial**" means any clinical trial, including any Epizyme Basket Trial, for any Licensed Product in the Field, which was not proposed to the JDC and which is conducted by any Epizyme Entity in one or more countries outside of the Territory. For clarity, an Epizyme Trial is not a Joint Global Trial or Rejected Global Trial.

1.68 "**ES**" means epithelioid sarcoma.

1.69 "**Executive Officer**" has the meaning set forth in Section 3.9.

1.70 "**EZH1**" means the catalytic subunit of the PRC2/EED-EZH1 complex, which methylates lysine-27 of histone H3.

1.71 "**EZH2**" means the catalytic subunit of PRC2, which methylates lysine-27 of histone H3.

1.72 "**FDA**" means the U.S. Food and Drug Administration or any successor agency thereto.

1.73 "**FD&C Act**" means the U.S. Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 et seq., as amended from time to time.

1.74 "**Field**" means all therapeutic and palliative uses of Licensed Product in humans for the Initial Indications and Additional Indications.

1.75 "**Finished Drug Product**" means the finished product formulation of a Licensed Product labeled and packaged in a form ready for administration.

1.76 "**First Commercial Sale**" means, with respect to each Licensed Product in the Territory, the first sale for which revenue has been recognized by Hutchmed or any other Hutchmed Entity for use or consumption by the general public of such Licensed Product in the Territory either (i) after Regulatory Approval (and Reimbursement Approval, if legally required for such sale) for such Licensed Product has been obtained in the Territory, or (ii) sales of Licensed Products in the Hainan Medical Tourism Zone prior to Regulatory Approval; provided, however, that the following shall not constitute a First Commercial Sale: (a) any sale to an Affiliate or Sublicensee unless the Affiliate or Sublicensee is the last entity in the distribution chain of the Licensed Product; (b) any use of such Licensed Product in clinical trials, non-clinical activities or other Development activities, or disposal or transfer of Licensed Products for a bona fide charitable purpose; and (c) treatment IND sales, named patient sales, or compassionate use.

1.77 "**FL**" means follicular lymphoma.

1.78 "**FTE**" means a qualified full time person, or more than one person working the equivalent of a full time person, where "full time" is based upon a total of [**] working hours per Calendar Year at an Epizyme Entity.

1.79 "**FTE Rate**" means the rate in Dollars set forth on Schedule 1.79 for each Calendar Year.

1.80 "**Fully-Burdened Cost**" means, with respect to any particular Licensed Product (whether in Drug Substance or Drug Product form), the costs as set forth on Schedule 1.80.

1.81 "**Global Brand Strategy**" means the global brand strategy that determines, among other aspects, product positioning, market access strategies, messaging strategies, trademark layout, and logos, all as determined by Epizyme for Licensed Products and updated from time to time and provided to Hutchmed.

1.82 "**Global Medical Affairs Strategy**" means the global Medical Affairs strategy for Licensed Products, as determined by Epizyme and updated from time to time and provided to Hutchmed.

1.83 "**Good Clinical Practices**" or "**GCP**" means the then-current good clinical practice standards, practices, and procedures promulgated or endorsed by any applicable Regulatory Authority as set forth in the guidelines imposed by such Regulatory Authority, as may be updated from time to time.

1.84 "**Good Laboratory Practices**" or "**GLP**" means the then-current good laboratory practice standards, practices, and procedures promulgated or endorsed by any applicable Regulatory Authority as set forth in the guidelines imposed by such Regulatory Authority, as may be updated from time to time.

1.85 "**Good Manufacturing Practices**" or "**GMP**" means the then-current good manufacturing practice standards, practices, and procedures promulgated or endorsed by any applicable Regulatory Authority as set forth in the guidelines imposed by such Regulatory Authority, as may be updated from time to time.

1.86 "**Good Pharmacovigilance Practices**" or "**GVP**" means the then-current good pharmacovigilance practice standards, practices, and procedures promulgated or endorsed by any applicable Regulatory Authority as set forth in the guidelines imposed by such Regulatory Authority, as may be updated from time to time.

1.87 "**Governmental Authority**" means any federal, foreign, national, multinational, state, provincial, county, city or local government or any court, arbitrational tribunal, administrative agency or commission or government authority acting under the authority of any federal, foreign, national, multinational, state, provincial, county, city or local government.

1.88 "**Hematological Indication**" means any disorder or disease of the blood, blood-forming organs such as bone marrow, or cells of the immune system, including any lymphoma (including indolent and aggressive lymphomas such as FL and DLBCL, respectively).

1.89 "**HIPAA**" has the meaning set forth in Section 2.6(a).

1.90 "**Hutchmed China**" means Hutchison MediPharma Limited (和记黄埔医药（上海）有限公司), a Chinese company, organized and existing under the laws of the People's Republic of China, having a place of business at Building 4, 720 Cai Lun Road, ZJ Hi-Tech Park, Shanghai, People's Republic of China.

1.91 "**Hutchmed Compound**" means an approved drug or pre-clinical or clinical stage drug candidate that is (a) proprietary to Hutchmed or any of its Affiliates and (b) Covered by Patent Rights that are Controlled by Hutchmed as of the Effective Date or at any time during the Term, including the compounds set forth on Schedule 1.91.

1.92 "**Hutchmed Dual Inhibitor Product**" means any compound that (a) is an EZH1/EZH2 dual inhibitor, (b) results from the preclinical program begun by Hutchmed as of the Effective Date, and (c) is proprietary to Hutchmed or any of its Affiliates and Covered by Patent Rights that are Controlled by Hutchmed.

1.93 "**Hutchmed Dual Inhibitor Product IP**" has the meaning set forth in Section 8.1(b).

1.94 "**Hutchmed Entity**" means, as applicable, (a) Hutchmed, (b) any of Hutchmed's Affiliates or (c) any direct or indirect Sublicensee, or Permitted Subcontractor of Hutchmed or any of Hutchmed's Affiliates with respect to any Licensed Compound or any Licensed Product (other than an Epizyme Entity).

1.95 "**Hutchmed In-License Agreement**" means any agreement other than this Agreement pursuant to which any Hutchmed Entity has in-licensed or otherwise acquired the right to practice, or in-licenses or otherwise acquires the right to practice, any Know-How related to, or Patent Rights that Cover, any of the Licensed Products in the Field outside the Territory as of the Effective Date or during the Term.

1.96 "**Hutchmed IP**" means Hutchmed Know-How and Hutchmed Patent Rights.

1.97 "**Hutchmed Know-How**" means any and all Know-How including any invention (whether or not patentable and whether or not claimed in any Patent Right) that:

(a) is Controlled by Hutchmed as of the Effective Date or during the Term, including Know-How that Hutchmed or any of its Affiliates acquires or obtains a license (with the right to sublicense) from a Third Party after the Effective Date including under a Hutchmed In-License Agreement accepted by Epizyme pursuant to Section 2.7(b), and

(b) comprises or encompasses, either generically or specifically, or is necessary or reasonably useful for the Development, Manufacture or Commercialization of the Licensed Compound or any Licensed Product (as a monotherapy or as part of a Combination Therapy), including for clarity Know-How that generically relates to the Development, Manufacture, or Commercialization of any Licensed Product (whether as a monotherapy or used with Other Combination Drug(s) as an Epizyme Combination Therapy) in the Field that is conceived, identified, discovered, authored, developed, or reduced to practice solely by or on behalf any Hutchmed Entity during the Term in the performance of any activity conducted under this Agreement; but excluding any Know-How to the extent related to any Hutchmed Compound that is not a component of a Joint Combination Therapy being Developed or Commercialized pursuant to this Agreement.

provided that in no event shall Hutchmed Know-How include any Joint Combination Therapy Know-How, Joint Know-How, Epizyme Combination Therapy Know-How, Epizyme Know-How or Epizyme Manufacturing Know-How.

1.98 "**Hutchmed Marks**" means any Trademarks Controlled by Hutchmed or its Affiliates, including Hutchmed corporate names and logos.

1.99 "**Hutchmed Non-Compete Field**" means the use of the Hutchmed Dual Inhibitor (a) as a monotherapy, or (b) as part of a combination therapy with any active pharmaceutical ingredient, other than any active pharmaceutical ingredient in the same Drug Class as an Other Combination Drug proposed by

Hutchmed pursuant to Section 4.3 and rejected by Epizyme pursuant to Section 3.10(b)(ii), in either case ((a) or (b)), for use in (i) the Field, or (ii) any other indication, other than any Rejected Additional Indication that was proposed by Hutchmed pursuant to Section 4.3 and rejected by Epizyme pursuant to Section 3.10(b)(i).

1.100 "**Hutchmed Patent Rights**" means any and all Patent Rights (a) Covering Hutchmed Know-How and (b) Controlled by Hutchmed as of the Effective Date or during the Term, including Patent Rights licensed to Hutchmed pursuant to a Hutchmed In-License Agreement accepted by Epizyme pursuant to Section 2.7(b). For clarity, Hutchmed Patent Rights exclude any Joint Combination Therapy Patent Rights, and Joint Patent Rights, and any Epizyme Combination Therapy Patent Rights, Epizyme Patent Rights and Epizyme Manufacturing Patent Rights assigned by Hutchmed to Epizyme pursuant to Section 11.1(b).

1.101 "**Hutchmed Product Data**" has the meaning set forth in Section 2.6(b).

1.102 "**Hutchmed Regulatory Documents**" means Regulatory Documents Controlled by Hutchmed or any other Hutchmed Entity at any time during the Term that relate to the Licensed Compound or a Licensed Product in the Territory.

1.103 "**IND**" means an Investigational New Drug application for submission to the FDA or any equivalent counterpart application in any country other than the United States (including a CTA), including all supplements and amendments thereto.

1.104 "**Initial Indication**" means (a) subject to Section 4.5(e), ES, (b) FL (second line and third line), or (c) DLBCL.

1.105 "**JCC**" or "**Joint Commercialization Committee**" has the meaning set forth in Section 3.1(a).

1.106 "**JDC**" or "**Joint Development Committee**" has the meaning set forth in Section 3.1(a).

1.107 "**JMC**" or "**Joint Manufacturing Committee**" has the meaning set forth in Section 3.1(a).

1.108 "**Joint Combination Therapy**" has the meaning set forth in Section 1.24.

1.109 "**Joint Combination Therapy IP**" means Joint Combination Therapy Know-How and Joint Combination Therapy Patent Rights.

1.110 "**Joint Combination Therapy Know-How**" means any and all Know-How including any invention (whether or not patentable and whether or not claimed in any Patent Right) that:

(a) comprises or encompasses, either generically or specifically, or is necessary or reasonably useful for the Development or Commercialization of, any Licensed Product used with Other Combination Drug(s) as a Joint Combination Therapy in the Field, and

(b) (i) is Controlled by either Party or any of its Affiliates as of the Effective Date or during the Term, or (ii) is conceived, identified, discovered, authored, developed, or reduced to practice (A) solely by or on behalf of any Hutchmed Entity, (B) solely by or on behalf of any Epizyme Entity, or (C) jointly by or on behalf of any Hutchmed Entity and Epizyme, in each case, during the Term in the performance of any activity conducted under this Agreement (including any Local Trial or, subject to Section 9.3(e), Joint Global Trial or subject to Section 9.3(d), Rejected Global Trial), or (iii) consists of safety data to the extent pertaining to an Joint Combination Therapy from any patient treated under this Agreement or outside of this Agreement provided under the Safety Data Exchange Agreement;

provided that in no event shall Joint Combination Therapy Know-How include any Epizyme Combination Therapy Know-How, Epizyme Know-How, Epizyme Manufacturing Know-How, or Joint Know-How. For clarity, Joint Combination Therapy Know-How includes any inventions assigned by the Parties pursuant to Section 11.1.

1.111 "**Joint Combination Therapy Patent Rights**" means any and all Patent Rights (a) Covering Joint Combination Therapy Know-How and (b) Controlled by a Party or any of its Affiliates as of the Effective Date or during the Term (including any such Patent Rights licensed to a Party pursuant to an Epizyme In-License Agreement or Hutchmed In-License Agreement, as applicable), or Controlled jointly by Epizyme or any of its Affiliates and Hutchmed and any of its Affiliates during the Term, including any such Patent Rights jointly owned by Hutchmed and Epizyme pursuant to Section 11.1(b).

1.112 "**Joint Global Trial**" means any clinical trial for any Licensed Product in the Field, the performance of which is proposed to, and approved by, the JDC and (a) which Hutchmed determines to participate in and is conducted by a Hutchmed Entity in the Territory, and (b) is conducted by any Epizyme Entity in one or more countries outside of the Territory, all in accordance with the terms and conditions of this Agreement. For clarity, the 301 Global Trial and the 302 Global Trial are each a Joint Global Trial, and a Joint Global Trial is not a Rejected Global Trial or Epizyme Trial.

1.113 "**Joint IP**" means Joint Know-How and Joint Patent Rights.

1.114 "**Joint Know-How**" means any and all Know-How, including any invention (whether or not patentable) and including for clarity any Know-How that generically relates to the Development, Manufacture, or Commercialization of any Licensed Product (whether as a monotherapy or used with Other Combination Drug(s) as an Epizyme Combination Therapy) that is conceived, identified, discovered, authored, developed or reduced to practice by or on behalf of any Epizyme Entity, on the one hand, and any Hutchmed Entity, on the other hand, during the Term as a result of activities under this Agreement; provided that in no event shall Joint Know-How include any Epizyme Know-How, Epizyme Combination Therapy Know-How, Epizyme Manufacturing Know-How, Joint Combination Therapy Know-How or Hutchmed Know-How.

1.115 "**Joint Patent Rights**" means any and all Patent Rights Covering Joint Know-How.

1.116 "**JSC**" or "**Joint Steering Committee**" has the meaning set forth in Section 3.1(a).

1.117 "**Jurisdiction**" has the meaning set forth in Section 1.181.

1.118 "**Know-How**" means inventions (whether or not patentable), discoveries, trade secrets, technology, information, Regulatory Documents, formulae, practices, methods, knowledge, know-how, processes, procedures, experience, results and test data (including physical, chemical, biological, toxicological, pharmacological, clinical, veterinary, analytical and quality control data), dosage regimens, control assays, product specifications, and marketing, pricing, distribution cost and sales data and descriptions; but excluding Patent Rights.

1.119 "**Launch Plan**" means the strategic plan for the Licensed Products in the Field in the Territory that details the activities to be conducted prior to launch, plans for launch and activities to be conducted during the Calendar Year in which the launch occurs, for which plan Hutchmed has in good faith taken the Global Brand Strategy and the Global Medical Affairs Strategy into consideration.

1.120 "**LCM Data**" means a summary of the clinical data and results (a) generated in any LCM Epizyme Trial and (b) Controlled by Epizyme.

1.121 "**LCM Epizyme Trial**" means an Epizyme Trial which is either (a) an Epizyme Basket Trial or (b) any other signal finding, non-Pivotal Trial of the Licensed Product (as a monotherapy or a Combination Therapy) which was conducted solely by or on behalf of Epizyme outside of the Territory and in which Epizyme did not request Hutchmed to participate.

1.122 "**LCM Pivotal Trial**" means a Pivotal Trial of a Licensed Product (as a monotherapy or a Combination Therapy) for an indication (a) for which Epizyme had developed LCM Data, and (b) that is initiated either (i) as a Joint Global Trial that Epizyme requested, and Hutchmed agreed, to participate in, or (ii) as a Local Trial by Hutchmed.

1.123 "**Licensed Compound**" means the compound referred to as Tazemetostat, and any amorphous forms, crystalline forms, co-crystals, homologs, stereoisomers, enantiomers, racemates, prodrugs, isomers, isotopic or radiolabeled substitutions, esters, chelates, metabolites, salts, free acids, free bases, clathrates, hydrates, hemihydrates, anhydrides, solvates, conformers, cogeners, conjugates, and polymorphs of such compound. For clarity, the Hutchmed Dual Inhibitor Product is not a Licensed Compound.

1.124 "**Licensed IP**" has the meaning set forth in Section 11.1(a).

1.125 "**Licensed Know-How**" has the meaning set forth in Section 11.3(a).

1.126 "**Licensed Patent Right**" has the meaning set forth in Section 11.2(a).

1.127 "**Licensed Product**" means any pharmaceutical product that (a) has the Licensed Compound as the sole active pharmaceutical ingredient, in any dosage, formulation, or form, and is used as a monotherapy, or (b) has the Licensed Compound as an active pharmaceutical ingredient, in any dosage, formulation, or form and is used, subject to Section 3.10(b)(ii), as part of a Combination Therapy with one or more Other Combination Drugs.

1.128 "**Local Trial**" means any clinical trial for any Licensed Product (as a monotherapy or as a Combination Therapy) in the Field, the performance of which is proposed to, and approved by, the JDC solely for the Territory, and which (a) Hutchmed determines to conduct and is conducted by a Hutchmed Entity in the Territory, and (b) does not include clinical sites in any country outside the Territory. A Local Trial may be, for example, a basket clinical trial or other proof-of-concept clinical trial or a Pivotal Trial.

1.129 "**Mainland China**" means the People's Republic of China, which for purposes of this Agreement shall exclude Taiwan, Hong Kong and Macau.

1.130 "**Manufacture**" means, as applicable, all activities associated with the production, manufacture, process of formulating, processing, filling, finishing, packaging, labeling, shipping, importing or storage of pharmaceutical compounds or materials, including process development, process validation, stability testing, manufacturing scale-up, pre-clinical, clinical and commercial manufacture and analytical development, product characterization, quality assurance and quality control development, testing and release. "Manufacturing" and "Manufactured" will be construed accordingly.

1.131 "**Manufacturing Activity**" has the meaning set forth in Section 7.4(b).

1.132 "**Manufacturing Activity Costs**" means the reasonable, and reasonably allocable in accordance with Accounting Standards, internal (including FTEs at the FTE Rate) and Out-of-Pocket Costs of any Epizyme Entity incurred in the performance of any activity described in Section 7.4. Any costs included in the Clinical Supply Price or the Commercial Supply Price shall not be a Manufacturing Activity Cost.

1.133 "**Manufacturing Improvement**" has the meaning set forth in Section 7.4(b).

1.134 "**Manufacturing Technology Transfer"** means the transfer of Epizyme Manufacturing Know-How (a) to Hutchmed with respect to the Manufacture of Drug Product or (b) to Hutchmed or a Permitted Subcontractor CMO with respect to the Manufacture of Drug Substance.

1.135 "**Manufacturing Technology Transfer Agreement**" has the meaning set forth in Section 7.2(a).

1.136 "**Manufacturing Technology Transfer Completion**" has the meaning set forth in Section 7.2(a).

1.137 "**Medical Affairs**" means matters relating to information services; publication, scientific and medical affairs; advisory and collaborative activities with opinion leaders and professional societies including medical education, symposia and other medical programs and communications; but excluding investigator sponsored trials and registry studies and other Development activities.

1.138 "**Milestone Event**" has the meaning set forth in Section 9.4(a).

1.139 "**Net Sales**" means with respect to any Licensed Product for any period, the gross amounts invoiced by a Hutchmed Entity (each, a "**Selling Party**") to Third Party customers for sales of such Licensed Product during such period, less the following deductions actually incurred, allowed, paid, accrued or specifically allocated in its financial statements in accordance with Accounting Standards, for:

(a) customary and reasonable trade, quantity, and cash discounts;

(b) wholesaler allowances and inventory management fees;

(c) customary and reasonable credits, rebates and charge backs (including those to managed-care entities and government agencies), and allowances or credits to customers on account of rejection or returns (including wholesaler and retailer returns) or on account of retroactive price reductions affecting such Licensed Product;

(d) freight, postage and duties, and transportation charges relating to such Licensed Product, including handling and insurance therefor;

(e) sales (such as VAT or its equivalent) and excise taxes, other consumption taxes, and customs duties (excluding any taxes paid on the income from such sales) to the extent the Selling Party is not otherwise entitled to a credit or a refund for such taxes, duties or payments made; and

(f) amounts previously included in Net Sales that are written-off by the Selling Party as uncollectible in accordance with the standard practices of such Selling Party for writing off uncollectible amounts, consistently applied; provided, however, that if any such written-off amounts are subsequently collected, such collected amounts shall be included in Net Sales in the period in which they are subsequently collected.

If non-monetary consideration is received for any Licensed Product in the Territory, Net Sales will be calculated based on the average price charged for such Licensed Product in the Territory during the preceding Calendar Quarter, or in the absence of such sales, the fair market value of the Licensed Product in the Territory, as determined by the Parties in good faith. If the Parties are unable to reach such an agreement, the Parties will refer such matter to a jointly selected Third Party with expertise in the pricing

of pharmaceutical products that is not an employee, consultant, legal advisor, officer, director or stockholder of, and does not have any conflict of interest with respect to, either Party for resolution. If the Parties are unable to agree on such a Third Party expert within [**] after a Party has notified the other Party that it desires to refer such matter to such a Third Party for resolution, either Party may request that the New York, New York office of the AAA appoint such an expert to resolve such matter. The resolution determined by any such expert that is either jointly selected or appointed by the AAA shall be final and binding on the Parties. Notwithstanding anything to the contrary herein, the transfer, disposal or use of Licensed Product, without consideration, for marketing, regulatory, development or charitable purposes, such as sampling, clinical trials, preclinical trials, compassionate use, named patient use, or indigent patient programs, shall not be deemed a sale hereunder.

Net Sales shall be determined on, and only on, the first sale by Hutchmed or any of its Affiliates or Sublicensees to a non-Sublicensee Third Party.

Hutchmed shall not, and shall cause its Selling Parties to not, use any Licensed Product as a loss leader or otherwise unfairly or inappropriately discount the gross invoiced sales price of a Licensed Product in a manner that is intended to benefit, or provide an incentive to enhance sales of, any other pharmaceutical product sold by Hutchmed or any of its Selling Parties. Sales of a Licensed Product between Hutchmed and any of its Selling Parties for resale shall be excluded from the computation of Net Sales, but the subsequent resale of such Licensed Product to a non-Sublicensee Third Party shall be included within the computation of Net Sales. In addition, sales of a Licensed Product by one Party or its Affiliates or Sublicensees to the other Party or its Affiliates or Sublicensees pursuant to a mutually agreed Manufacturing and supply relationship shall be excluded from the computation of Net Sales, but the subsequent resale of such Licensed Product by the purchasing Party or its Affiliate or Sublicensee to a non-Sublicensee Third Party shall be included within the computation of Net Sales.

If a Licensed Product is sold as part of a Combination Product in the Territory, Net Sales for any period will be the product of (i) Net Sales of the Combination Product calculated as above in the Territory for such period (i.e., calculated as for a non-Combination Product) and (ii) the fraction (A/(A+B)), where:

"A" is the average wholesale acquisition cost in the Territory of the Licensed Product comprising a Licensed Compound, as applicable, as the sole therapeutically active ingredient during such period; and

"B" is the average wholesale acquisition cost in the Territory of the other therapeutically active ingredients or Other Combination Drugs in the Combination Product when sold separately during such period.

If "A" or "B" cannot be determined by reference to non-Combination Product sales as described above, then Net Sales for purposes of determining royalty payments will be calculated as above, but the average wholesale acquisition cost in the above equation shall be determined by mutual agreement reached in good faith by the Parties prior to the end of the accounting period in question based on an equitable method of determining the same that takes into account, in the applicable country, variations in dosage units and the relative fair market value of each therapeutically active ingredient or Other Combination Drug in the Combination Product. If the Parties are unable to reach such an agreement prior to the end of the applicable accounting period, then the Parties will refer such matter to a jointly selected Third Party with expertise in the pricing of pharmaceutical products that is not an employee, consultant, legal advisor, officer, director or stockholder of, and does not have any conflict of interest with respect to, either Party for resolution. If the Parties are unable to agree on such a Third Party expert within [**] after a Party has notified the other Party that it desires to refer such matter to such a Third Party for resolution, either Party may request that the New York, New York office of the AAA appoint such an expert to resolve such matter.

The resolution determined by any such expert that is either jointly selected or appointed by the AAA shall be final and binding on the Parties.

As used in this Section 1.139, "**Combination Product**" means (i) a Combination Therapy co-packaged or otherwise sold for a single price, or (ii) a therapeutic or palliative product for use in humans comprising a Licensed Compound and one or more other active ingredients (whether co-formulated or co-packaged) that are not Licensed Compounds or Other Combination Drugs. Pharmaceutical dosage form vehicles, adjuvants, and excipients shall be deemed not to be "active ingredients."

1.140 "**NMPA**" means China National Medical Products Administration, (formerly known as "State Drug Administration"), including its divisions and the Center for Drug Evaluation, and local counterparts thereto, and any successor agency or authority thereto having substantially the same function.

1.141 "**Other Combination Drug**" has the meaning set forth in Section 1.24.

1.142 "**Out-of-Pocket Costs**" means amounts paid by a Party or any of its Affiliates to a Third Party for goods or services but shall not include such Party's, or any of its Affiliates', internal or general overhead costs or expenses.

1.143 "**Patent Rights**" means any and all (a) patents, (b) patent applications (including provisional applications), patent cooperation treaty (PCT) applications, substitutions, continuations, continuations-in-part, divisions and renewals and all patent right granted thereon, (c) all patents-of-addition, reissues, re-examinations, and extensions or restorations by existing or future extension or restoration mechanisms, including supplementary protection certificates and equivalents thereof, (d) inventor's certificates, letters patent, or (e) any other substantially equivalent form of government issued right substantially similar to any of the foregoing described in subsections (a) through (d) above, anywhere in the world.

1.144 "**Patent-Based Exclusivity**" means with respect to a Licensed Product in the Territory, that at least one Valid Claim of any Licensed Patent Right or Joint Combination Therapy Patent Right Covers such Licensed Product in the Territory, excluding Valid Claims included in any Licensed Patent Right or Joint Combination Therapy Patent Right that Covers any Know-How conceived, identified, discovered, authored, developed, or reduced to practice solely or jointly by or on behalf of any Hutchmed Entity in the performance of any activity conducted under this Agreement.

1.145 "**Permitted Subcontractor**" means:

(a) any Third Party contract research organization or Authorized Regulatory Agent engaged by Hutchmed in the Territory (following selection by Hutchmed and approval by the JDC, such approval not to be unreasonably withheld, conditioned, or delayed) that provides Development services for Licensed Products consisting of oversight and management of the conduct of a Joint Global Trial or providing central laboratory services supporting a Joint Global Trial;

(b) any Third Party contract manufacturing organization engaged by Hutchmed in the Territory (following selection by Hutchmed and approval by the JMC, such approval not to be unreasonably withheld, conditioned, or delayed) that provides Manufacturing services with respect to Drug Substance in accordance with this Agreement (each, a "**Permitted Subcontractor CMO**"); or

(c) any Third Party contractor, other than a Third Party under subsections (a) and (b) above, engaged by Hutchmed in the Territory, that provides services with respect to Licensed Compounds or Licensed Products in accordance with this Agreement, without any requirement for Hutchmed to obtain Epizyme's consent to subcontract to such Third Party.

For clarity, it shall not be unreasonable for a Committee to withhold, condition, or delay its approval with respect to a proposed Permitted Subcontractor if such Third Party does not (i) pass background screening to Epizyme's reasonable satisfaction, including confirmation that such Third Party is not on any relevant exclusion or debarment list, or (ii) possess and agree to maintain valid licenses and permits issued by any applicable Regulatory Authority or otherwise meet the qualification requirements under Applicable Law if such license, permits or qualifications are required for them to engage in the activities in the Territory as set out in this Section 1.145.

1.146 "**Personal Health Information**" or "**PHI**" has the meaning set forth in Section 2.6(a).

1.147 "**Phase 1 Trial**" means a clinical trial of a product in any country, the principal purpose of which is to determine the metabolism and pharmacological actions of the product in humans, the side effects associated with increasing doses and, if possible, to gain early evidence of effectiveness, as described in 21 C.F.R. 312.21(a), or a similar clinical study prescribed by the relevant Regulatory Authorities in a country other than the United States.

1.148 "**Phase 2 Trial**" means a clinical trial of a product in any country that would satisfy the requirements of 21 C.F.R. 312.21(b) and is intended to explore a variety of doses, dose response, and duration of effect, and to generate evidence of clinical safety and effectiveness for a particular indication or indications in a target patient population, or a similar clinical study prescribed by the relevant Regulatory Authorities in a country other than the United States; provided that, for purposes of this Agreement, Phase 2 Trial shall not include any Phase 2b clinical trial.

1.149 "**Pivotal Trial**" means a clinical trial of a product that is a registration trial designed to be sufficient to support the filing of an application for a Regulatory Approval for such product in an applicable country or some or all of an extra-national territory, as evidenced by (a) an agreement with or statement from an applicable Regulatory Authority, or (b) other guidance or minutes issued by an applicable Regulatory Authority, for such registration trial. For clarity, a Pivotal Trial includes any clinical trial which (i) satisfies the requirements of 21 C.F.R. §312.21(c), as amended, or its equivalent in any foreign jurisdiction, or (ii) satisfies the requirements of 21 C.F.R. §312.21(b), as amended, or its equivalent in any foreign jurisdiction and the data from such clinical trial serves as the basis for an effectiveness claim in support of a filing for Regulatory Approval for the product. As of the Effective Date, the 301 Global Trial and the 302 Global Trial are each a Pivotal Trial of a Licensed Product.

1.150 "**Pre-Clinical Research**" means preclinical and non-clinical research activities.

1.151 "**Prosecution**" means, with respect to a Patent Right, the preparation, filing, prosecution and maintenance of such Patent Right, as well as post grant review proceedings, reexaminations, reissues and the like with respect to such Patent Right, together with the conduct of interferences, the defense of oppositions and other similar proceedings with respect to such Patent Right. "Prosecute," "Prosecuted," and "Prosecuting" will be construed accordingly.

1.152 "**Quarterly Cost Report**" has the meaning set forth in Section 9.3(c)(iii).

1.153 "**Recipient**" has the meaning set forth in Section 1.34.

1.154 "**Regulatory Approval**" means, with respect to a particular regulatory jurisdiction, an approval, license, registration or authorization of any Governmental Authority (other than any Reimbursement Approval) that provides marketing approval for the marketing of a pharmaceutical product in one or more specified indications in such regulatory jurisdiction.

1.155 "**Regulatory Authority**" means, in a particular country or jurisdiction, any applicable Governmental Authority involved in granting Regulatory Approval in such country or jurisdiction, including (a) in the United States, the FDA and any other applicable Governmental Authority in the United States having jurisdiction over pharmaceutical products, (b) in the European Union, the European Medicines Agency ("**EMA**"), (c) in Mainland China, the NMPA and (d) any other applicable Governmental Authority in the Territory having jurisdiction over pharmaceutical products.

1.156 "**Regulatory Documents**" means all (a) applications (including all INDs and Drug Approval Applications), registrations, licenses, authorizations, approvals (including Regulatory Approvals) and marketing or regulatory exclusivities; (b) correspondence and reports submitted to or received from Regulatory Authorities (including minutes and official contact reports relating to any communications with any Regulatory Authority) and all supporting documents with respect thereto, including all regulatory drug lists, advertising and promotion documents, adverse event files and complaint files; and (c) preclinical, clinical and other data, results, analyses, publications, and reports contained or referred to in any of the foregoing. For the avoidance of doubt, Regulatory Documents include Regulatory Approvals and Regulatory Filings.

1.157 "**Regulatory Filings**" means all applications, filings, dossiers and the like submitted to a Regulatory Authority for the purpose of Developing, Manufacturing or Commercializing a product, including obtaining Regulatory Approval from that Regulatory Authority. Regulatory Filings include all INDs, Drug Approval Applications and other Regulatory Approval and Reimbursement Approval applications.

1.158 "**Regulatory Liaisons**" has the meaning set forth in Section 5.2(c).

1.159 "**Regulatory-Based Exclusivity**" means with respect to a Licensed Product in the Territory, that (a) a Hutchmed Entity has been granted the exclusive legal right by a Regulatory Authority (or is otherwise entitled to the exclusive legal right by operation of law) in the Territory to market the Licensed Product or the active ingredient comprising such Licensed Product in the Territory, or (b) the data and information submitted by a Hutchmed Entity to the relevant Regulatory Authority in the Territory for purposes of obtaining Regulatory Approval may not be disclosed, referenced or relied upon in any way by such Regulatory Authority (including by relying upon the Regulatory Authority's previous findings regarding the safety or effectiveness of the Licensed Product) to support the Regulatory Approval or marketing of any product by a Third Party in the Territory.

1.160 "**Reimbursement Approval**" means an approval, agreement, determination, or other decision by any applicable Regulatory Authority or other Governmental Authority that establishes prices at which a pharmaceutical product may be priced, or will be reimbursed by the Regulatory Authorities or other applicable Governmental Authorities, in a particular country or jurisdiction.

1.161 "**Rejected Additional Indication**" has the meaning set forth in Section 3.10(b)(i).

1.162 "**Rejected Combination Therapy**" has the meaning set forth in Section 3.10(b)(ii).

1.163 "**Rejected Global Trial**" means any clinical trial of any Licensed Product in the Field, the performance of which is proposed to the JDC, and which (a) Hutchmed determines not to participate in the conduct of, and (b) Epizyme determines to conduct with any Epizyme Entity in one or more countries or jurisdictions outside of the Territory and, subject to Section 4.6, with the option but not the requirement to include clinical sites in the Territory. For clarity, a Rejected Global Trial is not a Joint Global Trial or an Epizyme Trial.

1.164 "**Rejected Local Trial**" has the meaning set forth in Section 14.7(c).

1.165 "**Representatives**" has the meaning set forth in Section 10.1.

1.166 "**ROFN**" has the meaning set forth in Section 8.1(a).

1.167 "**ROFN Epizyme Territory**" has the meaning set forth in Section 8.1(b).

1.168 "**ROFN Negotiation Period**" has the meaning set forth in Section 8.1(b).

1.169 "**ROFN Notice**" has the meaning set forth in Section 8.1(a).

1.170 "**ROFN POC Date**" has the meaning set forth in Section 8.1(a).

1.171 "**ROFN Term**" has the meaning set forth in Section 8.1(a).

1.172 "**ROFN Term Payment**" has the meaning set forth in Section 9.7.

1.173 "**Royalty Term**" has the meaning set forth in Section 9.6(a).

1.174 "**Safety Data Exchange Agreement**" means that agreement between the Parties regarding receipt, investigation and reporting of product complaints, adverse events, product recalls, and any other information related to the safety of the Licensed Products as set forth in Section 5.5.

1.175 "**Selling Party**" has the meaning set forth in Section 1.139.

1.176 "**Solid Tumor Indication**" means any disease or disorder characterized by an abnormal mass of tissue that usually does not contain cysts or liquid areas, including sarcomas and carcinomas.

1.177 "**Subcommittee**" has the meaning set forth in Section 3.1(b).

1.178 "**Sublicensee**" means any Third Party to whom Hutchmed or any of its Affiliates grants a sublicense of its rights hereunder to Develop, Manufacture, or Commercialize Licensed Compound or Licensed Products in the Field and in the Territory in accordance with Section 2.4, excluding all Permitted Subcontractors.

1.179 "**Tax**" means any present or future taxes, levies, imposts, duties, tariffs, charges, assessments or fees of any nature imposed by a Governmental Authority in the exercise of its taxing power (including interest, penalties and additions thereto), including value-added tax ("**VAT**") and withholding tax.

1.180 "**Term**" has the meaning set forth in Section 14.1.

1.181 "**Territory**" means, individually or collectively, as the context requires, the following jurisdictions (each, a "**Jurisdiction**"): (a) Mainland China, (b) Taiwan, (c) Hong Kong Special Administrative Region ("**Hong Kong**"), and (d) Macau Special Administrative Region ("**Macau**").

1.182 "**Third Party**" means any person or entity other than the Parties and their Affiliates.

1.183 "**Third Party IP**" has the meaning set forth in Section 2.7(a).

1.184 "**Trade Control Laws**" shall refer to U.S. Applicable Laws which prohibit or limit export, distribution or sales of goods from the United States and their re-export from other countries into certain

countries, referred to as "Sanctioned Countries." More specifically and for purpose of performing this Agreement, Trade Control Laws shall refer to the U.S. Export Administration Regulations and the economic sanctions, rules and regulations implemented under statutory authority or President's Executive Orders and administered by the U.S. Treasury Department's OFAC.

1.185 "**Trademark**" means any trademark, trade name, service mark, service name, corporate name, brand, domain name, trade dress, logo, slogan or other indicia of origin or ownership, including the goodwill of the business and activities associated with each of the foregoing.

1.186 "**True-Up Payment**" has the meaning set forth in Section 9.3(e).

1.187 "**U.S.**" or "**United States**" means the United States of America, including its districts, territories and possessions.

1.188 "**U.S. NDA Data**" means (a) all data included in the U.S. New Drug Applications for the Licensed Product for FL and ES, and (b) any other data from the 101 Trial and the 202 Trial, in each case, to the extent necessary or reasonably useful for filing with the Regulatory Authorities for Regulatory Approval for the Licensed Product for ES or FL in the Territory.

1.189 "**Valid Claim**" means (a) any claim of any Patent Right that has issued, is unexpired and has not been rejected, revoked or held unenforceable or invalid by a final, non-appealable (or unappealed within the time allowable for appeal) decision of a court or other Governmental Authority of competent jurisdiction or (b) any claim of any patent application that has (i) been pending for [**] or less from the date of issuance of the first substantive patent office action considering the patentability of such claim by the applicable patent office in the applicable country or jurisdiction and (ii) not been cancelled, withdrawn, abandoned or finally rejected by an administrative agency action from which no appeal can be taken.

1.190 "**Warrant**" has the meaning set forth in Section 9.2.

ARTICLE 2. LICENSES; EXCLUSIVITY

2.1 **License Grants to Hutchmed**. Subject to the terms and conditions of this Agreement (including Sections 2.3, 2.5, 2.8, 9.3(d) and 9.3(e)), Epizyme hereby grants to Hutchmed:

(a) a co-exclusive (with the Epizyme Entities), sublicensable (only in accordance with Section 2.4), non-transferable (except in accordance with Section 16.1) license under the Epizyme IP and Epizyme's interest in the Joint IP to Develop any Licensed Product (as a monotherapy or as the Licensed Product component of any Combination Therapy) in the Field and in the Territory in accordance with this Agreement;

(b) an exclusive (including as to the Epizyme Entities), royalty-bearing, sublicensable (only in accordance with Section 2.4), non-transferable (except in accordance with Section 16.1) license under the Epizyme IP and Epizyme's interest in the Joint IP to Commercialize any Licensed Product (as a monotherapy or as the Licensed Product component of any Combination Therapy) in the Field and in the Territory in accordance with this Agreement;

(c) a co-exclusive (with the Epizyme Entities), sublicensable (only in accordance with Section 2.4), non-transferable (except in accordance with Section 16.1) license under the Epizyme Combination Therapy IP and Epizyme's interest in the Joint Combination Therapy IP or Joint IP to Develop any Combination Therapy in the Field and in the Territory in accordance with this Agreement;

(d) a non-exclusive, royalty-free (except as provided in Section 2.7(a)), fully-paid-up, sublicensable, non-transferable (except in accordance with Section 16.1) license under Epizyme's interest in the Joint Combination Therapy IP and Joint IP to Commercialize Hutchmed Compounds outside the Territory as part of Joint Combination Therapies;

(e) an exclusive (including as to the Epizyme Entities), royalty-bearing, sublicensable (only in accordance with Section 2.4), non-transferable (except in accordance with Section 16.1) license under the Epizyme IP, Epizyme Combination Therapy IP and Epizyme's interest in the Joint Combination Therapy IP and Joint IP to Commercialize any Combination Therapy in the Field in the Territory in accordance with this Agreement; and

(f) a co-exclusive (with any Permitted Subcontractor CMO approved in accordance with this Agreement and with the Epizyme Entities and their respective CMOs), royalty-bearing (solely as set forth in Section 9.6 and not for any additional consideration), sublicensable (only in accordance with Section 2.4), non-transferable (except in accordance with Section 16.1) license under the Epizyme Manufacturing IP and Epizyme's interest in Joint IP for Hutchmed, itself or through a Permitted Subcontractor CMO, to Manufacture in the Territory Drug Substance and Drug Product solely for the purpose of Developing and Commercializing Licensed Products in the Field in the Territory in accordance with this Agreement, provided that Hutchmed will not exercise the license granted under this Section 2.1(f) until the Manufacturing Technology Transfer Agreement between Hutchmed and Epizyme has been executed.

2.2 **License Grants to Epizyme**. Subject to the terms and conditions of this Agreement (including Sections 2.3, 2.5 and 2.8), during the Term Hutchmed hereby grants to Epizyme:

(a) a co-exclusive (with the Hutchmed Entities), royalty-free, fully-paid-up, transferable, sublicensable license under the Hutchmed IP and Hutchmed's interest in the Joint IP to Develop and Manufacture the Licensed Compound and any Licensed Product (as a monotherapy or as the Licensed Product component of any Combination Therapy) in the Field and in the Territory in accordance with this Agreement;

(b) a co-exclusive (with the Hutchmed Entities), royalty-free, fully-paid-up, sublicensable, non-transferable (except in accordance with Section 16.1) license under Hutchmed's interest in the Joint Combination Therapy IP and Joint IP to Develop any Combination Therapy in the Field and in the Territory in accordance with this Agreement;

(c) a non-exclusive, royalty-free (except as provided in Section 2.7(b)), fully-paid-up, sublicensable, non-transferable (except in accordance with Section 16.1) license under Hutchmed's interest in the Joint Combination Therapy IP and Joint IP to Commercialize Licensed Products outside the Territory as part of Joint Combination Therapies; and

(d) an exclusive (including as to the Hutchmed Entities), royalty-free (except as provided in Section 2.7(b)), fully-paid-up, transferable, sublicensable license under Hutchmed IP and Hutchmed's interest in the Joint IP to Develop and Commercialize outside the Territory the Licensed Compound and any Licensed Product (as a monotherapy or as the Licensed Product component of any Joint Combination Therapy).

2.3 **Rights to Other Combination Drugs**. The licenses granted by Epizyme and Hutchmed pursuant to Section 2.1(c) and (e) in the Territory and Section 2.2(b) and (c) in and outside the Territory, respectively, shall not be construed as a grant by a Party to the other Party of any rights with respect to the composition of matter, manufacture, or use as a monotherapy of any Other Combination Drug that is part of the applicable Combination Therapy. Subject to the terms and conditions of this Agreement, including Sections 2.8, 7.6, and 9.3, each Party shall be responsible for obtaining any Third Party rights, if any, related to an

Other Combination Drug that are needed in order to Develop, Manufacture or Commercialize any Combination Therapy in accordance with the terms of this Agreement.

2.4 **Rights to Sublicense or Subcontract**. Hutchmed may only sublicense any of the rights granted to Hutchmed by Epizyme under Section 2.1 or Exhibit D to: (a) without the need for review, consent or approval of Epizyme, an Affiliate of Hutchmed or Permitted Subcontractor or (b) a Third Party (other than those described in Section 2.4(a)) that has passed background screening to the reasonable satisfaction of Epizyme (including confirmation that such Third Party is not on any relevant exclusion or debarment list) and for which Epizyme provides prior written consent, which consent shall not be unreasonably withheld, conditioned, or delayed. Hutchmed may only subcontract any of Hutchmed's obligations hereunder (subject to Sections 2.6(b) and 9.10) to Affiliates of Hutchmed or to Permitted Subcontractors. For clarity, a sublicense or subcontract to an Affiliate of Hutchmed shall automatically terminate if such entity ceases to be an Affiliate of Hutchmed, and, subject to Section 14.7(a), any sublicense or subcontract to an Affiliate of Hutchmed or a Third Party shall automatically terminate if the relevant license granted to Hutchmed by Epizyme under Section 2.1 terminates.

Any sublicense to a Sublicensee shall be granted under a written agreement that is consistent with the applicable terms and conditions of this Agreement and that (i) requires each Sublicensee to comply with the terms of this Agreement that are expressly applicable to such sublicense including Sections 2.6(b), 2.7, and 2.8, the intellectual property provisions of Article 11, and the obligations of confidentiality and non-use at least as stringent as those set forth in Article 10 except that if, despite the good faith efforts of Hutchmed, a Sublicensee does not agree to terms at least as stringent as those set forth in Article 10, the term of such obligations shall be a customary duration given the nature of the sublicense and Sublicensee, but in no event less than the term of the sublicense plus [**], (ii) requires (to the extent applicable) each Sublicensee to make the representations, warranties, and covenants of Sections 12.2, 12.5, 12.6 and 12.7, (iii) precludes the granting of further sublicenses in contravention with the terms of this Agreement, and (iv) includes Epizyme as an intended third party beneficiary with the right to enforce the applicable terms of the sublicense agreement. Hutchmed shall provide a true and complete copy of any sublicense agreement with any Affiliate or Third Party or any subcontract with a Permitted Subcontractor contract research organization for any Joint Global Trials as described in Section 1.145(a) (and if any such sublicense agreement or subcontract is not in English, an English translation thereof), and otherwise a summary of other material subcontracts in English, in each case, subject to Hutchmed's right to redact any confidential or proprietary information contained therein that is not necessary for Epizyme to determine the scope of the sublicense or subcontract or the compliance with the terms and conditions of this Agreement.

Hutchmed will be responsible for ensuring that all agreements with Sublicensees or Permitted Subcontractors: (A) do not conflict with the terms of this Agreement, (B) allow Hutchmed to provide Epizyme with access to and use of the data and samples (with respect to samples to the extent permitted by Applicable Law) generated or obtained in the performance of activities under this Agreement to the extent Hutchmed would be obligated to provide such access and use, and other information and documents as required pursuant to this Agreement (and in no event less than the same use rights granted to Epizyme (to the extent applicable)), (C) do not impose a new obligation, whether direct, indirect, or contingent, upon Epizyme that is not set forth in this Agreement, and (D) comply with Applicable Law. For clarity, Hutchmed China is an Affiliate of Hutchmed and shall be a permitted sublicensee of all rights granted to Hutchmed pursuant to this Agreement.

Hutchmed shall use Commercially Reasonable Efforts to ensure that all Hutchmed Entities comply in all material respects with all applicable provisions of this Agreement and Applicable Law. Hutchmed shall remain primarily liable to Epizyme for the performance of all of its obligations under, and Hutchmed's compliance with all provisions of, this Agreement. Hutchmed shall be fully responsible and liable for the acts or omissions of all Hutchmed Entities with respect to this Agreement including any breach of the terms

of this Agreement by any Hutchmed Entity to the same extent as if Hutchmed has committed any such breach and will terminate promptly the agreement with any Sublicensee or Permitted Subcontractor if such Sublicensee or Permitted Subcontractor takes or fails to take any action that, if taken or not taken by Hutchmed, as applicable, would constitute a material breach of this Agreement and does not cure such breach in a timely manner in accordance with Section 14.4.

Epizyme shall use Commercially Reasonable Efforts to ensure that all Epizyme Entities comply in all material respects with all applicable provisions of this Agreement and Applicable Law. Epizyme shall remain primarily liable to Hutchmed for the performance of all of its obligations under, and Epizyme's compliance with all provisions of, this Agreement. Epizyme shall be fully responsible and liable for the acts or omissions of all Epizyme Entities with respect to this Agreement including any breach of the terms of this Agreement by any Epizyme Entity to the same extent as if Epizyme has committed any such breach and will terminate promptly the agreement with any Epizyme Entity if such Epizyme Entity takes or fails to take any action that, if taken or not taken by Epizyme, as applicable, would constitute a material breach of this Agreement and does not cure such breach in a timely manner in accordance with Section 14.4.

2.5 **No Other Rights and Retained Rights**. Nothing in this Agreement shall be interpreted to grant either Party any rights under any Patent Rights or Know-How Controlled by the other Party that are not expressly granted herein, whether by implication, estoppel or otherwise, and, notwithstanding the foregoing provisions of Sections 2.1, 2.2 and 2.3, neither Party grants any right or license in this Agreement to the other Party under Patent Rights or Know-How Controlled by such Party with respect to active pharmaceutical ingredients or drug products other than the Licensed Compound and Licensed Products. Any rights not expressly granted to a Party by the other Party under this Agreement are hereby retained by such other Party. For clarity, Epizyme and any of its Affiliates may, subject to Section 4.6, Develop Licensed Products (as monotherapies or as the Licensed Product component of Combination Therapies) and may Manufacture Licensed Products in the Territory, in each case in support of the global Development and Commercialization of the Licensed Products outside the Territory or to support its activities set forth on Schedule 2.8(b). Nothing in this Agreement shall be construed as a grant by Epizyme to any Hutchmed Entity of any right with respect to any companion diagnostic or complimentary diagnostic for use with Licensed Products; provided that the foregoing shall not prevent any Hutchmed Entity from exercising any of the rights granted hereunder for purposes of identifying or selecting patients for clinical trials or treatment with Licensed Products in the Field in accordance with this Agreement. Nothing in this Agreement shall be construed as a grant by Epizyme to any Hutchmed Entity of any right under any of Epizyme's Patent Rights, Know-How or Confidential Information with respect to Hutchmed Dual Inhibitor Products.

2.6 **Data Transfer**.

(a) Epizyme Product Data. Epizyme shall provide the following clinical and preclinical data relating to the Licensed Products to Hutchmed:

(i) a copy of the CTA Data, which CTA Data shall be provided within [**] after the Effective Date;

(ii) to the extent not previously provided to Hutchmed as CTA Data, a copy of the U.S. NDA Data, which data shall be provided (x) within [**] after the Effective Date with respect to the data included in the U.S. NDA for the Licensed Product for FL and ES, and (y) with respect to data from the 101 Trial and the 202 Trial to the extent necessary or reasonably useful for filing with the Regulatory Authorities for Regulatory Approval for the Licensed Product for FL and ES in the Territory, within [**] after the Effective Date for data that exists as of the Effective Date or within [**] after completion or interim analysis of the 101 Trial or 202 Trial, as applicable, for data that does not exist as of the Effective Date;

(iii) a copy of any LCM Data, which data will be provided with [**] after completion or interim analysis of the LCM Epizyme Trial or relevant cohort of the applicable LCM Epizyme Trial, as applicable; and

(iv) to the extent not previously provided to Hutchmed as CTA Data, US NDA Data, or LCM Data, upon request of Hutchmed and subject to the payment terms of Sections 9.3(d) and 9.3(e), all data within Epizyme's Control during the Term of this Agreement that is necessary or reasonably useful for Regulatory Filings for the Licensed Product by Hutchmed in the Field and in the Territory, which may include data from Joint Global Trials, Rejected Global Trials, or Epizyme Trials (other than data from LCM Epizyme Trials, which is subject to subsection (iii) above) (such data, the "**Epizyme Product Filing Data**," and along with the CTA Data, U.S. NDA Data and LCM Data, individually and collectively referred to as the "**Epizyme Product Data**"), which such Product Filing Data shall be provided within [**] after completion or interim analysis of the relevant clinical trial or trial cohort or, if such Product Filing Data did not result from a clinical trial, within [**] after the end of the Calendar Quarter in which the relevant activity was completed.

Notwithstanding the foregoing, safety and pharmacovigilance data will be provided within the time periods set forth in Safety Data Exchange Agreement. Specific Epizyme Product Data that is provided to a Committee under this Agreement is not required to also be provided under this Section 2.6(a). The Epizyme Product Data shall be considered Epizyme's Know-How and shall be subject to the licenses granted to Hutchmed under Section 2.1 and the obligations of confidentiality and non-use under Article 10.

Epizyme shall use Commercially Reasonable Efforts to ensure that any contract executed after the Effective Date between Epizyme and any Third Party pertaining to the conduct by such Third Party of any Development activities for Licensed Product including clinical trials (including investigator-initiated trials) contains an obligation for such Third Party to provide the data resulting from such activity to Epizyme with the right to transfer to Hutchmed; provided that the Parties acknowledge that a transfer to Hutchmed of data under a contract between Epizyme and a Third Party for the provision of any materials (including Other Combination Drugs) from the Third Party for use in any Development activity for the Licensed Product shall be subject to any confidentiality restrictions imposed by the Third Party.

Notwithstanding the foregoing, Epizyme shall not be obligated to provide to Hutchmed any Epizyme Product Data that consists of individually identifiable health information ("**Personal Health Information**" or "**PHI**") as defined under the Health Insurance Portability and Accountability Act of 1996, as amended from time to time, together with any rules, regulations, and compliance guidance promulgated thereunder as well as foreign equivalents thereof ("**HIPAA**") to the extent providing such Epizyme Product Data would violate HIPAA; to the extent Hutchmed comes into possession of any PHI by or through Epizyme under this Agreement in violation of HIPAA, Hutchmed shall return such PHI to Epizyme. Epizyme shall use Commercially Reasonable Efforts to ensure that the patient informed consent forms used by Epizyme and any other Epizyme Entity permit the transfer of patient information to Hutchmed; provided that, if despite the exercise of such Commercially Reasonable Efforts, such transfer is not permitted by the patient's informed consent form, then Epizyme shall not be obligated to provide any such patient information or results to Hutchmed.

The information and documents provided by Epizyme under this Section 2.6(a) shall be in English. In the event Hutchmed requests that Epizyme provide novel data analysis or the generation of novel datasets that (A) cannot be performed by any Hutchmed Entity in the Territory and (B) is necessary for obtaining the Regulatory Approval for the Licensed Product in the Territory, then Epizyme shall conduct such work and Hutchmed shall reimburse Epizyme for such work at the FTE Rate within [**] after receipt of an invoice therefor.

(b) Hutchmed Product Data. Except to the extent prohibited by Applicable Law and Regulatory Authorities in the Territory, Hutchmed shall make available to Epizyme copies of all of Hutchmed's and other Hutchmed Entities' preclinical and clinical data and results (including clinical efficacy data and, subject to Section 5.5, safety and pharmacovigilance data) that is conceived, identified, discovered, authored, developed, or reduced to practice during the Term in the performance of any activity under this Agreement (collectively, the "**Hutchmed Product Data**") and Epizyme may use such Hutchmed Product Data for any purpose related to Licensed Products or Combination Therapies (subject to any restrictions imposed by a Third Party and agreed upon by the Parties below), including to comply with its obligations under any Epizyme In-License Agreement. Hutchmed Product Data shall be provided within [**] after completion or interim analysis of the relevant clinical trial or, if such Hutchmed Product Data did not result from a clinical trial, within [**] after the end of the Calendar Quarter in which the relevant activity was completed, except safety and pharmacovigilance data which will be provided within the time periods set forth in Safety Data Exchange Agreement. For clarity, Hutchmed shall not provide data or results pertaining to its Hutchmed Dual Inhibitor Product to Epizyme other than as provided in Section 8.1. The Hutchmed Product Data shall be considered Hutchmed's Know-How and shall be subject to the licenses granted to Epizyme under Section 2.2 and the obligations of confidentiality and non-use under Article 10.

Hutchmed shall use Commercially Reasonable Efforts to ensure that any contract executed after the Effective Date between Hutchmed and any Third Party pertaining to the conduct by such Third Party of any Development activities for Licensed Product including clinical trials (including investigator-initiated trials) contains an obligation for such Third Party to provide the data resulting from such activity to Hutchmed with the right to transfer to Epizyme; provided that the Parties acknowledge that a transfer to Epizyme of data under a contract between Hutchmed and a Third Party for the provision of any materials (including Other Combination Drugs) from the Third Party for use in any Development activity for the Licensed Product shall be subject to any confidentiality restrictions imposed by the Third Party.

Notwithstanding the foregoing, Hutchmed shall not be obligated to provide to Epizyme any Hutchmed Product Data that consists of PHI to the extent providing such Hutchmed Product Data would violate HIPAA; to the extent Epizyme comes into possession of any PHI by or through Hutchmed under this Agreement in violation of HIPAA, Epizyme shall return such PHI to Hutchmed. Hutchmed shall use Commercially Reasonable Efforts to ensure that the patient informed consent forms used by Hutchmed and any other Hutchmed Entity permit the transfer of patient information to Epizyme; provided that, if despite the exercise of such Commercially Reasonable Efforts, such transfer is not permitted by the patient's informed consent form, then Hutchmed shall not be obligated to provide any such patient information or results to Epizyme.

Specific Hutchmed Product Data that is provided to a Committee under this Agreement is not required to also be provided under this Section 2.6(b). In the event Epizyme requests that Hutchmed provide novel data analysis or the generation of novel datasets, and if Hutchmed agrees to conduct such work, then Epizyme shall reimburse Hutchmed for such work at the FTE Rate within [**] after receipt of an invoice therefor.

(c) Each Party shall ensure that, in the case of Hutchmed, the Hutchmed Product Data, and in the case of Epizyme, the Epizyme Product Data, will be provided to the other Party in compliance with all applicable local data privacy Laws and rules on cross-border data transmission, including the Cybersecurity Law of Mainland China, the Data Security Law of Mainland China, and relevant regulations or policies on protection of personal data, data privacy and cross-border transmission, as applicable.

2.7 **In-License Agreements**.

(a) Epizyme New In-License Agreements. Subject to Section 16.2, Epizyme shall be free to

negotiate with a Third Party for any agreement pursuant to which Epizyme would acquire or license in the Territory (or in and outside the Territory) any Patent Right or Know-How (which, for the purposes of Section 2.7, shall not include data which is covered by Section 2.6) of such Third Party that is necessary or reasonably useful for the Development, Manufacture, or Commercialization of any Licensed Compound or Licensed Product in the Field ("**Third Party IP**"). If Epizyme does not obtain the right to sublicense such Third Party IP to Hutchmed in the Territory, then Epizyme shall so notify Hutchmed and shall not enter into any agreement with respect to such Third Party IP that includes any grant of rights in the Field in the Territory. Epizyme will promptly provide Hutchmed with notice and a copy of any such executed Third Party agreement in which Epizyme has the right to sublicense Third Party IP to Hutchmed in the Territory (redacted as necessary to comply with any confidentiality obligations of Epizyme to such Third Party) and a schedule of all obligations that would be applicable to Hutchmed as a sublicensee under such Third Party IP. Within [**] following receipt of such notice, Hutchmed will decide, in its sole discretion, whether it will accept the applicable Third Party agreement as an Epizyme New In-License Agreement, and provide notice of such decision to Epizyme. For clarity, Epizyme shall not be obligated to acquire or license any Third Party IP in the Territory for any reason.

In the event that Hutchmed declines to accept such Third Party agreement as an Epizyme New In-License Agreement, then (i) such Third Party agreement shall not be deemed to be an "Epizyme New In-License Agreement" hereunder, (ii) Epizyme shall have no obligation to license or acquire rights to such Third Party IP in the Territory, and (iii) any rights to such Third Party IP in the Territory that are granted to Epizyme under such Third Party agreement will not be deemed to be "Controlled" by Epizyme or licensed to Hutchmed under this Agreement.

In the event that Hutchmed accepts such Third Party agreement as an Epizyme New In-License Agreement, then, upon effectiveness of such Third Party agreement, (A) such Third Party agreement will be included within the definition of "Epizyme New In-License Agreement," (B) any rights to Third Party IP granted to Epizyme under such Epizyme New In-License Agreement will be deemed to be "Controlled" by Epizyme and sublicensed to Hutchmed in the Territory pursuant to the terms of this Agreement; (C) the sublicenses granted by Epizyme to Hutchmed in this Agreement will be subject to the terms of such Epizyme New In-License Agreement, to the extent described in the schedule provided by Epizyme to Hutchmed pursuant to the first paragraph of this Section 2.7(a), including the scope of the license granted to Epizyme or any Affiliate thereunder and the rights retained by such Third Party counterparties and any other Third Parties (including Governmental Authorities) set forth therein, and (D) Hutchmed shall reimburse [**] percent ([**]%) of the amounts payable to the Third Party arising from and allocable to the exercise of rights by a Hutchmed Entity under such Epizyme New In-License Agreement and after the application of all available discounts, reductions, and offsets available under such Epizyme New In-License Agreement. Without limiting the foregoing, if any Epizyme New In-License Agreement provides for tiered royalty rates based on sales of the applicable products or therapies, then the royalty payments subject to reimbursement by Hutchmed shall be determined by allocating the royalty-bearing sales by Hutchmed in proportion to Hutchmed's and Epizyme's (and their respective Affiliates' and (sub)licensees') total royalty-bearing sales.

Hutchmed acknowledges and agrees that certain of the rights, licenses and sublicenses granted by Epizyme to Hutchmed in this Agreement (including any sublicense rights) are subject to the terms of the Epizyme In-License Agreements, including the Eisai Agreement, and the rights granted to the Third Party counterparties thereunder, the scope of the licenses granted to Epizyme or any applicable Affiliate thereunder and the rights retained by such Third Party counterparties and any other Third Parties (including Governmental Authorities) set forth therein. Hutchmed shall, and shall ensure that each Hutchmed Entity shall, perform and take such actions to allow Epizyme and its Affiliates to comply with their obligations under each Epizyme In-License Agreement, to the extent applicable to Hutchmed's rights or obligations under this Agreement and to the extent set forth in Schedule 2.7(a) (with respect to the Eisai Agreement)

or as set forth in the schedule provided by Epizyme to Hutchmed pursuant to the first paragraph of this Section 2.7(a). Without limiting the foregoing, each Hutchmed Entity shall prepare and deliver to Epizyme, or assist Epizyme in preparing, any additional reports required under any Epizyme In-License Agreement, in each case reasonably sufficiently in advance to enable Epizyme and its Affiliates to comply with their obligations thereunder.

(b) Hutchmed In-License Agreements. Subject to Section 16.2, Hutchmed shall be free to negotiate with any Third Party for any agreement pursuant to which Hutchmed would acquire or license Third Party IP in the Territory (or in and outside the Territory). If Hutchmed does not obtain the right to sublicense such Third Party IP to Epizyme outside the Territory, then Hutchmed shall so notify Epizyme and shall not enter into any agreement with respect to such Third Party IP that includes any grant of rights in the Field outside the Territory. Hutchmed will promptly provide Epizyme with notice and a copy of any such executed Third Party agreement in which Hutchmed has the right to sublicense Third Party IP to Epizyme outside the Territory (redacted as necessary to comply with any confidentiality obligations of Hutchmed to such Third Party) and a schedule of all obligations that would be applicable to Epizyme as a sublicensee under such Third Party IP. Within [**] following receipt of such notice, Epizyme will decide, in its sole discretion, whether it will accept the applicable Third Party agreement as a Hutchmed In-License Agreement, and provide notice of such decision to Hutchmed. For clarity, Hutchmed shall not be obligated to acquire or license any Third Party IP outside the Territory for any reason.

In the event that Epizyme declines to accept such Third Party agreement as a Hutchmed In-License Agreement, then (i) such Third Party agreement shall not be deemed to be a "Hutchmed In-License Agreement" hereunder, (ii) Hutchmed shall have no obligation to license or acquire rights to such Third Party IP outside the Territory, and (iii) any rights to such Third Party IP outside the Territory that are granted to Hutchmed under such Third Party agreement will not be deemed to be "Controlled" by Hutchmed or licensed to Epizyme under this Agreement.

In the event that Epizyme accepts such Third Party agreement as a Hutchmed In-License Agreement, then, upon effectiveness of such Third Party agreement, (A) such Third Party agreement will be included within the definition of "Hutchmed In-License Agreement," (B) any rights to Third Party IP granted to Hutchmed under such Hutchmed In-License Agreement will be deemed to be "Controlled" by Hutchmed and sublicensed to Epizyme outside the Territory pursuant to the terms of this Agreement; (C) the sublicenses granted by Hutchmed to Epizyme in this Agreement will be subject to the terms of such Hutchmed In-License Agreement, to the extent described in the schedule provided by Hutchmed to Epizyme pursuant to the first paragraph of this Section 2.7(b) including the scope of the license granted to Hutchmed or any Affiliate thereunder and the rights retained by such Third Party counterparties and any other Third Parties (including Governmental Authorities) set forth therein, and (D) Epizyme shall reimburse [**] percent ([**]%) of the amounts payable to the Third Party arising from and allocable to the exercise of rights by a Epizyme Entity under such Hutchmed In-License Agreement and after the application of all available discounts, reductions, and offsets available under such Hutchmed In-License Agreement. Without limiting the foregoing, if any Hutchmed In-License Agreement provides for tiered royalty rates based on sales of the applicable products or therapies, then the royalty payments subject to reimbursement by Epizyme shall be determined by allocating the royalty-bearing sales by Epizyme in proportion to Hutchmed's and Epizyme's (and their respective Affiliates' and (sub)licensees') total royalty-bearing sales.

Epizyme acknowledges and agrees that certain of the rights, licenses and sublicenses granted by Hutchmed to Epizyme in this Agreement (including any sublicense rights) may be subject to the terms of the Hutchmed In-License Agreements, and the rights granted to the Third Party counterparties thereunder, the scope of the licenses granted to Hutchmed or any applicable Affiliate thereunder and the rights retained by such Third Party counterparties and any other Third Parties (including Governmental Authorities) set forth therein. Epizyme shall, and shall ensure that each Epizyme Entity shall, perform and take such actions

to allow Hutchmed and its Affiliates to comply with their obligations under each Hutchmed In-License Agreement, to the extent applicable to Epizyme's rights or obligations under this Agreement or as set forth in the schedule provided by Hutchmed to Epizyme pursuant to the first paragraph of this Section 2.7(b). Without limiting the foregoing, each Epizyme Entity shall prepare and deliver to Hutchmed, or assist Hutchmed in preparing, any additional reports required under any Hutchmed In-License Agreement, in each case reasonably sufficiently in advance to enable Hutchmed and its Affiliates to comply with their obligations thereunder.

2.8 **Exclusivity**.

(a) Hutchmed Restrictions. Subject to Sections 16.2 and 16.3, during the Term, Hutchmed shall not, and Hutchmed shall ensure that any Hutchmed Entity shall not, itself or with or through any Third Party, without the prior written consent of Epizyme, directly or indirectly engage in the Development, Manufacture, or Commercialization of any Competing Product in any indication in the Territory, or license, sell, assign or otherwise grant rights to any Third Party under any Know-How or Patent Rights Controlled by Hutchmed to do any of the foregoing. Notwithstanding the foregoing, the restrictions set forth in this Section 2.8(a) shall not apply to: the Development, Manufacture or Commercialization of (i) Licensed Compound and Licensed Products in the Field and Territory as explicitly provided in this Agreement, or (ii) any exploitation (including Development, Manufacture or Commercialization) of Hutchmed Dual Inhibitor Products in any field anywhere in the world (other than as limited by Sections 2.5 and 8.1).

Hutchmed shall not, and shall ensure that any Hutchmed Entity shall not, itself or with or through any Third Party directly or indirectly (A) market, promote, or distribute Licensed Compound or Licensed Product in any form outside the Territory, or (B) conduct marketing or sales of any Licensed Product in any form outside the Territory.

Each Hutchmed Entity will use Commercially Reasonable Efforts to monitor and prevent exports or resale of Licensed Products from or outside the Territory for Development or Commercialization outside of the Territory using methods commonly used in the industry for such purpose, and shall promptly inform Epizyme of any such actual or suspected exports from the Territory, and the actions taken to prevent such exports. Hutchmed shall take, and shall ensure that each Hutchmed Entity takes, reasonable actions requested in writing by Epizyme that are consistent with Applicable Law to prevent such exports. If Hutchmed or any other Hutchmed Entity or, to Hutchmed's or any of Hutchmed Entity's knowledge, any other Hutchmed Entity receives a request or order to Develop, Manufacture or Commercialize any Licensed Compound or Licensed Product outside of the Territory, Hutchmed shall immediately notify Epizyme thereof, shall not accept such request or order, and shall direct the relevant individual or entity to Epizyme.

(b) Epizyme Restrictions. Subject to Sections 16.2 and 16.3, during the Term, Epizyme shall not, and Epizyme shall ensure that any Epizyme Entity shall not, itself or with or through any Third Party, without the prior written consent of Hutchmed, directly or indirectly engage in the Development or Commercialization of any Competing Product in any indication in the Territory, or license, sell, assign or otherwise grant rights to any Third Party under any Know-How or Patent Rights Controlled by Epizyme to do any of the foregoing. Notwithstanding the foregoing, the restriction set forth in this Section 2.8(b) shall not apply to: (i) the Development and Manufacture of Licensed Compound and Licensed Products in the Field and Territory by an Epizyme Entity as explicitly provided in this Agreement, including the ongoing or planned activities in the Territory to the extent related to the Development and Manufacture of Licensed Compound and Licensed Product by Epizyme or any other Epizyme Entity as described on Schedule 2.8(b), or (ii) any activity under any license agreement which may be entered into between Hutchmed and Epizyme entered into pursuant to Section 8.1, or in the event the Parties do not execute a license agreement pursuant to Section 8.1, any activity related to the Development, Manufacture, or Commercialization of any

compound that is an EZH1/EZH2 dual inhibitor (other than a Hutchmed Dual Inhibitor Product) after the expiration of the ROFN Term and ROFN Negotiation Period, if applicable.

Each Epizyme Entity will use Commercially Reasonable Efforts to monitor and prevent import or resale of Licensed Products into the Territory for Development or Commercialization in the Territory using methods commonly used in the industry for such purpose, and shall promptly inform Hutchmed of any such actual or suspected imports into the Territory, and the actions taken to prevent such imports. Epizyme shall take, and shall ensure that each Epizyme Entity takes, reasonable actions requested in writing by Hutchmed that are consistent with Applicable Law to prevent such imports. If Epizyme or any Affiliate of Epizyme or, to Epizyme's or any of its Affiliates' knowledge, any other Epizyme Entity receives a request or order to Develop, Manufacture (after a Manufacturing Technology Transfer) or Commercialize any Licensed Compound or Licensed Product in the Territory, Epizyme shall immediately notify Hutchmed thereof, shall not accept such request or order, and shall direct the relevant individual or entity to Hutchmed.

(c) Scope. Each Party acknowledges and agrees that the exclusivity obligations set forth in this Section 2.8, including the duration and scope thereof, are intended, in part, to protect the Parties' trade secrets and other Confidential Information. In the event that any arbitrator or court determines that the duration or scope of any provision of this Section 2.8 is unreasonable and that any such provision is to that extent unenforceable, each Party agrees that such provision shall remain in full force and effect for the greatest time period and to the greatest scope that would not render it unenforceable. The Parties intend that the provisions of this Section 2.8 be deemed to be a series of separate covenants, one for each and every product, indication and jurisdiction where such provision is intended to be effective.

ARTICLE 3. GOVERNANCE

3.1 **General**.

(a) The Parties shall establish (i) a Joint Steering Committee ("**JSC**") to oversee and coordinate the overall conduct of the Development, Manufacture, and Commercialization of Licensed Compound and Licensed Products in the Field in the Territory, (ii) a Joint Development Committee ("**JDC**") to oversee and coordinate the Development of the Licensed Products in the Field in the Territory, (iii) a Joint Commercialization Committee ("**JCC**") to oversee the Commercialization of the Licensed Products in the Field in the Territory and (iv) a Joint Manufacturing Committee ("**JMC**") to oversee and coordinate the Manufacturing and supply of Licensed Product (including Drug Substance and Drug Product) for the Development and Commercialization of the Licensed Products in the Field in the Territory. The JSC, the JDC, the JCC, and the JMC shall each be referred to as a "**Committee**". Each Committee shall have decision-making authority with respect to the matters within its purview to the extent expressly provided herein.

(b) From time to time, each Committee may establish one or more subcommittees or working groups to oversee particular projects or activities, as it deems necessary or advisable (each, a "**Subcommittee**"). Each Subcommittee shall consist of such number of members as the applicable Committee determines is appropriate from time to time. Such members shall be individuals with expertise and responsibilities in the relevant areas. Each Subcommittee shall discuss matters within the scope of such Subcommittee's oversight and shall report the outcome of the discussions of such Subcommittee to the Committee that formed such Subcommittee promptly after each meeting. Following the receipt of the report from such Subcommittee, the Committee that formed such Subcommittee shall make any required decisions regarding matters set forth in such report.

3.2 **Joint Steering Committee**. Within [**] following the Effective Date, the Parties shall establish the JSC. The JSC shall:

(a) monitor and discuss the strategic direction of the Development, Manufacturing, and Commercialization of the Licensed Products in the Field in the Territory;

(b) monitor and discuss the progress of the Development and Commercialization of the Licensed Products in the Field in the Territory and serve as a forum for exchanging information regarding the strategic plans for the Development and Commercialization of the Licensed Products in the Field in the Territory;

(c) oversee and coordinate all of the matters within the responsibilities of the Committees hereunder;

(d) determine whether to create any additional Committee;

(e) serve as a forum for dispute resolution in accordance with Section 3.9 with respect to matters that are not resolved at the JDC, JCC or JMC; and

(f) perform such other duties as are specifically assigned to the JSC under this Agreement.

3.3 **Joint Development Committee**. Within [**] following the Effective Date, the Parties shall establish the JDC. The JDC shall:

(a) discuss and approve any Additional Indication or Combination Therapy to be Developed in the Territory, or any clinical trial to be performed in whole or in part in the Territory, in each case, that is not set forth in the then-current Clinical Development Plan and is proposed by a Party in accordance with Section 4.3. If Hutchmed proposes a Local Trial to be added to the Clinical Development Plan, the JDC may approve converting such Local Trial into a Joint Global Trial;

(b) discuss the current Clinical Development Plan and approve any updates or amendments to the Clinical Development Plan, including the addition of any Additional Indication, Combination Therapy or Local Trial or Joint Global Trial not set forth in the then-current Clinical Development Plan, and discuss the use of any relevant diagnostic in the Territory;

(c) monitor and discuss the alignment of Hutchmed Entities' Development of Licensed Products in the Territory with Epizyme's Development of the Licensed Products outside of the Territory, and discuss and provide strategic guidance on the Development of the Licensed Products in the Field in the Territory;

(d) discuss whether Hutchmed shall participate in a global trial for the Licensed Product presented by Epizyme, which would include clinical sites both in the Territory and outside the Territory;

(e) discuss the clinical sites in the Territory to be included in each Local Trial and each Joint Global Trial;

(f) discuss the protocols for each Local Trial and Joint Global Trial and discuss the status and progress thereof;

(g) coordinate the operations of the Hutchmed Entities and Epizyme Entities with respect to Joint Global Trials;

(h) discuss the budget for the Joint Global Trials (and approve the budget for costs under Section 9.3(c)(iii)) to be conducted under this Agreement; provided that each Party shall solely determine the budget for its activities in its respective territory;

(i) discuss and approve the Permitted Subcontractors defined in Section 1.145(a), if any, that may be used for Joint Global Trials by Hutchmed in the Territory;

(j) discuss Pre-Clinical Research activities with respect to the Licensed Products that any Hutchmed Entity wishes to conduct in the Territory, and discuss the status and progress of such activities;

(k) provide a forum for the Parties to share information with respect to the Development of the Licensed Products in the Field, including reasonably detailed updates on progress and status of Local Trials and Joint Global Trials in the Territory and updates regarding interactions with Regulatory Authorities;

(l) coordinate plans and provide updates regarding attendance at conferences and congresses and interactions with key opinion leaders by the Parties, subject to Section 4.9;

(m) discuss the plans for any publication or presentation proposed by Hutchmed and related to the Development of Licensed Products, subject to Section 10.5(a);

(n) discuss the Hutchmed Entities' Medical Affairs strategy for the Licensed Products in the Territory and take into account Epizyme's Global Medical Affairs Strategy;

(o) discuss the Hutchmed Entities' regulatory strategy for the Licensed Products in the Territory in the Field, including regulatory strategy for meetings with the Regulatory Authorities and the clinical and preclinical portions of the Drug Approval Application for the Licensed Product in the Territory;

(p) review and discuss the content of any IND or Drug Approval Application for any Licensed Product in the Territory (other than the chemistry, manufacturing and controls ("**CMC**") module of such IND or Drug Approval Application, which shall be reviewed by the JMC);

(q) discuss the status and progress of any LCM Epizyme Trial being performed by Epizyme or other Epizyme Entities, for which Epizyme will provide regular updates to the JDC;

(r) establish, within [**] after the establishment of the JDC, a Subcommittee to oversee and coordinate activities related to the 302 Global Trial, which Subcommittee shall meet [**] unless otherwise agreed; and

(s) determine whether to create any other Subcommittee, and perform such other duties as are specifically assigned to the JDC under this Agreement.

3.4 **Joint Commercialization Committee**. Not later than [**] prior to the anticipated First Commercial Sale of Licensed Product in the Territory, the Parties shall establish the JCC. The JCC shall:

(a) discuss the Commercialization Plan (including the Launch Plan) and any updates thereto, and discuss the status of Commercialization activities by Hutchmed under this Agreement;

(b) discuss Hutchmed's market access strategy for Licensed Products in the Territory, including pricing and timing of reimbursement application (NRDL) and discuss the status of market access activities and Licensed Product pricing;

(c) discuss plans for compliance training and oversight;

(d) discuss Hutchmed Entities' sales achieved during the then-preceding [**] and the forecasted sales numbers for the next [**]; and

(e) determine to create any Subcommittee and perform such other duties as are specifically assigned to the JCC under this Agreement.

3.5 **Joint Manufacturing Committee**. Within [**] following the Effective Date, the Parties shall establish the JMC and the JMC shall hold its first meeting. The JMC shall:

(a) oversee and coordinate the clinical supply of Licensed Products to Hutchmed for Hutchmed's Development activities in the Territory;

(b) oversee and coordinate the Manufacturing Technology Transfer (including determining the activities and budget required for the Manufacturing Technology Transfer and timing thereof, and oversee implementation of the Manufacturing Technology Transfer) to Hutchmed for the Manufacture of Drug Product in the Territory by Hutchmed for Development and Commercialization in the Territory;

(c) oversee and coordinate the Manufacturing Technology Transfer (including determining the activities and budget required for the Manufacturing Technology Transfer and timing thereof, and oversee implementation of the Manufacturing Technology Transfer) to Hutchmed or its Permitted Subcontractor CMO (if such Permitted Subcontractor CMO has been approved by the JMC) for the Manufacture of Drug Substance in the Territory by Hutchmed or such Permitted Subcontractor CMO for Development and Commercialization in the Territory;

(d) with respect to any quantities of Drug Product, if any, to be supplied by Epizyme for Commercialization by Hutchmed in the Territory prior to Manufacturing Technology Transfer Completion, oversee and coordinate the commercial supply of Drug Product to Hutchmed for Hutchmed's Commercialization of Licensed Products in the Territory;

(e) oversee and coordinate proposed and planned Manufacturing Activities, including approving the budget for Manufacturing Activity Costs to be incurred and monitor the Parties' activities and expenses against such budget;

(f) subject to Section 1.145(b), approve a Permitted Subcontractor CMO, if any, for the Manufacture of Drug Substance on behalf of Hutchmed in the Territory following the Manufacturing Technology Transfer;

(g) discuss and approve the content of CMC module (Module 3 or its equivalent) of any IND and Drug Approval Application filing for the Licensed Product in the Territory, and approve the regulatory strategy for the CMC meetings with the Regulatory Authorities;

(h) discuss any updates regarding the development or implementation of any Manufacturing Activity under Section 7.4; and

(i) determine whether to create any Subcommittee, and perform such other duties as are specifically assigned to the JMC under this Agreement or under the Clinical Supply Agreement, Commercial Supply Agreement, if any, or Manufacturing Technology Transfer Agreement.

3.6 **Membership**. Each Committee shall be composed of [**] representatives from each of Epizyme and Hutchmed, each of which representatives shall be of the seniority and experience appropriate for service on the applicable Committee in light of the functions, responsibilities and authority of such Committee and the status of activities within the scope of the authority and responsibility of such Committee. Any representative from either Party can represent such Party on more than one Committee. Each Party may replace any of its representatives on any Committee at any time with written notice to the other Party;

provided that such replacement meets the standard described in the preceding sentence. Each Party's representatives and any replacement of a representative shall be bound by obligations of confidentiality and non-use applicable to the other Party's Confidential Information that are at least as stringent as those set forth in Article 10. Each Party may invite a reasonable number of its or its Affiliates' employees and, with the consent of the other Party, its or its Affiliates' consultants or other contractors, as required or useful to discuss the applicable agenda items.

Each Committee shall appoint two co-chairpersons from among its members, with one chairperson being a representative of Epizyme and the other chairperson being a representative of Hutchmed. The co-chairpersons shall be responsible for establishing the Committee schedules and agendas, and for finalizing the minutes of each meeting. Within [**] following each Committee meeting, the co-chairpersons of the applicable Committee shall alternate responsibility for circulating to all Committee members a draft of the minutes of such meeting. The Committee shall then approve, by mutual agreement, such minutes within [**] following circulation; provided that if the Committee does not approve, by mutual agreement, such minutes during such period, then the Committee shall consider the matter in dispute at its next meeting and resolve such matter in accordance with this Agreement. No co-chairperson of any Committee shall have any greater authority than any other representative of such Committee and each co-chairperson of any Committee may delegate the administrative aspects of his or her co-chairperson responsibilities to a member of his or her project team.

3.7 **Meetings**. Each Committee shall hold an initial meeting within [**] after its formation or as otherwise agreed by the Parties. Thereafter, unless the Parties otherwise agree, each Committee (except the JDC) shall meet in person, or by phone or video conference [**] per Calendar Year, with at least [**] in person or by video teleconference, and with respect to the JCC only, with [**] in the [**]. Unless the Parties otherwise agree, the JDC shall meet in person, or by phone or video conference [**], with at least [**] in person. All in-person meetings for each Committee shall be held at the offices of Epizyme or Hutchmed or other locations as mutually agreed by the Parties. Each Party shall be responsible for all of its own personnel and travel costs and expenses relating to participation in Committee meetings.

3.8 **Committee Decision Making**. A quorum of each Committee will exist whenever there is present at a meeting at least one representative appointed by each Party. All decisions of a Committee shall be made by unanimous vote, with each Party's representatives collectively having one (1) vote, and shall be set forth in minutes approved by both Parties. If the JDC, JCC, JMC or any other Committee (other than the JSC) is unable to reach agreement on any matter within [**] after the matter is referred to it or first considered by it, such matter shall be referred to the JSC for resolution. If the JSC is unable to reach agreement on any matter within [**] after the matter is referred to it or first considered by it, such matter shall be referred to the Executive Officers for resolution in accordance with Section 3.9.

3.9 **Executive Officers; Disputes**. Each Party shall ensure that an executive officer is designated for such Party at all times during the Term for dispute resolution purposes (each such individual, such Party's "**Executive Officer**"), and shall promptly notify the other Party of its initial, or any change in its Executive Officer. Unless otherwise set forth in this Agreement, in the event of a dispute arising under this Agreement between the Parties, the Parties shall refer such dispute to the Executive Officers, who shall attempt in good faith to resolve such dispute. If the Executive Officers are unable to resolve such dispute within [**], then the final decision-making authority of the Parties shall be as set forth in Section 3.10.

3.10 **Final Decision-Making Authority**. The Party with final decision-making authority shall make its decision in good faith, subject to the terms and conditions of this Agreement as follows:

(a) By Hutchmed. Hutchmed shall have final decision-making authority with respect to the following:

(i) whether Hutchmed will perform any Pre-Clinical Research activities or Local Trial and, if Hutchmed determines to perform a Local Trial, Hutchmed will have final decision-making authority with respect to the protocol, informed consent forms, the selection of clinical sites, the number of subjects to be studied in such Local Trial, the day-to-day management of such Local Trial, and the portion of the CDP that specifically relates to such Local Trial or Pre-Clinical Research activities, but in no event in a manner to the detriment of the CDP as of the Effective Date;

(ii) whether Hutchmed will participate in a proposed Joint Global Trial (other than the 301 Global Trial and 302 Global Trial) and, if Hutchmed does participate, Hutchmed will have final decision-making authority with respect to the conduct of any such Joint Global Trial in the Territory (including selection of clinical sites); provided that in no event shall Hutchmed use its decision-making authority to decrease the number of patients to be enrolled and treated by Hutchmed in any Joint Global Trial to less than twenty percent (20%) of the total number of patients to be treated at all sites globally;

(iii) any matter related to filing, obtaining, and maintaining Regulatory Approvals of Licensed Product in the Territory (other than as provided in Section 3.10(b)(iii));

(iv) after Manufacturing Technology Transfer, the day-to-day management of the transferred Manufacturing activities in the Territory (other than approval of any Permitted Subcontractor CMO in the Territory, which is subject to Section 3.10(b)(iii)); provided that Hutchmed shall not act in a manner inconsistent with the license under Section 2.1(f);

(v) any matter related to Medical Affairs for Licensed Products in the Field and in the Territory, including any portions of the CDP relating to Medical Affairs, taking into consideration in good faith the Global Medical Affairs Strategy; and

(vi) any matter related to the Commercialization of Licensed Products in the Field and in the Territory, including the Commercialization Plan, subject to Article 6.

(b) By Epizyme. Epizyme will have final decision-making authority with respect to any matter related to the Development and Manufacture of Licensed Products in and outside the Territory that is not a matter for which Hutchmed has final decision-making authority under Section 3.10(a) above and any matter related to the Commercialization of Licensed Products outside the Territory, including:

(i) the approval of an Additional Indication for Licensed Product to be Developed or continue to be Developed; provided that (A) Epizyme shall approve any indication for the Licensed Product proposed by Hutchmed that (1) is reasonable from a safety and potential efficacy perspective in the Territory or (2) is being Developed or Commercialized by Epizyme outside the Territory that is not at such time included in the Field, and (B) Hutchmed may reject and not be obligated to pursue the Development, Manufacture (after a Manufacturing Technology Transfer) or Commercialization of Licensed Products in the Territory for an Additional Indication proposed by Epizyme (even if approved by Epizyme) if Hutchmed reasonably and in good faith determines that pursuing such Development, Manufacture (after a Manufacturing Technology Transfer) or Commercialization of the Licensed Product for such Additional Indication in the Territory is not commercially reasonable or would lead to a safety issue for the Licensed Product in the Territory (any such rejected Additional Indication, a "**Rejected Additional Indication**");

(ii) the approval of the Other Combination Drug of any Combination Therapy to be Developed or continue to be Developed; provided that (A) Epizyme shall approve any Other

Combination Drug (including any Hutchmed Compound) that is proposed by Hutchmed that is reasonable from a safety and potential efficacy perspective in the Territory, and (B) with respect to any Other Combination Drugs proposed by Epizyme, Hutchmed may (1) reject the use of any Hutchmed Compound in any Joint Combination Therapy if Hutchmed reasonably and in good faith determines that the use of such Hutchmed Compound in the Development or Commercialization of such Joint Combination Therapy is not commercially reasonable or would lead to a safety issue for the Hutchmed Compound or Joint Combination Therapy, or (2) reject and not be obligated to pursue the Development or Commercialization in the Territory of an Epizyme Combination Therapy proposed by Epizyme (even if approved by Epizyme) if Hutchmed reasonably and in good faith determines that pursuing the Development or Commercialization of such Epizyme Combination Therapy in the Territory is not commercially reasonable or would lead to a safety issue for the Licensed Product or Epizyme Combination Therapy in the Territory (any such rejected Combination Therapy, a "**Rejected Combination Therapy**"); and

(iii) any matter related to the Manufacture of Licensed Products for use in the Territory or outside the Territory and any matter to be determined or approved by the JMC that is not resolved under Section 3.10(a)(iv) (including the approval of any Permitted Subcontractor CMO, if any, under Section 3.5(f), and the approval of the CMC module under Section 3.5(g)), except that (A) Epizyme shall not use its final decision-making authority to require Hutchmed to accept any new Dosage Form Change, and (B) Epizyme shall not use its final decision-making authority to take any action contrary to the terms of the Clinical Supply Agreement, Commercial Supply Agreement, or Manufacturing Technology Transfer Agreement executed by the Parties.

For clarity, Epizyme shall have final decision-making authority regarding whether to conduct a Joint Global Trial proposed by Hutchmed, the conduct of any clinical trial outside of the Territory, the study design of any Joint Global Trial or any clinical trial outside of the Territory, and the budget under Section 9.3(c)(iii). Notwithstanding the foregoing, in no event shall Epizyme use its decision-making authority to increase the number of patients to be enrolled and treated by Hutchmed in any Joint Global Trial to greater than twenty percent (20%) of the total number of patients to be treated at all sites globally.

Any decision made by a Party in accordance with this Section 3.10 shall be deemed to be a decision of the relevant Committee.

3.11 **Limitations on Decision-Making**.

(a) Neither Party shall have the deciding vote on, and no Committee shall have decision-making authority regarding, any of the following matters: (i) the imposition of any requirements on the other Party to undertake increased costs or obligations, or to forgo any of its rights, under this Agreement; (ii) the imposition of any requirements that the other Party takes or declines to take any action that would result in a violation of any Applicable Law or any agreement with any Third Party or the infringement of intellectual property rights of any Third Party; (iii) the resolution of a dispute involving the breach or alleged breach of this Agreement; (iv) the determination of whether a Hutchmed Entity exerts Commercially Reasonable Efforts under this Agreement; (v) any decision that is expressly stated to require the mutual agreement (or similar language) of a Committee or the Parties or the approval of the other Party (but not "approval" of a Committee); (vi) any matters that would excuse such Party from any of its obligations under, or waive any term of, this Agreement; or (vii) modifying the terms of this Agreement or taking any action to expand or narrow the responsibilities of any Committee. In no event may the decision-making Party unilaterally determine that it has fulfilled any obligations hereunder or that the non-deciding Party has breached any obligations hereunder. In no event may Hutchmed unilaterally determine that any events required for the

payment of milestone payments have not occurred and in no event may Epizyme unilaterally determine that the events required for the payment of milestone payments have occurred.

(b) In no event shall Hutchmed exercise its final decision-making authority with respect to the Licensed Products in the Territory in a manner that Epizyme has notified Hutchmed (including through the applicable Committee or Subcommittee) is reasonably expected to have a material adverse effect on the Manufacturing, Development or Commercialization for any Licensed Product outside the Territory, or scope, validity or enforceability of any Licensed IP. In no event shall Epizyme exercise its final decision-making authority with respect to the Licensed Products outside the Territory in a manner that Hutchmed has notified Epizyme (including through the applicable Committee or Subcommittee) is reasonably expected to have a material adverse effect on the Development or Commercialization of any Licensed Product in the Territory.

For clarity, approval by a Committee shall not be understood to mean approval by a Party.

3.12 **Scope of Governance**. Notwithstanding the creation of each of the Committees or anything to the contrary in this Article 3, each Party shall retain the rights, powers and discretion granted to it under this Agreement, and no Committee shall be delegated or vested with rights, powers or discretion unless such delegation or vesting is expressly provided herein, or the Parties expressly so agree in writing. It is understood and agreed that issues to be formally decided by a particular Committee are only those specific issues that are expressly provided in this Agreement to be decided by such Committee, as applicable. For clarity, no Committee shall have any rights, powers or discretion to make any decision regarding the Development, Manufacturing or Commercialization of the Licensed Products outside of the Field or outside of the Territory, and, with respect to such matters relating to Licensed Products that are so excluded from the Committees' scope of authority, Epizyme retains all such rights, powers and discretion.

3.13 **Alliance Managers**. Each of the Parties shall appoint a single individual to manage Development, Manufacturing and Commercialization obligations between the Parties under this Agreement (each, an "**Alliance Manager**"). The role of the Alliance Manager is to act as a single point of contact between the Parties to ensure a successful relationship under this Agreement. The Alliance Managers may attend any Committee and Subcommittee meetings. Each Alliance Manager shall be a non-voting participant in such Committee and Subcommittee meetings, unless s/he is also appointed a member of such Committee; provided, however, that an Alliance Manager may bring any matter to the attention of a Committee if such Alliance Manager reasonably believes that such matter warrants such attention. Each Party may change its designated Alliance Manager at any time upon written notice to the other Party. Any Alliance Manager may designate a substitute to temporarily perform the functions of that Alliance Manager by written notice to the other Party. Each Party's Alliance Manager and any substitute for an Alliance Manager shall be bound by obligations of confidentiality and non-use applicable to the other Party's Confidential Information that are at least as stringent as those set forth in Article 10. Each Alliance Manager will also: (a) plan and coordinate cooperative efforts and internal and external communications; and (b) facilitate the governance activities hereunder and the fulfillment of action items resulting from Committee meetings.

ARTICLE 4. LICENSED PRODUCT DEVELOPMENT

4.1 **Development in the Field in the Territory**. The Development of Licensed Products in the Field in the Territory shall be governed by the Clinical Development Plan, and no Hutchmed Entity may Develop any Licensed Product in the Field in the Territory other than in accordance with the Clinical Development Plan or as otherwise approved by the JDC in advance. Hutchmed shall use Commercially Reasonable Efforts to execute and to perform, or cause to be performed, the activities assigned to it in the Clinical Development Plan, in each case in accordance with the terms of this Agreement including Section 4.4. Hutchmed shall use Commercially Reasonable Efforts to Develop Licensed Products in the Territory for

each Initial Indication and any Additional Indication (other than a Rejected Additional Indication). Hutchmed will use Commercially Reasonable Efforts to identify Hutchmed Compounds (including those listed on Schedule 1.91) to combine with Licensed Products as potential Joint Combination Therapies in the Territory, and propose such Hutchmed Compounds to the JDC in accordance with Section 4.3(b).

4.2 **Clinical Development Plan**. The Parties shall ensure at all times that the Clinical Development Plan (a) is consistent with the terms and conditions of this Agreement, (b) is focused on efficiently obtaining Regulatory Approval for Licensed Products (whether as a monotherapy or as part of a Combination Therapy) in each Initial Indication and Additional Indication (other than a Rejected Additional Indication) in the Territory, (c) does not include activities that could reasonably be expected to have a material adverse effect on the Development, Manufacture or Commercialization of Licensed Compound or Licensed Products outside of the Territory; and (d) does not include activities that constitute or potentially constitute a violation of the requirements set out in Applicable Law in the Territory.

The Clinical Development Plan shall provide a summary of each bridging study, Local Trial, Joint Global Trial, investigator sponsored trial and registry study to be conducted any Hutchmed Entity in the Territory, including in reasonable detail (i) all material Development activities reasonably anticipated to be undertaken by the Hutchmed Entities or Hutchmed Entities and Epizyme Entities, (ii) the endpoints for all clinical trials contemplated by such plan, (iii) identification of the clinical trials that are intended to be a Pivotal Trials, (iv) all material regulatory activities and Regulatory Authority interactions anticipated to be conducted by the Hutchmed Entities in support of Regulatory Approval of the Licensed Products in the Field in the Territory, including all planned material Regulatory Filings to be submitted in connection with such approvals, and (v) the budget for Hutchmed's share of costs associated with participation in Joint Global Trials in accordance with Section 9.3(c)(iii). Each Party shall be responsible for determining the budget for its activities in its respective territory for Joint Global Trials.

4.3 **CDP Updates**. Either Party may propose to the JDC that the Clinical Development Plan be updated, including:

(a) that a Licensed Product be Developed, Manufactured and Commercialized in the Territory for an indication other than the Initial Indications or any previously-approved Additional Indication. In the event any such additional indication is proposed by a Party, then the JDC shall determine whether to approve such additional indication for inclusion in the Clinical Development Plan (any such approved additional indication, an "**Additional Indication**"); provided that, for clarity, an Additional Indication in the Territory shall not include any Rejected Additional Indication pursuant to Section 3.10(b)(i);

(b) that a Licensed Product be Developed, Manufactured and Commercialized in the Territory as part of a Combination Therapy (in addition to the Combination Therapies that are being studied as part of the 301 Global Trial and 302 Global Trial or any previously approved Combination Therapy), including that a Hutchmed Compound be part of a potential Joint Combination Therapy in the Territory; provided that, for clarity, a Combination Therapy in the Territory shall not include any Rejected Combination Therapy pursuant to Section 3.10(b)(ii); or

(c) that one or more Local Trials be conducted in the Territory or Joint Global Trials be conducted globally (with clinical sites in the Territory).

Any proposal by either Party to the JDC shall include sufficient information for the other Party to assess the proposal and shall include, at a minimum, the scientific rationale for the proposed Development activity and an overview of the plan to accomplish such Development activity, including the Development and Regulatory Approval strategy, timelines, relevant competitive landscape, epidemiology, Manufacturing requirement, and pre-clinical activities, if any.

Notwithstanding any other provision of this Agreement, neither Party shall be obligated to propose any clinical trial or Development activity for any Licensed Product (including any Combination Therapy) for any indication to the JDC for inclusion in the Clinical Development Plan, and Epizyme shall be free at its discretion, itself or with Third Parties, to perform any clinical trial of, or otherwise Develop, any Licensed Product or Combination Therapy in any indication in one or more countries outside of the Territory, including any Epizyme Trial.

At least [**], the JDC shall review and update the Clinical Development Plan. Each Party may submit to the JDC from time to time proposed amendments to the Clinical Development Plan. The JDC shall review and may approve such proposed amendments or any other proposed amendments that the JDC may consider from time to time in its discretion and, upon any such approval by the JDC, the Clinical Development Plan shall be amended accordingly (and a copy of any such updated Clinical Development Plan shall be provided to each Party and shall be attached to the minutes of the next meeting, but shall not require an amendment to this Agreement).

4.4 **Conduct of Local Trials**. Hutchmed may conduct Local Trials of the Licensed Product (including, subject to Section 3.10(b)(ii), any Combination Therapy) in the Field (including, subject to Section 3.10(b)(i), any Additional Indication) and in the Territory. Each Local Trial conducted in the Territory shall be conducted in accordance with the Clinical Development Plan, the study protocol approved by the JDC and any relevant Regulatory Authority, and Applicable Law in the Territory. Hutchmed shall be solely responsible for its performance in the Territory (including handling relevant Regulatory Filings for any Local Trials in the Territory at its own cost, as applicable, in accordance with Article 5). Unless prohibited by Applicable Law, Hutchmed, itself or with or through any other Hutchmed Entity, shall be the CTA owner or Authorized Regulatory Agent of each Local Trial, as determined by Hutchmed in its sole discretion. For each Local Trial, Hutchmed shall provide Epizyme with a synopsis of each clinical trial protocol and specific sections of the protocol as reasonably requested by Epizyme, in English.

Hutchmed will be responsible for ensuring that all informed consent forms for use in the Territory in any Local Trial: (i) allow Hutchmed to provide Epizyme and its Affiliates with access to and use of data and samples generated or obtained in such trials (and in no event less than the same use rights granted to Hutchmed and with respect to samples to the extent permitted by Applicable Law), and (ii) comply with Applicable Law.

4.5 **Conduct of Joint Global Trials**.

(a) Potential Global Clinical Trials. Epizyme may present any potential clinical trial of the Licensed Product that includes clinical sites both in the Territory and outside the Territory, along with the plan for such global study, to Hutchmed via the JDC. Hutchmed may also present a potential global study of the Licensed Product to the JDC. The JDC shall discuss and decide in good faith whether the Parties will conduct such trial as a Joint Global Trial, subject to Epizyme's final decision-making authority under Section 3.10(b); provided that Hutchmed shall have final decision-making authority regarding whether to participate in any such global study as provided in Section 3.10(a)(ii).

(b) Obligations of the Parties. The Parties will be responsible for the performance of any Joint Global Trial as determined by the JDC. The conduct of any Joint Global Trial in the Territory shall be in accordance with the Clinical Development Plan, Epizyme's study protocol (approved by any relevant Regulatory Authority), and Applicable Law in the Territory. Unless otherwise agreed by the Parties, for the 301 Global Trial, 302 Global Trial and any other Joint Global Trial, and subject to the other provisions in this Section 4.5, Epizyme shall, either by itself or through a Third Party contract research organization (the "**Epizyme CRO**"), at Epizyme's sole cost and expense (subject to Section 9.3(c)(iii)), provide oversight of the clinical trial operations in the Territory to ensure consistency with the clinical trial

operations outside the Territory. The JDC shall determine the timing of the inclusion of clinical sites in the Territory for each Joint Global Trial, with the understanding that Hutchmed will identify and manage clinical sites in the Territory for any relevant Joint Global Trials. A copy of all clinical trial related documents for each Joint Global Trial, including protocols, informed consent forms, and safety data shall be provided to Epizyme in the language in which they were drafted; any such documents that are not received in English will be translated into English at Epizyme's request by the Epizyme CRO, at Epizyme's cost. Unless prohibited by Applicable Law, Hutchmed, itself or with or through any other Hutchmed Entity, shall be the Authorized Regulatory Agent of each Joint Global Trial in the Territory. Hutchmed will be responsible for ensuring that all informed consent forms for use in the Territory in any Joint Global Trial: (i) allow Hutchmed to provide Epizyme and its Affiliates with access to and use of data and samples generated or obtained in such trials (and in no event less than the same use rights granted to Hutchmed and with respect to samples to the extent permitted by Applicable Law), and (ii) comply with Applicable Law.

(c) Hutchmed Minimum Patient Obligation. Hutchmed shall use Commercially Reasonable Efforts, either by itself, through any Hutchmed Entity or through the Epizyme CRO, to recruit, enroll, treat, and provide follow-up in a timely manner of twenty percent (20%) of the total number of patients to be treated under the protocol approved by the FDA and NMPA (or such increased or decreased total number of patients as may be required by a Regulatory Authority inside or outside the Territory) for the 301 Global Trial, the 302 Global Trial, and any other Joint Global Trial; provided that a Hutchmed Entity shall not enroll any patients in any clinical trial, and shall not be in breach of this Agreement for not having enrolled any such patients (so long as Hutchmed is using Commercially Reasonable Efforts to pass an in-person quality audit), until Hutchmed has passed, to Epizyme's reasonable satisfaction, an in-person quality audit conducted by Epizyme or its designee. For clarity, once Hutchmed has passed such quality audit, then the proviso in the foregoing sentence shall not apply to any subsequent Joint Global Trial.

(d) 302 Global Trial. Notwithstanding anything to the contrary in this Agreement, in the event that the Regulatory Authorities in Mainland China determine that the 302 Global Trial cannot be used as the confirmatory trial for a conditional Regulatory Approval of the Licensed Product as a monotherapy to treat relapsed/refractory FL, then Hutchmed shall provide Epizyme with a copy of all Regulatory Documents relating to such determination by the Regulatory Authority (in English) and Hutchmed shall continue to use Commercially Reasonable Efforts to conduct the 302 Global Trial in compliance with Section 4.5(c), except (i) Epizyme shall reimburse Hutchmed for all internal and Out-of-Pocket Costs incurred by Hutchmed Entities to enroll and treat such patients in the 302 Global Trial in the Territory after such notice in accordance with, and not in excess of, the budget proposed by Hutchmed for the 302 Global Trial in the Territory as discussed at the JDC in accordance with Section 3.3(h), and (ii) the 302 Global Trial shall be a Rejected Global Trial for the purposes of Sections 9.3(d) and 14.7(c), and shall remain a Joint Global Trial for all other purposes.

(e) 301 Global Trial. Notwithstanding anything to the contrary in this Agreement, in the event Epizyme determines, after consultation with the FDA, to discontinue the 301 Global Trial outside the Territory, then (i) the 301 Global Trial shall no longer be a Joint Global Trial and Hutchmed shall no longer be obligated to participate in such clinical trial, and (ii) ES shall no longer be an Initial Indication for purposes of this Agreement.

4.6 **Conduct of Rejected Global Trials**. Epizyme may, itself or with or through any other Epizyme Entity, perform any Rejected Global Trial and include one or more clinical sites in the Territory; provided that the Parties shall discuss the inclusion of clinical sites in the Territory in such Rejected Global Trial and Epizyme shall reasonably consider any concerns raised by Hutchmed about the use of such clinical sites. Epizyme shall use Hutchmed as a contract research organization in the Territory for such Rejected Global Trial (so long as the costs of using Hutchmed are not greater than the costs a reputable Third Party contract research organization would charge Epizyme for such work), unless Hutchmed notifies Epizyme that

Hutchmed does not agree to serve as the contract research organization for such Rejected Global Trial, in which case Epizyme may use any Third Party as a contract research organization. The Parties agree that Section 9.3(d) shall apply with respect to such Rejected Global Trial.

4.7 **Samples**. To the extent permissible under Applicable Law, Epizyme or its designee shall own all biological samples obtained in connection with any Joint Global Trial, and, at Epizyme's request, Hutchmed shall transfer to Epizyme or its designee a reasonable quantity as mutually agreed of any such biological samples in Hutchmed's possession or control. If Applicable Law prohibits such ownership or transfer, the Parties will work together to provide Epizyme or its designee with rights and access to such biological samples as close to those described in the preceding sentence as is permitted by Applicable Law.

4.8 **Meetings**. Hutchmed may hold meetings with investigators engaged in clinical trials of Licensed Products in the Territory and advisory board meetings to discuss the Development of Licensed Products in the Territory, all as appropriate and compliant with Applicable Law including Anti-Corruption Law. To the extent practicable and permissible by Applicable Law and Regulatory Authorities, Hutchmed shall use good faith efforts to accommodate Epizyme so that Epizyme may have up to [**] employees or other representatives (who are bound by written obligations of nondisclosure and non-use no less stringent than those set forth in Article 10) participate at any material meetings with such investigators in the Territory; provided that any exercise of such right by Epizyme shall not require Hutchmed to delay the Development or Commercialization of the Licensed Product, including in arranging any such meeting or delaying in responding to such investigators. Hutchmed shall provide Epizyme with reasonable notice prior to any such meetings.

4.9 **Conferences and Key Opinion Leaders**. As commercially reasonable and in compliance with Applicable Law including Anti-Corruption Laws, Hutchmed (a) shall attend and have the right to lead the presence of the Parties at Territory-specific conference or congresses relevant to the Licensed Product in the Territory, (b) may attend international conferences or congresses relevant to the Licensed Product outside the Territory; provided, that Epizyme shall be responsible for leading the presence of the Parties at any such conference or congress, (c) shall be responsible for establishing appropriate relationships with key opinion leaders who are within the Territory, and (d) shall provide Epizyme with an update of its attendance at any conference or congress and of any key opinion leaders met. Epizyme may attend conferences or congresses in the Territory, at its option; provided, however, that Hutchmed shall be responsible for leading the presence of the Parties at any Territory-specific conference or congress, and Epizyme shall be responsible for leading the presence of the Parties at any international conference or congress in the Territory.

4.10 **Development Updates**. In addition to the transfer of Hutchmed Product Data under Section 2.6(b), at each meeting of the JDC in each [**], Hutchmed shall provide the JDC with a summary of the Development activities for the Licensed Products in the Field in the Territory (including a clinical trial operational update) performed by the Hutchmed Entities in the Calendar Quarter prior to such meeting of the JDC. Within [**] after the end of each Calendar Year, Hutchmed shall provide Epizyme with a written report that updates the previous [**] report provided to Epizyme and that details the Development activities for the Licensed Product in the Field in the Territory. In addition, Hutchmed shall provide a prompt written notice to Epizyme of any clinical holds, Regulatory Filings, Regulatory Approvals and clinical trial initiation or completion, in each case, in the Field in the Territory, which notice shall be not later than [**] with respect to clinical holds, Regulatory Filings and Regulatory Approvals and not later than [**] with respect to any other events such as clinical trial initiation or completion.

4.11 **Pre-Clinical Research**. Hutchmed, itself or through other Hutchmed Entities, shall conduct any Pre-Clinical Research in the Territory in relation to Licensed Products solely to support clinical Development

of Licensed Products, in accordance with the Clinical Development Plan and as determined by the JDC. Hutchmed shall bear all costs related to such Pre-Clinical Research activities.

4.12 **Standards of Conduct**. The Hutchmed Entities shall perform all Development activities under the Clinical Development Plan (a) in a good scientific manner, (b) in accordance with all applicable GLP, GVP, GCP, and all applicable local regulations promulgated or endorsed by any applicable Regulatory Authority in the Territory, or as otherwise specified in the Clinical Development Plan, (c) in accordance with the quality plan agreed upon by the Parties to verify Hutchmed's GxP compliance, and (d) in compliance in all material respects with Applicable Laws.

4.13 **Records**. The Hutchmed Entities shall maintain written or electronic records in sufficient detail, in a good scientific manner (in accordance with all applicable GLP, GVP and GCP promulgated or endorsed by any applicable Regulatory Authority in the Territory, or as otherwise specified in the Clinical Development Plan) and appropriate for regulatory and patent purposes, which are complete and accurate in all material respects and reflect all material Development work performed under the Clinical Development Plan. Epizyme shall have the right, upon reasonable advance notice, and no more than [**], to inspect and copy all such records (for clarity, including all applicable clinical, regulatory and quality records).

ARTICLE 5. LICENSED PRODUCT REGULATORY OBLIGATIONS

5.1 **Hutchmed Responsibility**. Other than the CTA for the 302 Global Trial (which was filed by Epizyme with the Regulatory Authorities in Mainland China and Taiwan prior to the Effective Date), and subject to Sections 3.10(a) and 4.1, Hutchmed shall use Commercially Reasonable Efforts to prepare Regulatory Filings and obtain (or cause to be obtained) and maintain Regulatory Approval and, if applicable, Reimbursement Approval, for a Licensed Product in each Initial Indication and Additional Indication in each of (i) Mainland China, (ii) Taiwan and (iii) Hong Kong and Macau (with it being agreed that, if Regulatory Approval is obtained in Hong Kong, Hutchmed shall not also be required to separately obtain Regulatory Approval in Macau, or vice versa) at Hutchmed's expense; provided that all IND or Drug Approval Applications for any Licensed Product in the Territory shall be filed only after approval by the JDC. All Regulatory Filings and communications with Regulatory Authorities in the Territory shall accurately reflect the datasets as presented by Epizyme in its Regulatory Filings outside of the Territory and provided to Hutchmed. For clarity, subject to Section 4.6, Epizyme may, without approval of the JDC, file an IND in the Territory for any Rejected Global Trial that includes clinical sites in the Territory; provided that Epizyme will provide a copy of such proposed IND to Hutchmed sufficiently in advance of the proposed filing of such IND and shall consider in good faith all comments made by Hutchmed with respect to such IND.

5.2 **Regulatory Documents**.

(a) **Epizyme Regulatory Documents**. Within [**] following the Effective Date, Epizyme shall make available to Hutchmed copies of the Epizyme Regulatory Documents listed on Schedule 5.2. Subject to Section 9.3(d) and (e), throughout the Term, to the extent required and permitted by Applicable Law, Epizyme shall, as soon as practicable, solely to the extent necessary to support Hutchmed's preparation and filing of any IND or Drug Approval Application with respect to any Licensed Product in the Field in the Territory, make available to Hutchmed copies of material Epizyme Regulatory Documents for the Licensed Product submitted to or received from the FDA after the Effective Date. Hutchmed shall reimburse Epizyme for any reasonable Out-of-Pocket Costs incurred by Epizyme or any of its Affiliates in fulfilling Epizyme's obligations under this Section 5.2(a) within [**] of receipt of an invoice therefor. Epizyme shall provide Hutchmed a reasonable opportunity to review all material Regulatory Filings outside the Territory for Joint Global Trials. For clarity, all Regulatory Documents made available by Epizyme hereunder shall be in the language in which they were prepared, and if not prepared in English or Mandarin Chinese,

Epizyme shall provide Hutchmed an English summary thereof. All Regulatory Filings and Regulatory Approvals outside the Territory shall be prepared, filed, and maintained at Epizyme's sole expense. Any Confidential Information of Hutchmed or any of its Affiliates that is incorporated into any Regulatory Documents filed in the name of or owned by any Epizyme Entity shall remain Confidential Information of Hutchmed or its applicable Affiliate(s). Any minutes from meetings with the FDA or a Regulatory Authority in the Territory regarding the Licensed Products shall be provided to Hutchmed in the language in which such minutes were drafted. Subject to the terms and conditions of this Agreement, during the Term Epizyme hereby grants to Hutchmed a "right of reference," as that term is defined in 21 C.F.R. § 314.3(b) and any non-U.S. counterpart to such regulation, pursuant to which the Hutchmed Entities shall be entitled at no cost to access, use, and reference the Epizyme Regulatory Documents for the Development, Manufacture or Commercialization of the Licensed Compound or Licensed Products in accordance with this Agreement. Upon request by Hutchmed, Epizyme shall provide a signed statement to this effect in accordance with 21 C.F.R. §314.50(g)(3) or any non-U.S. counterpart to such regulation.

(b) **Hutchmed Regulatory Documents.** Throughout the Term, Hutchmed shall make available to Epizyme copies of all Hutchmed Regulatory Documents to the extent described in this Section 5.2(b). Epizyme shall reimburse Hutchmed for any reasonable Out-of-Pocket Costs incurred by any Hutchmed Entities in fulfilling Hutchmed's obligations under this Section 5.2(b) within [**] of receipt of an invoice therefor. Hutchmed shall provide access to any material Regulatory Filing and an English summary thereof (if not drafted in English) as soon as practicable and provide Epizyme with an opportunity to review and comment on all material Regulatory Filings in the Territory and, subject to Section 3.10, shall consider Epizyme's comments in good faith. All Regulatory Filings and Regulatory Approvals in the Field in the Territory shall be prepared, filed, and maintained at Hutchmed's sole expense. Any Confidential Information of Epizyme or any of its Affiliates that is incorporated into any Regulatory Documents filed in the name of or owned by any Hutchmed Entity shall remain Confidential Information of Epizyme or its applicable Affiliate(s). Any minutes from meetings with a Regulatory Authority regarding the Licensed Products in the Territory shall be provided to Epizyme in the language in which such minutes were drafted. Subject to the terms and conditions of this Agreement, during the Term Hutchmed hereby grants to Epizyme a "right of reference," as that term is defined in 21 C.F.R. § 314.3(b) and any non-U.S. counterpart to such regulation, pursuant to which the Epizyme Entities shall be entitled at no cost to access, use, and reference the Hutchmed Regulatory Documents for the Development, Manufacture or Commercialization of the Licensed Compound or Licensed Products in accordance with this Agreement or outside the Territory. Upon request by Epizyme, Hutchmed shall provide a signed statement to this effect in accordance with 21 C.F.R. §314.50(g)(3) or any non-U.S. counterpart to such regulation.

(c) **Regulatory Liaisons**. Promptly (but in no event later than [**]) following the Effective Date, the Parties shall each designate an employee with responsibility for regulatory activities to consult with the other Party's representative with respect to the transfer of Regulatory Documents between the Parties (such representatives, the "**Regulatory Liaisons**"). The Regulatory Liaisons shall discuss and provide input to each other, at such times, places and frequencies as mutually agreed, on all material issues with respect to the sharing and transfer of Regulatory Documents; provided that all final decisions related to Regulatory Filings and Regulatory Approvals shall be made by the Party with the right to control such decision as set forth in Section 3.10.

5.3 **Ownership of Regulatory Filings and Approvals**. Epizyme shall transfer to Hutchmed the CTA for the 302 Global Trial in Mainland China and Taiwan as soon as practicable after the Effective Date. All Regulatory Filings and resulting Regulatory Approvals for Licensed Product in the Territory (and all corresponding applications for marketing or regulatory exclusivity) shall be applied for in the name of and exclusively owned by Hutchmed. If at the time of a Regulatory Filing, the Regulatory Authorities and Applicable Law in the Territory prohibit Hutchmed from filing and owning such Regulatory Filings and Regulatory Approvals in the Territory, then (a) all such Regulatory Filings and Regulatory Approvals shall

be applied for by Hutchmed in the name of and exclusively owned by Epizyme with Epizyme appointing Hutchmed and Hutchmed acting as Epizyme's sole Authorized Regulatory Agent, and (b) Epizyme will cooperate with Hutchmed, and provide necessary assistance to Hutchmed, to transfer such Regulatory Filings and Regulatory Approvals to Hutchmed at such time as Applicable Law no longer prohibits Hutchmed from filing and owning such Regulatory Filings and Regulatory Approvals in the Territory; provided that upon termination (but not expiration) of this Agreement for any reason all such Regulatory Filings and Regulatory Approvals will revert to the exclusive ownership of Epizyme, at no cost to Epizyme, and Hutchmed shall be obligated to take all actions and execute all documents as required by the Regulatory authority under Applicable Law to effect the transfer of such Regulatory Filings and Regulatory Approvals to Epizyme. All Regulatory Filings for any Rejected Global Trial that includes clinical sites in the Territory, if any, for the Development of Licensed Product in the Territory shall be applied for by Epizyme in the name of and exclusively owned by Epizyme unless and until Hutchmed makes a Buy-In Right Payment with respect to such Rejected Global Trial in which case the rest of this Section 5.3 will apply to such Regulatory Filings.

5.4 **Meetings with Regulatory Authorities**. To the extent practicable and permissible by Applicable Law and Regulatory Authorities, Hutchmed shall use good faith efforts to accommodate Epizyme so that Epizyme may have up to [**] employees or other representatives (who are bound by written obligations of nondisclosure and non-use no less stringent than those set forth in Article 10) participate at any material meetings with Regulatory Authorities in the Territory to discuss the Development or Commercialization of Licensed Products; provided that any exercise of such right by Epizyme shall not require Hutchmed to delay the Development or Commercialization of the Licensed Product, including by delaying in responding to Regulatory Authorities or in arranging any such meeting. Hutchmed shall provide Epizyme with reasonable notice prior to any such meetings.

5.5 **Adverse Drug Events**. Upon the earlier of [**] after the Effective Date or the date the first patient is enrolled into the first clinical trial of the Licensed Product in the Territory, the Parties shall enter into the Safety Data Exchange Agreement. Such Safety Data Exchange Agreement shall provide for Epizyme to hold and control, subject to Section 9.3(c)(iii), the global safety database for Tazemetostat and for the exchange by the Parties in English of any information of which a Party becomes aware concerning any adverse event experienced by a subject or patient being administered Tazemetostat, whether or not such adverse event is determined to be attributable to Tazemetostat, including any such information received by either Party from any Third Party (subject to receipt of any required consents from such Third Party). It is understood that each Party and, in the case of Epizyme, the Epizyme Entities, and, in the case of Hutchmed, the Hutchmed Entities, shall have the right to disclose such information if such disclosure is reasonably necessary to comply with Applicable Laws or requirements of any applicable Regulatory Authority. Hutchmed shall be responsible for handling all returns, recalls, suspensions and withdrawals of each Licensed Product in the Territory at its sole expense. The Safety Data Exchange Agreement will detail Hutchmed's responsibilities relating to such returns, recalls, suspensions and withdrawals.

5.6 **Complaints**. Each Party shall maintain a record of all non-medical and medical product-related complaints it receives with respect to the Licensed Compound or any Licensed Product. Each Party shall notify the other Party in English of any such complaint received by it in sufficient detail and in accordance with the timeframes and procedures for reporting established by the Parties, and in any event in sufficient time to allow each Epizyme Entity and each Hutchmed Entity to comply with any and all regulatory requirements imposed upon it, including in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ("ICH") guidelines. The Party that holds the applicable Regulatory Filing(s) in a particular country shall investigate and respond to all such complaints in such country with respect to the Licensed Compound or any Licensed Product as soon as reasonably practicable. All such responses shall be made in accordance with the procedures established

pursuant to the ICH, FDA, EMA, NMPA and other applicable guidelines. The Party responsible for responding to such complaint shall promptly provide the other Party a copy of any such response.

5.7 **No Admissions by Hutchmed**. If Hutchmed or any other Hutchmed Entity receives any complaint relating to the quality or condition of any Licensed Product or its packaging, or any Epizyme Trademark, from any Third Party, Hutchmed shall forthwith acknowledge receipt of such complaint but shall use good faith efforts not to make any admissions in respect thereof which it believes could reasonably be expected to result in liability to Epizyme (or any other Epizyme Entity), through indemnification or otherwise. Hutchmed shall notify Epizyme in writing as soon as practicable (and, to the extent permitted by Applicable Law, prior to notifying any Regulatory Authority), and in any event in sufficient time to permit all applicable Epizyme Entities to comply with all Applicable Laws for any matter relating to the safety of the Licensed Product, of receipt of such complaint. Hutchmed shall offer reasonable cooperation to Epizyme (and other Epizyme Entities designated by Epizyme) in investigating any complaint and the circumstances surrounding it and shall comply with any operating procedures that the Parties may agree upon in their Safety Data Exchange Agreement, Clinical Supply Agreement, Commercial Supply Agreement or Manufacturing Technology Transfer Agreement.

ARTICLE 6. LICENSED PRODUCT COMMERCIALIZATION

6.1 **Commercialization Plan**. In accordance with the Commercialization Plan (including the Launch Plan), Hutchmed (itself or through any other Hutchmed Entities) shall have the sole discretion and right to, and shall use Commercially Reasonable Efforts to, Commercialize (including booking sales, establishing pricing and related interactions with Governmental Authorities to be listed on the central or provincial reimbursement list, warehousing, commercial distribution, order processing, invoicing and collection) the Licensed Products in the Field in the Territory at its sole expense in each of (a) Mainland China, (b) Taiwan and (c) Hong Kong and Macau (it being understood that, if Hutchmed Commercializes Licensed Products in Hong Kong, it may be commercially reasonable to not separately also Commercialize Licensed Products in Macau).

The Commercialization Plan will be developed on a [**] rolling basis and include the then-current [**] and the following [**]. At least [**] prior to anticipated approval of the first Drug Approval Application for a Licensed Product in the Field in the Territory, Hutchmed shall present the draft Commercialization Plan (including the Launch Plan) to the JCC for review, discussion and approval (so long as it is consistent with the terms and conditions of this Agreement and Hutchmed has taken into consideration in good faith the Global Brand Strategy). Notwithstanding the foregoing, if the first approval of the first Drug Approval Application for a Licensed Product in the Field in the Territory may be obtained such that is not possible for Hutchmed to present a draft Commercialization Plan [**] in advance, Hutchmed shall present such draft Commercialization Plan as soon as possible. Within [**] prior to the anticipated approval of the first Drug Approval Application for a Licensed Product in the Field in the Territory, Hutchmed shall submit to the JCC the final Commercialization Plan (including the Launch Plan) for review, discussion, and approval. Each [**] after the approval of the first Drug Approval Application for a Licensed Product in the Field in the Territory, Hutchmed shall submit to the JCC the Commercialization Plan for review, discussion, and approval. The Parties shall ensure at all times that the Commercialization Plan is consistent with the terms and conditions of this Agreement, and Hutchmed shall consider in good faith the Global Brand Strategy and the Global Medical Affairs Strategy.

6.2 **Promotional Materials**. Hutchmed shall ensure that all promotional materials for the Licensed Products in the Territory are consistent with the approved labeling for such Licensed Products in the Territory and that the Global Brand Strategy has been considered in good faith. Hutchmed shall have sole responsibility for ensuring that such promotional materials comply in all respects with Applicable Law in the Territory including the Advertising Law of Mainland China and relevant regulations on advertisement

of pharmaceutical products. Hutchmed shall share the promotional materials used in the Territory by any Hutchmed Entity in connection with the Licensed Products in the Territory with the JCC on a regular basis, and the JCC shall have the right to review and comment on, which comments shall be considered in good faith by the Hutchmed Entities, any of the Hutchmed Entities' promotional materials prior to their use in the Territory.

6.3 **Commercialization Reports**. At least [**] in advance of each meeting of the JCC, for any meeting of the JCC following the First Commercial Sale of any Licensed Product in the Field in the Territory, Hutchmed shall provide the JCC with (a) a written report that summarizes Commercialization and Medical Affairs activities performed during the prior [**] period with respect to each Licensed Product in the Territory, (b) detailed sales reports for each [**] of the prior [**] period of each Licensed Product in the Territory, and (c) [**] sales forecasts for each Licensed Product in the Territory for the next [**]. Hutchmed shall provide an update of such report at each JCC meeting.

6.4 **Pricing**. Hutchmed will be solely responsible for pricing decisions for Licensed Products in the Territory. Notwithstanding the foregoing, Hutchmed's decision-making with respect to pricing decisions for Licensed Products in the Territory shall be subject to the following considerations: (i) Hutchmed will only discount the price for Licensed Products in the Territory in a manner consistent with the customary discounts that Hutchmed applies to its other oncology/hematology products that are covered by a composition of matter Patent Right in the Territory, and (ii) Hutchmed will not price Licensed Product as a "loss leader" in order to stimulate sales of its other oncology/hematology products, including for Other Combination Drugs that are Hutchmed Compounds.

6.5 **Standards of Conduct**. The Hutchmed Entities shall perform all Commercialization activities with respect to Licensed Products in the Field in the Territory (a) in a manner that takes the Global Brand Strategy into consideration in good faith, (b) in a professional and ethical business manner, (c) in compliance in all material respects with Applicable Laws and quality standards. Hutchmed shall ensure that the Medical Affairs strategy that each applicable Hutchmed Entity pursues for the Licensed Products in the Territory has taken into consideration in good faith the Global Medical Affairs Strategy.

6.6 **Trademarks**. Hutchmed shall use the Epizyme Marks and Epizyme Domains only in connection with Hutchmed's Development, Manufacture, and Commercialization of the Licensed Products in the Territory in accordance with the terms and conditions of this Agreement, including the trademark license terms set forth in Exhibit D, which are incorporated herein. Epizyme shall retain ownership of all of the Epizyme Marks and Epizyme Domains. Except as expressly provided in this Agreement, or except as otherwise required by Applicable Law or agreed by the Parties in advance in writing, neither Party shall have any right to use the other Party's or the other Party's Affiliates', and Hutchmed shall not have any right to use any Epizyme Entity's, Trademarks in connection with any Development, Manufacture or Commercialization of any Licensed Product. At Epizyme's option, and if permitted by local Applicable Laws in the Territory, each Licensed Product in the Territory shall be co-branded with the Epizyme name and Epizyme-designated corporate trademark, in a manner to be reasonably agreed by the Parties and subject to the terms of this Agreement, including the trademark license terms set forth in Exhibit D, with the Global Brand Strategy having been taken into consideration. If Hutchmed co-brands any Licensed Product with a Hutchmed Mark, the Global Brand Strategy having been taken into consideration, then all Hutchmed Marks will at all times during and after the Term remain the sole and exclusive property of Hutchmed, all use of, and goodwill associated with, the Hutchmed Marks will inure to the sole and exclusive benefit of Hutchmed, the Epizyme Marks and Hutchmed Marks will at all times remain separate trademarks, owned by their respective owners, and neither Party will "lock up" or otherwise combine Epizyme Marks and Hutchmed Marks to create a unitary composite mark. Except as set forth in Exhibit D, neither Party shall use any Trademark of the other Party in combination with another word, symbol, or design, without the prior written approval of the other Party.

ARTICLE 7. LICENSED PRODUCT MANUFACTURE AND SUPPLY

7.1 **Clinical Supply Agreement**. Within [**] after the Effective Date, or at such earlier or later date as may be mutually agreed in writing, the Parties will negotiate in good faith and enter into an agreement for clinical supply by Epizyme to Hutchmed of Drug Substance or Drug Product and a related quality agreement, each on terms consistent with this Agreement and otherwise on commercially reasonable terms (collectively, the "**Clinical Supply Agreement**"). The Clinical Supply Agreement will contain commercially reasonable terms including terms addressing forecasting, ordering, delivery, acceptance and rejection procedures, indemnification, limitations of liability, and quality assurance and control.

From and after the execution of the Clinical Supply Agreement and until Manufacturing Technology Transfer Completion, and subject to the terms of such Clinical Supply Agreement and this Agreement and compliance with Applicable Law, Epizyme will, either itself or through Third Parties, Manufacture and supply Hutchmed with Drug Substance and Drug Product in sufficient quantities for the Development activities for Licensed Products in the Field in the Territory by the Hutchmed Entities in accordance with the Clinical Development Plan, including supply by Epizyme of Drug Product for clinical sites in the Territory for Joint Global Trials and Local Trials. Hutchmed Entities shall not use any quantity of Drug Substance or Drug Product supplied by Epizyme hereunder for any purpose other than Pre-Clinical Research, Local Trials, or Joint Global Trials in the Field in the Territory in accordance with the CDP and the terms of this Agreement. For clarity, in no event shall Epizyme supply to Hutchmed under the Clinical Supply Agreement any quantity of Drug Substance or Drug Product co-formulated with an Other Combination Drug. For any quantity of Drug Substance or Drug Product supplied by Epizyme to Hutchmed pursuant to the Clinical Supply Agreement for the Development of Licensed Products in the Field in the Territory, Hutchmed shall pay to Epizyme the Clinical Supply Price for such quantity, payable within [**] after receipt of an invoice therefor.

7.2 **Drug Substance and Drug Product Manufacturing Technology Transfer**.

(a) Manufacturing Technology Transfer Plan. The Parties agree that the principles set forth on Schedule 7.2 shall form the basis for the Manufacturing Technology Transfer from Epizyme to Hutchmed which shall be conducted to enable Hutchmed to Manufacture clinical and commercial quantities of Drug Product and to enable Hutchmed or a Permitted Subcontractor CMO to Manufacture clinical and commercial quantities of Drug Substance, and which shall include the ongoing transfer of Manufacturing Activities under Section 7.4. At the first meeting of the JMC, the Parties shall commence formulating the detailed plan and budget based on Schedule 7.2 for the Manufacturing Technology Transfer to Hutchmed, which plan will be agreed upon by the JMC and set forth in an agreement to be executed by the Parties (the "**Manufacturing Technology Transfer Agreement**"). The Manufacturing Technology Transfer shall begin as soon as is practicable and continue until Hutchmed's facilities for DP or Hutchmed's or its Permitted Subcontractor CMO's facilities for DS have been qualified and otherwise received all Regulatory Approvals required to Manufacture DS or DP, as applicable ("**Manufacturing Technology Transfer Completion**"). The Parties agree to use Commercially Reasonable Efforts to achieve Manufacturing Technology Transfer Completion within [**] after commencement of the Manufacturing Technology Transfer (subject to the ongoing transfer of Manufacturing Activities under Section 7.4).

Except for the ongoing transfer of Manufacturing Activities under Section 7.4, Epizyme shall not be obligated to provide a Manufacturing Technology Transfer for Drug Substance and Drug Product more than [**], unless otherwise agreed upon by the Parties. All Drug Substance and Drug Product Manufactured by Hutchmed or a Permitted Subcontractor CMO shall be used solely in the Development and Commercialization of Licensed Compounds and Licensed Products in the Territory by Hutchmed Entities in accordance with the terms of this Agreement. Hutchmed and its Permitted Contractor CMO shall not

Manufacture any quantity of Drug Substance or Drug Product co-formulated with an Other Combination Drug.

The Manufacturing Technology Transfer shall be at Hutchmed's cost and expense to the extent incurred in accordance with the budget to be included in the Manufacturing Technology Transfer Agreement, and shall be at Epizyme's costs and expense to the extent in excess of such budget. Hutchmed shall pay to Epizyme an amount equal to all of Epizyme's and its Affiliates' reasonable, documented internal costs (for FTEs at the FTE Rate) and Out-of-Pocket Costs related to any further activities in connection with such Manufacturing Technology Transfer in accordance with such budget.

(b) Manufacture by Hutchmed. Following Manufacturing Technology Transfer Completion, Hutchmed shall be responsible for producing, at its sole expense, Drug Substance and Drug Product, including labeling and packaging activities, for Development and Commercial use in the Field and in the Territory. Hutchmed shall only be permitted to Manufacture Drug Substance itself or through a Permitted Subcontractor CMO or Drug Product itself. Hutchmed shall conduct such Manufacturing in compliance with GMP and all Applicable Laws. Following Manufacturing Technology Transfer Completion, the Clinical Supply Agreement and Commercial Supply Agreement, if any, shall terminate, and Epizyme shall have no further obligation to supply Drug Substance or Drug Product for Development or Commercial use by Hutchmed. Epizyme shall have the right, at Epizyme's sole cost and expense, no more than [**] or more frequently if Epizyme has reason to believe (as demonstrated by reasonable evidence and provided to Hutchmed) that Hutchmed is in material breach of its obligations under this Agreement relating to Manufacturing, at any time upon reasonable advance notice of no less than [**], to inspect Hutchmed's or the applicable Permitted Subcontractor CMO's facilities in which Drug Substance or Drug Product are Manufactured.

(c) Epizyme Manufacturing Know-How. Hutchmed shall provide to Epizyme all Epizyme Manufacturing Know-How conceived, identified, discovered, authored, developed, or reduced to practice by or on behalf of any Hutchmed Entity during the Term. These documents shall be provided to Epizyme in English if drafted in English or, if not drafted in English, then in the original version with a summary in English.

(d) Specifications. Hutchmed shall ensure that any Manufacturing of Licensed Compound or Licensed Products conducted by Hutchmed or a Permitted Subcontractor CMO is to specifications attached to the Manufacturing Technology Transfer Agreement, as such specifications may be updated in accordance with the terms of the Manufacturing Technology Agreement and is consistent with the license granted to Hutchmed in Section 2.1(f).

(e) Secondary Source. The Manufacturing Technology Transfer Agreement shall include the option for Epizyme to obtain DS from Hutchmed's Permitted Subcontractor CMO as a secondary supplier on commercially reasonable terms to be mutually agreed.

7.3 **Commercial Supply**. In the event that it is anticipated that Manufacturing Technology Transfer Completion will not be achieved sufficiently in advance of the launch of the first Licensed Product in the Territory, or at such earlier or later date as may be mutually agreed in writing, the Parties will negotiate in good faith and enter into an agreement for commercial supply by Epizyme to Hutchmed of Drug Substance or Drug Product, as applicable, and a related quality agreement, each on terms consistent with this Agreement and otherwise on commercially reasonable terms (collectively, the "**Commercial Supply Agreement**"). The Commercial Supply Agreement contain commercially reasonable terms including terms addressing forecasting, ordering, delivery, acceptance and rejection procedures, indemnification, limitations of liability, and quality assurance and control.

From and after the execution of the Commercial Supply Agreement and until Manufacturing Technology Transfer Completion under Section 7.2, and subject to the terms of such Commercial Supply Agreement and this Agreement and compliance with Applicable Law, Epizyme will, either itself or through Third Parties, Manufacture and supply Hutchmed with Drug Product in reasonably sufficient quantities for the Commercialization of Licensed Products in the Field in the Territory by the Hutchmed Entities in accordance with the Commercialization Plan and the terms of this Agreement. Hutchmed Entities shall not use any quantity of Drug Product supplied by Epizyme for any purpose other than Commercialization in the Field and Territory in accordance with the Commercialization Plan and the terms of this Agreement, and Epizyme shall not be obligated under the Commercial Supply Agreement to supply quantities of Drug Product in excess of the forecasted quantity that Hutchmed notifies Epizyme, and Epizyme reasonably agrees, is needed to perform the Commercialization activities in the Territory. In addition, in no event shall Epizyme supply to Hutchmed under the Commercial Supply Agreement any quantity of Drug Product co-formulated with an Other Combination Drug. For any quantity of Drug Product supplied by Epizyme to Hutchmed for purposes of Commercialization of Licensed Products in the Field in the Territory, Hutchmed shall pay to Epizyme the Commercial Supply Price for such quantity, payable within [**] after receipt of an invoice therefor.

7.4 **Other Manufacturing Activities and Costs**.

(a) CMC Section Filings. Upon written request of Hutchmed, Epizyme shall reasonably support the development of data or information for the submission of the CMC section of any Regulatory Filing in the Territory under Article 5, and Hutchmed shall pay Epizyme the Manufacturing Activity Cost associated with such support within [**] after receipt of any invoice therefor.

(b) Process Development. Epizyme may (in its discretion) or shall (as mutually agreed by the Parties or required by any Regulatory Authority), perform or support the development and implementation of (i) a new dosage, form, or formulation changes for any Licensed Product (each, a "**Dosage Form Change**"), or (ii) process development, process improvement, manufacturing lifecycle management, or other Manufacturing activities to improve the yield, efficiency, or proprietary nature of the Manufacturing process for any Licensed Product (each, a "**Manufacturing Improvement**" and, along with a Dosage Form Change, individually and collectively referred to as a "**Manufacturing Activity**").

As more fully described in the Clinical Supply Agreement, Commercial Supply Agreement, and Manufacturing Technology Transfer Agreement, in the event Epizyme undertakes any Manufacturing Activity in its discretion, as mutually agreed, or as required by any Regulatory Authority in the Territory, and it results in a Dosage Form Change or Manufacturing Improvement, then such Dosage Form Change or Manufacturing Improvement, as applicable shall automatically be included within the Epizyme Manufacturing Know-How. If such Manufacturing Activity was developed at Hutchmed's request or required by a Regulatory Authority only for the Territory, then Hutchmed shall pay the full Manufacturing Activity Costs associated therewith; provided, however, that if such Manufacturing Activity has applicability for Licensed Products outside the Territory, then Hutchmed shall only be obligated to pay the portion of the Manufacturing Activity Costs associated therewith as reasonably allocated to jurisdictions outside the Territory on a proportionate basis. In addition to the Clinical Supply Price and Commercial Supply Price payments, Hutchmed shall pay to Epizyme any Manufacturing Activity Costs due and payable under this Section on a [**] basis, within [**] of receipt of an invoice therefor.

7.5 **Epizyme Supply Chain Security Requirements**. Hutchmed commits to refrain, and to use Commercially Reasonable Efforts to cause each Hutchmed Entity to refrain, from selling Licensed Product to unauthorized Third Parties or end users under Trade Control Laws such as any military and law enforcement parties of comprehensively Sanctioned Countries, including military hospitals where prohibited by applicable Trade Control Laws. Hutchmed shall perform this Agreement in the Territory in

compliance with Trade Control Laws as defined herein and within the limits set forth by any applicable OFAC Authorization. Hutchmed acknowledges and will use Commercially Reasonable Efforts to ensure that any Hutchmed Entity shall comply in connection herewith with Trade Control Laws and the scope of any applicable OFAC Authorization. Hutchmed shall use Commercially Reasonable Efforts to ensure that this duty to comply with such Trade Control Laws and the prohibitions or restrictions it involves will be reflected in the agreement to be entered into by Hutchmed and each Hutchmed Entity. Such OFAC Authorization or Trade Control Laws may restrict the selling of Licensed Products to specific Third Parties as mentioned therein. While storing, handling or distributing the Licensed Products, Hutchmed Entities shall make all reasonable efforts to comply with Epizyme supply chain security requirements set forth in Schedule 7.5 attached hereto, as may be amended by Epizyme from time to time, in order in particular to verify the security and integrity of the Licensed Products through all points of the supply chain. Hutchmed shall also use Commercially Reasonable Efforts to ensure that any Permitted Subcontractors used by Hutchmed in the distribution of the Licensed Products are duly informed of such requirements and make reasonable efforts to comply with these requirements. Hutchmed expressly agrees it will not do anything under this Agreement, directly or knowingly indirectly, which foreseeably would cause Epizyme to be in breach of Trade Control Laws. In the event that, in connection with the activities contemplated by this Agreement, Hutchmed violates any Trade Control Law or the terms or conditions set by the OFAC Authorization to any Sanctioned Countries (or in the case of a Hutchmed Entity, the Hutchmed Entity commits such violation and Hutchmed fails to terminate its agreement with the Hutchmed Entity upon becoming aware of such violation), or breaches any provision in this Section 7.5, Epizyme shall have the right to unilaterally terminate this Agreement pursuant to Section 14.4, except that the cure period set forth therein shall not apply.

7.6 **Supply of Certain Other Combination Drugs**.

(a) As mutually agreed by the Parties, any Other Combination Drugs that are part of any Epizyme Combination Therapy that is the subject of any Joint Global Trial or Local Trial of such Epizyme Combination Therapy and at the relevant time are (i) Controlled by Epizyme, shall be supplied to Hutchmed by Epizyme, or (ii) Controlled by Hutchmed or readily available from any Third Party, shall be obtained by Hutchmed, at Hutchmed's expense for Joint Global Trials in the Territory or Local Trials. With respect to any Other Combination Drugs supplied by Epizyme hereunder, (1) the quantity shall be agreed upon at the JDC in advance on a [**] basis, (2) Hutchmed shall only use such Other Combination Drugs in the Territory in the Joint Global Trial, or Local Trial and (3) Hutchmed shall pay to Epizyme the Fully-Burdened Cost of any such quantity of such Other Combination Drugs in advance within [**] of receipt of an invoice therefor.

(b) Hutchmed shall supply to Epizyme the Other Combination Drugs that (i) are at the relevant time Controlled by Hutchmed, and (ii) are part of any Joint Combination Therapy that is the subject of any Joint Global Trial or Rejected Global Trial of such Joint Combination Therapy. The quantity of such Other Combination Drugs to be supplied by Hutchmed hereunder shall be agreed upon at the JDC in advance on a [**] basis, and Epizyme shall only use such Other Combination Drugs outside the Territory in the performance of a Joint Global Trial or in and outside the Territory in the performance of a Rejected Global Trial. Epizyme shall pay to Hutchmed the Fully-Burdened Cost of any such quantity of such Other Combination Drugs in advance within [**] of receipt of an invoice therefor.

ARTICLE 8. EPIZYME'S RIGHTS TO NEGOTIATE

8.1 **Epizyme ROFN outside the Territory**.

(a) Grant of ROFN. Subject to the terms of this Section 8.1, during the ROFN Term, Epizyme will have a one-time exclusive right of first negotiation ("**ROFN**") with respect to Hutchmed Dual Inhibitor

Products outside of the Territory. In the event Epizyme provides written notice to Hutchmed during the ROFN Term that it wishes to obtain the exclusive or co-exclusive (with Hutchmed) right to Develop and Commercialize Hutchmed Dual Inhibitor Products outside of the Territory ("**ROFN Notice**"), Hutchmed will provide Epizyme with data and information regarding the status of the Development and Commercialization of the Hutchmed Dual Inhibitor Products.

As used in this Agreement, "**ROFN Term**" means the period of time commencing on [**] and ending on [**]; provided that, if the last day of the month in which Hutchmed provides notice to Epizyme that the ROFN POC Date has occurred is prior to the commencement of the ROFN Term, then the ROFN shall lapse unless, at Epizyme's discretion, Epizyme pays the ROFN Term Payment for each month between the ROFN POC Date and [**] pursuant to Section 9.7. If Epizyme does not pay the ROFN Term Payment after the ROFN POC Date and until the commencement of the ROFN Term pursuant to Section 9.7, the ROFN will expire on the ROFN POC Date. As used in this Agreement, "**ROFN POC Date**" means the earlier of (i) the date upon which Hutchmed or any Affiliate or licensee [**] Hutchmed Dual Inhibitor Product in the Territory or (ii) the date upon which Hutchmed or any Affiliate or licensee [**] Hutchmed Dual Inhibitor Product in the Territory. Hutchmed shall provide prompt written notice to Epizyme of the occurrence of the ROFN POC Date.

From the Effective Date and until the expiration of the ROFN Term and ROFN Negotiation Period, if any, Hutchmed and its Affiliates shall not: (A) Develop any Hutchmed Dual Inhibitor Product for use as part of a combination therapy in or outside the Territory in the Hutchmed Non-Compete Field, (B) Develop any Hutchmed Dual Inhibitor Product for use as a monotherapy in or outside the Territory in the Hutchmed Non-Compete Field, provided that, notwithstanding the foregoing, Hutchmed or its Affiliates may conduct in or outside the Territory one or more Phase 1 Clinical Trial and only one Phase 2 Clinical Trial of the Hutchmed Dual Inhibitor as a monotherapy per indication in any indication, (C) Commercialize any Hutchmed Dual Inhibitor Product outside the Territory, (D) negotiate or engage in discussions with, nor grant any rights of any kind to, any Third Party with respect to the Development or Commercialization of any Hutchmed Dual Inhibitor Product and Hutchmed Dual Inhibitor Product IP outside of the Territory, or (E) Develop or Commercialize in or outside of the Territory the Hutchmed Dual Inhibitor Product for use in any combination therapy where any other active pharmaceutical ingredient in such combination therapy is in the same Drug Class as an Other Combination Drug that is part of a Combination Therapy with a Licensed Product being Developed or Commercialized by a Hutchmed Entity under this Agreement or by an Epizyme Entity.

(b) License Agreement Negotiations. During the period commencing with the date of the ROFN Notice and continuing for [**] (or such longer period as the Parties may agree) (the "**ROFN Negotiation Period**"), the Parties shall negotiate in good faith the commercially reasonable terms and conditions of a license agreement for a royalty-bearing license, with the right to sublicense, under any Patent Rights and Know-How Controlled by Hutchmed during the term of the license agreement that comprise or encompass, generically or specifically, or are necessary or reasonably useful for the Development or Commercialization of any Hutchmed Dual Inhibitor Product (whether as a monotherapy or a combination therapy) (the "**Hutchmed Dual Inhibitor Product IP**"), which license shall be (i) either, at Epizyme's discretion, an exclusive or co-exclusive (with Hutchmed) license to Develop Hutchmed Dual Inhibitor Products, and (ii) either, at Epizyme's discretion, an exclusive or co-exclusive (with Hutchmed) license to Commercialize Hutchmed Dual Inhibitor Products, in each case ((i) and (ii)) in one or more countries outside of the Territory as selected by Epizyme (the "**ROFN Epizyme Territory**"). The license agreement will include customary terms including the following terms: (A) payment by Hutchmed to Epizyme of a royalty of [**] percent ([**]%) on net sales by Hutchmed or any Affiliate or licensee in the Territory of any Hutchmed Dual Inhibitor Product (whether as a monotherapy or combination therapy) for ten (10) years from the date of first commercial sale of the Hutchmed Dual Inhibitor Product, (B) payment by Epizyme to Hutchmed of reasonable upfront payment, milestone fees, and royalties on net sales of Hutchmed Dual Inhibitor Products

(whether as a monotherapy or combination therapy) in the ROFN Epizyme Territory, and (C) terms pertaining to the supply or Manufacture of Hutchmed Dual Inhibitor Products for the ROFN Epizyme Territory.

(c) No License Agreement Finalized. In the event that Epizyme fails to provide the ROFN Notice during the ROFN Term or the Parties fail to execute a license agreement under the Hutchmed Dual Inhibitor Product IP for Hutchmed Dual Inhibitor Products within the ROFN Negotiation Period, then except as set forth below, the ROFN shall expire, Hutchmed shall have no further obligation to Epizyme under this Agreement with regard to Hutchmed's interest in such Hutchmed Dual Inhibitor Product IP and Hutchmed Dual Inhibitor Products, and Hutchmed may license such Hutchmed Dual Inhibitor Product IP to any Third Party or freely exploit itself or through its Affiliates such Hutchmed Dual Inhibitor Product IP; provided, however, that if Epizyme provided the ROFN Notice during the ROFN Term but the Parties did not execute a license agreement, (i) Hutchmed shall not enter into a license agreement within [**] after the end of the ROFN Negotiation Period with any Third Party for Hutchmed Dual Inhibitor Products and Hutchmed Dual Inhibitor IP in the ROFN Epizyme Territory under license terms that Hutchmed reasonably believes are more favorable to the Third Party than the terms last offered by Epizyme to Hutchmed for the Hutchmed Dual Inhibitor Products and Hutchmed Dual Inhibitor Product IP (taking into account any differences between the scope of the proposed license agreement with such Third Party and with Epizyme, including any differences between the ROFN Epizyme Territory and the territory of such Third Party license), unless such terms are first offered to Epizyme during such [**] period and Epizyme declines such terms, and (ii) Hutchmed shall pay Epizyme (A) a royalty of [**] percent ([**]%) of net sales by Hutchmed, or any Affiliate or licensee of any Hutchmed Dual Inhibitor Product (whether as a monotherapy or combination therapy) in the Territory for a period of ten (10) years from the date of first commercial sale of the Hutchmed Dual Inhibitor Product, and (B) a royalty of [**] percent ([**]%) on net sales by Hutchmed, or any Affiliate or licensee of any Hutchmed Dual Inhibitor Product (whether as a monotherapy or combination therapy) outside of the Territory in any country in which Licensed Product is sold for a period of ten (10) years from the date of first commercial sale of the Hutchmed Dual Inhibitor Product in such country.

(d) No Rights. In no event shall any Licensed IP, Joint Combination Therapy IP, Confidential Information of Epizyme, Epizyme Product Data, Epizyme Regulatory Documents or any quantity of Licensed Compound or Licensed Product provided by Epizyme under this Agreement be used in the Development, Manufacture, or Commercialization of any Hutchmed Dual Inhibitor Product by any Hutchmed Entity inside or outside of the Territory at any time. For clarity, as of the Effective Date, Epizyme does not Control the Hutchmed Dual Inhibitor Product or any intellectual property rights therein and will not Control the Hutchmed Dual Inhibitor Product or any intellectual property rights therein unless and until Epizyme exercises its ROFN below and the Parties execute a license agreement pertaining to the Hutchmed Dual Inhibitor Product as provided in this Section 8.1. Epizyme is not obligated under this Agreement to provide, and shall not provide, any assistance to Hutchmed with respect to the Hutchmed Dual Inhibitor unless and until the Parties enter into a license agreement under this Section 8.1.

8.2 **Potential Collaboration for Hutchmed Compounds and Joint Combination Therapies**. Commencing as soon as practicable after the Effective Date, the Parties agree to discuss and negotiate in good faith the commercially reasonable terms and conditions of a written agreement pursuant to which Epizyme and Hutchmed shall collaborate in the Development or Commercialization in the United States of one or more Joint Combination Therapies consisting of Licensed Compound and Hutchmed Compounds; provided that, neither Party is under any obligation to enter into such a written agreement pursuant to this Section 8.2, and either Party can discontinue such negotiations at any time after the Effective Date without obligation to the other Party.

ARTICLE 9. CONSIDERATION

9.1 **Upfront Payment**. Within [**] after the Effective Date, Hutchmed shall pay Epizyme a one-time, non-refundable, non-creditable upfront payment of Twenty-five Million Dollars ($25,000,000) by wire transfer.

9.2 **Warrant**. Concurrently with the Effective Date, the Parties will execute a warrant in the form attached hereto as Exhibit C (the "**Warrant**").

9.3 **Development Costs and Other Hutchmed Costs**.

(a) Hutchmed Responsibilities. Hutchmed shall pay to Epizyme the amounts described elsewhere in this Agreement including in Sections 2.6(a) and 5.2 and Article 7 in accordance with the procedures set forth in such Sections.

(b) Each Party's Responsibility. Except as expressly provided in this Agreement or the Clinical Development Plan, each Party shall bear its own internal and Out-of-Pocket Costs incurred in the performance of its obligations under Article 4. For clarity, Hutchmed shall be responsible for all Development costs and expenses incurred for Local Trials of the Licensed Product in the Territory.

(c) Joint Global Trial. Notwithstanding anything to the contrary in Section 9.3(b), for any Joint Global Trial and except as provided in Section 4.5(d) and (e):

(i) Hutchmed shall be responsible for all costs for patients enrolled and treated in such Joint Global Trial in the Territory for up to its twenty percent (20%) share of the total number of patients enrolled and treated globally in such Joint Global Trial, including the Fully-Burdened Cost of Licensed Product or any Other Combination Drug included in a Combination Therapy for such patients;

(ii) Epizyme shall be responsible for (A) all costs for patients enrolled and treated in such Joint Global Trial in the Territory in excess of Hutchmed's share of twenty percent (20%) of such patients enrolled and treated globally in such Joint Global Trial under subsection (i) above, including internal and Out-of-Pocket Costs incurred by Hutchmed, and (B) all costs incurred by Epizyme Entities for patients enrolled and treated in such Joint Global Trial outside of the Territory; and

(iii) the Parties will share any global costs that are not territory-specific (e.g., costs of a global safety database or Epizyme CRO costs solely for global activities and not costs related to the enrollment of patients in clinical sites) incurred by Epizyme Entities for any Joint Global Trial in accordance with and not in excess of the budget approved by the JDC pursuant to Section 3.3(h), with Epizyme bearing eighty percent (80%) of such costs and Hutchmed bearing twenty percent (20%) of such costs. Within [**] (or if such payment is being made from an account in Mainland China, including where Hutchmed is receiving funds from Hutchmed China for such payment, [**]) following the end of each Calendar Quarter in which a Joint Global Trial is being conducted, Epizyme shall provide to Hutchmed a report setting forth in reasonable detail all such costs incurred by Epizyme Entities during the preceding Calendar Quarter, along with reasonable supporting documentation, and the latest budget for such costs that are projected for the next Calendar Quarter (the "**Quarterly Cost Report**"). Concurrent with providing a Quarterly Cost Report, Epizyme shall invoice Hutchmed for the amounts set forth in this Section and Hutchmed shall pay all undisputed amounts payable under such invoice within [**] after receipt of the invoice.

(d) Buy-In Right Payment. Notwithstanding Hutchmed's rights pursuant to Section 2.1 or Hutchmed's access rights pursuant to Sections 2.6(a), 2.7(a) or 5.3, for any Rejected Global Trial, after the completion of such Rejected Global Trial and upon request by Hutchmed, Epizyme shall provide to Hutchmed the data generated from such Rejected Global Trial in sufficient detail for Hutchmed to assess its interest in exercising its Buy-In Right hereunder and a summary of Epizyme's and Epizyme Entities' internal costs and Out-of-Pocket Costs incurred with regard to such Rejected Global Trial on a worldwide basis solely for Hutchmed's use in determining whether to purchase rights to access, use and refer to such data in accordance with this Section 9.3(d). If after reviewing the data, Hutchmed decides in its sole discretion that it wishes to obtain the access and right of reference to all of the data or Epizyme Regulatory Documents arising out of such Rejected Global Trial, Hutchmed shall so notify Epizyme, Epizyme shall invoice Hutchmed [**] percent ([**]%) of Epizyme's and Epizyme Entities' internal costs and Out-of-Pocket Costs incurred with regard to such Rejected Global Trial on a worldwide basis ("**Buy-In Right Payment**") and Hutchmed shall pay such Buy-In Right Payment within [**] after receipt of the invoice. Upon the receipt of the Buy-In Right Payment from Hutchmed, all such data shall be transferred to Hutchmed and shall automatically become Epizyme Product Data. For clarity, at all times, safety data from both within and outside the Territory shall be shared between the Parties under this Agreement and the Safety Data Exchange Agreement at no cost to the recipient Party in order to fulfill regulatory requirements.

(e) True-Up Payment. The Parties agree that clinical data from any Joint Global Trial will not be subject to a Buy-In Right Payment obligation under Section 9.3(d), except that, notwithstanding Hutchmed's rights pursuant to Section 2.1 or Hutchmed's access rights pursuant to Sections 2.6(a), 2.7(a) or 5.3, if Hutchmed or other Hutchmed Entities participate in a Joint Global Trial but do not enroll and treat in the Territory twenty percent (20%) of the total number of patients enrolled or treated globally, then upon completion of such Joint Global Trial, Hutchmed will not have the right to access or use or right of reference to the clinical data or Epizyme Regulatory Documents arising out of such Joint Global Trial unless and until Hutchmed pays Epizyme an amount equal to the product of (i) twenty percent (20%) less the quotient of (A) the total number of patients enrolled and treated in such Joint Global Trial in the Territory divided by (B) the total number of patients enrolled and treated globally in such Joint Global Trial (including such patients enrolled and treated in the Territory), multiplied by (ii) Epizyme's and Epizyme Entities' internal costs and Out-of-Pocket Costs incurred in the performance of such Joint Global Trial on a worldwide basis, and (iii) [**] percent ([**]%) (the "**True-Up Payment**"). Upon receipt of the True-Up Payment from Hutchmed, all such Regulatory Documents from such Joint Global Trial shall automatically become Epizyme Regulatory Documents, all such clinical data from such Joint Global Trial shall automatically become Epizyme Product Data, and all other Know-How arising out of such Joint Global Trial shall automatically become Epizyme Know-How. For clarity, at all times, safety data from both within and outside the Territory shall be shared by the Parties under this Agreement and the Safety Data Exchange Agreement at no cost to the recipient Party in order to fulfill regulatory requirements. Epizyme shall invoice Hutchmed for any True-Up Payment and Hutchmed shall pay such amount within [**] after receipt of the invoice.

By way of example and not limitation, if the following figures apply to a Joint Global Trial, then the True-Up Payment shall be $[**].

[**]

9.4 **Licensed Product Development Milestone Payment**.

(a) Hutchmed shall make the non-refundable, non-creditable, one-time milestone payments to Epizyme set forth in the table below no later than [**] (or if such payment is being made from an account in Mainland China, including where Hutchmed is receiving funds from Hutchmed China for such payment, [**]) after the earliest date on which the corresponding milestone event ("**Milestone Event**") has been

achieved by any Hutchmed Entity with respect to any Licensed Product to achieve such milestone event, regardless of whether such milestone event was achieved for such Licensed Product as a monotherapy or as part of a Combination Therapy. Each of the milestone payments set forth in this Section 9.4(a) is payable only upon the first achievement of the corresponding Milestone Event by the first Licensed Product to achieve such Milestone Event and shall not be payable by any subsequent Licensed Product that achieves such Milestone Event For clarity, none of the Development milestone payments shall be payable more than once.

Development and Regulatory Milestone Event	Milestone Payment
[**]	[**]
[**]	[**]
[**]	[**]
[**]	[**]
[**]	[**]
[**]	[**]
[**]	[**]
[**]	[**]
[**]	[**]
[**]	[**]
[**]	[**]
[**]	[**]
[**]	[**]

(b) Notwithstanding the foregoing, with respect to each of Milestone Events [**] through [**] above, the corresponding milestone payment will be made in full upon the achievement of such Milestone Event in [**] prior to its achievement in [**], and in the event any such Milestone Event is achieved in [**] prior to its achievement in [**], then [**] percent ([**]%) of the relevant milestone payment shall be made upon the achievement of the Milestone Event in [**], and the remaining [**] percent ([**]%) of the relevant milestone payment shall be made upon the achievement of the Milestone Event in [**]. For the clarity, the first achievement in [**] or [**] of any Milestone Event [**] through [**] above will not trigger any milestone payment obligations with respect to such Milestone Events. With respect to each of Milestone Events [**] through [**] above, if an applicable [**] hereunder, then the milestone payment for the applicable Milestone Event [**] through [**] shall become due upon [**]. For clarity, only one payment of either $[**] or $[**] shall become due upon the achievement of each of Milestone Events [**].

(c) Upon achievement by any Hutchmed Entity of any of the Milestone Events listed above, Hutchmed shall promptly (but in no event more than [**] (or if such payment is being made from an account in the Mainland China, including where Hutchmed is receiving funds from Hutchmed China for such payment, [**]) after such achievement) notify Epizyme of such achievement. For the avoidance of doubt,

the maximum aggregate amount payable by Hutchmed to Epizyme pursuant to this Section 9.4 is One Hundred Ten Million Dollars ($110,000,000).

9.5 **Licensed Product Sales Milestone Payments**. Hutchmed shall pay to Epizyme the following non-refundable and non-creditable amounts after the first achievement of aggregate Net Sales of all Licensed Products (whether as a monotherapy or as part of a Combination Therapy) in the Territory in a Calendar Year that meet or exceed the minimum annual Net Sales thresholds set forth below, which payment shall be made no later than [**] (or if such payment is being made from an account in the Mainland China, including where Hutchmed is receiving funds from Hutchmed China for such payment, [**]) after the end of the Calendar Quarter within which the applicable Calendar Year threshold(s) is(are) met or exceeded:

Sales Milestone Threshold	Milestone Payment
$[**] in aggregate Net Sales of Licensed Products in the Territory	$[**]
$[**] in aggregate Net Sales of Licensed Products in the Territory	$[**]
$[**] in aggregate Net Sales of Licensed Products in the Territory	$[**]
$[**] in aggregate Net Sales of Licensed Products in the Territory	$[**]

Each milestone payment in this Section 9.5 shall be payable only once upon the first achievement of such milestone in a given Calendar Year and no amounts shall be due for subsequent or repeated achievements of such milestone in subsequent Calendar Years. For clarity, the Net Sales of all Licensed Products in the Territory in a Calendar Year shall be aggregated for purposes of determining whether any milestone in the table above has been met. If more than one of the milestones set forth in the table above are first achieved in a single Calendar Year, then Hutchmed shall pay to Epizyme in such Calendar Year all of the payments corresponding to all of the milestones achieved in such Calendar Year under this Section 9.5.

9.6 **Royalties**.

(a) Licensed Product Royalty Rate. In addition to any royalties due to Third Parties under any Epizyme New In-License Agreements accepted by Hutchmed under Section 2.7(a), and subject to the remainder of this Section 9.6, Hutchmed shall pay Epizyme the following royalties on aggregate Net Sales of all Licensed Products (whether as a monotherapy or as part of a Combination Therapy) in the Territory, at an incremental royalty rate determined by aggregate Net Sales of all Licensed Products in each Calendar Year during the Royalty Term in the Territory:

Calendar Year Cumulative Net Sales in the Territory	Royalty Rate
Portion of Net Sales less than $[**]	[**]%
Portion of Net Sales equal to or greater than $[**] and less than $[**]	[**]%
Portion of Net Sales equal to or greater than $[**] and less than $[**]	[**]%
Portion of Net Sales equal to or greater than $[**]	[**]%

By way of example and not limitation, if aggregate Net Sales of all Licensed Products in the Territory in a Calendar Year are [**] Dollars ($[**]) and there are no Epizyme New In-License Agreements, then the royalty due to Epizyme shall be [**].

Running royalties paid by Hutchmed under this Section 9.6(a) shall be paid on a Licensed Product-by-Licensed Product and Jurisdiction-by-Jurisdiction basis commencing with the First Commercial Sale of

such Licensed Product in the such Jurisdiction and continuing until the latest of (i) the expiration of Patent-Based Exclusivity with respect to such Licensed Product in such Jurisdiction, (ii) expiration of Regulatory-Based Exclusivity with respect to such Licensed Product in such Jurisdiction, or (iii) the tenth (10th) anniversary of the First Commercial Sale of such Licensed Product in such Jurisdiction (each, a "**Royalty Term**"). Following the expiration of the Royalty Term with respect to a particular Licensed Product in the Field in the Territory (but not following an earlier termination of this Agreement), the licenses granted by Epizyme to Hutchmed pursuant to Section 2.1 with respect to such Licensed Product in the Field in the Territory shall be perpetual, irrevocable, fully-paid and royalty-free, and freely sublicensable through multiple tiers and not subject to Section 2.4 and Net Sales of such Licensed Product shall no longer be included in the aggregate Net Sales calculation in Section 9.5 or 9.6(a). For clarity, the Royalty Term is determined on a Jurisdiction-by-Jurisdiction basis but the applicable royalty rate in the table above for each Jurisdiction is determined based on cumulative Calendar Year Net Sales in the Territory.

(b) Royalty Reductions.

(i) No Patent-Based or Regulatory-Based Exclusivity. The foregoing provisions of this Section 9.6 notwithstanding, the royalties payable with respect to Net Sales of Licensed Products shall be reduced, on a Licensed Product-by-Licensed Product basis, to [**] percent ([**]%) of the amounts otherwise payable pursuant to Section 9.6(a) during any portion of the Royalty Term when either Patent-Based Exclusivity or Regulatory-Based Exclusivity does not apply to such Licensed Product in the Territory.

(ii) Royalty Reduction for Comparable Third Party Product Competition. If on a Licensed Product-by-Licensed Product and Calendar Quarter-by-Calendar Quarter basis, during the applicable Royalty Term (or portion thereof), (A) Comparable Third Party Product Competition is present with respect to such Licensed Product in the Territory during such Calendar Quarter, or (B) a court or a Governmental Authority of competent jurisdiction requires Epizyme or any Hutchmed Entity to grant a compulsory license to a Third Party permitting such Third Party to make and sell such Licensed Product in the Territory (such Licensed Product when sold by such Third Party, a "**Compulsory Third Party Product**"), and such Compulsory Third Party Product(s) have a market share of [**] percent ([**]%) or more of the aggregate market in the Territory of the applicable Licensed Product and the Compulsory Third Party Product(s) collectively (based on sales of units of such Licensed Product and such Compulsory Third Party Product(s), as reported by IQVIA, or if such data are not available, such other reliable data source as reasonably determined by Epizyme and Hutchmed (as used herein, a "unit" of a product means the equivalent amount of product used for an equivalent treatment cycle of such product)), then, in each case of clause (A) or (B), the royalty rate under Section 9.6(a) applicable to the Net Sales of such Licensed Product in the Territory and Calendar Quarter shall be reduced by [**] percent ([**]%) of the royalty rate otherwise payable pursuant to Section 9.6(a).

(iii) Third Party Payments.

(A) Hutchmed In-License Agreements. Hutchmed shall be entitled to credit against the royalties due to Epizyme on Net Sales of a Licensed Product in the Territory an amount equal to [**] percent ([**]%) of all upfront payments, milestone payments, royalties, and other amounts paid by Hutchmed or other Hutchmed Entities to Third Parties with respect to license rights to Third Party intellectual property licensed by Hutchmed or the other Hutchmed Entity from the applicable Third Party that are necessary or reasonably useful for the Development, Manufacture, or Commercialization of such Licensed Product in such country; provided, however, that, to the extent that any such Third Party license includes a license to Third Party intellectual property that is applicable to products being

or to be developed or commercialized by Hutchmed or other Hutchmed Entities other than such Licensed Product in the Territory, then Hutchmed shall reasonably allocate all upfront payments, milestone payments and other non-royalty amounts between the Licensed Product and such other products, and Hutchmed shall only be entitled to credit against the royalties due Epizyme hereunder on Net Sales of such Licensed Product [**] percent ([**]%) of the amounts that are reasonably allocable to the Licensed Product.

(B) Epizyme New In-License Agreements. In the event Epizyme enters into any Third Party IP license necessary for the Development, Manufacture, or Commercialization of a Licensed Product in the Territory, under which Epizyme is entitled to grant a sublicense to Hutchmed, and Hutchmed accepts such sublicense from Epizyme under Section 2.7(a), then, subject to any reductions or allocations pursuant to Section 2.7(a), Hutchmed shall pay [**] percent ([**]%) of the amounts payable to the Third Party on account of such sublicense arising out of Hutchmed's exercise of rights under such sublicenses and otherwise allocated to Hutchmed pursuant to Section 2.7(a) (either directly to the Third Party licensor or to Epizyme, as the Parties shall reasonably agree with the goal of ensuring timely payment to the Third Party) and Hutchmed shall be entitled to credit against the royalties due to Epizyme on Net Sales of such Licensed Product in the Territory in an amount equal to [**] percent ([**]%) of the amounts paid by Hutchmed (either directly or indirectly through Epizyme) to such Third Party with respect to such license rights for such Licensed Product in the Territory.

(iv) Aggregate Limitation on Deductions. Notwithstanding anything to the contrary herein, under no circumstances shall the combined effect of all reductions to the royalties payable to Epizyme under this Section 9.6, on a Licensed Product-by-Licensed Product basis in the Territory, reduce the effective royalties payable by Hutchmed pursuant to this Agreement for any Calendar Quarter below [**] percent ([**]%) of the otherwise applicable royalties pursuant to Section 9.6(a); provided that, Hutchmed shall have the right to carry forward for application against royalties payable to Epizyme with respect to Net Sales of Licensed Product in the Territory in future periods any amount that is not so credited due to the limitation in this Section 9.6(b)(iv).

(c) Blended Royalty. Hutchmed acknowledges that (i) the licensed Know-How and the Know-How included in the Epizyme Regulatory Documents are proprietary and valuable and that without such Know-How and Epizyme Regulatory Documents Hutchmed would not be able to obtain and maintain Regulatory Approvals with respect to the Licensed Products in the Territory, (ii) such Regulatory Approvals may allow Hutchmed to obtain and maintain Regulatory-Based Exclusivity with respect to the Licensed Products, (iii) access to Epizyme's Know-How and the rights with respect to the Epizyme Regulatory Documents have provided Hutchmed with a competitive advantage in the marketplace, and (iv) the milestone payments and royalties set forth in this Article 9 are, in part, intended to compensate Epizyme for such exclusivity and such competitive advantage. The Parties agree that the royalty rates set forth in Section 9.6 reflect and efficient and reasonable blended allocation of the value provided to Hutchmed by Epizyme.

(d) Royalty Reports. On a Licensed Product-by-Licensed Product basis, until the expiration of the Royalty Term with respect to such Licensed Product in the Territory, Hutchmed agrees to (i) send an email to Epizyme within [**] after the end of each Calendar Quarter with a good faith, non-binding estimate of the amount of the royalties owed with respect to such Licensed Product in the Territory in such Calendar Quarter and (ii) provide quarterly written reports to Epizyme within [**] after the end of each Calendar Quarter, covering all Net Sales of such Licensed Product in the Territory by any Hutchmed Entity, each such written report stating for the period in question the number of units sold of each Licensed Product in Mainland China, Taiwan, Hong Kong, and Macau during the applicable Calendar Quarter (including such amounts expressed in local currency and as converted to Dollars), the gross sales for each Licensed Product,

as applicable, a calculation of the adjustments to Net Sales for Combination Products (if applicable) and the calculation of the royalty payment due on such Net Sales for such Calendar Quarter pursuant to this Article 9. Such report shall also include a calculation of the amount of royalty payment due on Net Sales for such Calendar Quarter that are payable pursuant to any Epizyme New In-License Agreement, or if such calculation cannot be made by Hutchmed, such report shall include the information reasonably needed from Hutchmed in order for Epizyme to make such calculation, as communicated in writing by Epizyme to Hutchmed. The information contained in each report under this Section 9.6(d) shall be considered the Confidential Information of Hutchmed.

(e) Royalty Payments. Hutchmed shall make the royalty payments due hereunder (including royalties owed under any Epizyme New In-License Agreement) within [**] after the end of each Calendar Quarter.

9.7 **ROFN Term Payments**. In the event Epizyme determines, pursuant to Section 8.1, to pay to prevent the ROFN from lapsing during any month after the ROFN POC Date and the commencement of the ROFN Term, Epizyme shall make a non-refundable, non-creditable payment to Hutchmed in the amount of [**] Dollars ($[**]) for each such month (each, a "**ROFN Term Payment**"), which amount will be pro-rated for any partial month period. Hutchmed shall invoice Epizyme for such amount on a Calendar Quarter basis and Epizyme shall pay each such invoice within [**] after receipt thereof.

9.8 **Recordkeeping**.

(a) Each Hutchmed Entity shall keep full, clear and accurate records of Licensed Products that are made, used or sold under this Agreement and of any costs borne by such Hutchmed Entity for any Joint Global Trial, in accordance with the Accounting Standards, for a period of at least [**] after the end of the Calendar Year to which the records relate, setting forth the sales of Licensed Products in sufficient detail to enable royalties and other amounts payable to Epizyme and Hutchmed's payment obligations under Sections 5.2, 9.3(c), 9.3(d), and 9.3(e) and Article 7 hereunder to be determined. Each Hutchmed Entity further agrees to permit its books and records to be examined by an independent accounting firm selected by Epizyme and reasonably acceptable to Hutchmed no more than [**], to verify any reports and payments delivered under this Agreement during the [**], upon reasonable notice (which shall be no less than [**] prior notice) and during regular business hours and subject to a reasonable confidentiality agreement. The Parties shall reconcile any underpayment or overpayment within [**] after the accounting firm delivers the results of any audit. Such examination is to be made at the expense of Epizyme, except in the event that the results of the audit reveal an underpayment by Hutchmed of [**] percent ([**]%) or more during the period being audited, in which case reasonable audit fees for such examination shall be paid by Hutchmed.

(b) Each Epizyme Entity shall keep full, clear and accurate records of internal costs and Out-of-Pocket Costs for the performance of each Joint Global Trial and costs incurred in accordance with Sections 5.2 and Article 7 (including Epizyme's Fully-Burdened Cost and Manufacturing Activity Costs), in accordance with the Accounting Standards, for a period of at least [**] after the end of the Calendar Year to which the records relate, in sufficient detail to enable Hutchmed's payment obligations under Sections 5.2, 9.3(c), 9.3(d), and 9.3(e) and Article 7 to be determined. Each Epizyme Entity further agrees to permit its books and records to be examined by an independent accounting firm selected by Hutchmed and reasonably acceptable to Epizyme no more than [**], to verify any invoices delivered under Sections 5.2, 9.3, and Article 7 during the [**], upon reasonable notice (which shall be no less than [**] prior notice) and during regular business hours and subject to a reasonable confidentiality agreement. The Parties shall reconcile any underpayment or overpayment within [**] after the accounting firm delivers the results of any audit. Such examination is to be made at the expense of Hutchmed, except in the event that the results of the audit reveal an overcharging by Epizyme of [**] percent ([**]%) or more during the period being audited, in which case reasonable audit fees for such examination shall be paid by Epizyme.

(c) To the extent required by any agreement between Epizyme and RPI Finance Trust pertaining to RPI Finance Trust's purchase of royalties on future sales of Tazemetostat, Hutchmed agrees that Epizyme shall provide any such required financial information to RPI Finance Trust, subject to written obligations of nondisclosure and non-use no less stringent than those set forth in Article 10.

9.9 **Currency Conversion**. Wherever it is necessary to convert currencies for Net Sales invoiced in a currency other than the Dollar, such conversion shall be made into Dollars at the conversion rate used by Hutchmed for its own financial reporting purposes in connection with its other products or accounts, consistently applied, in accordance with Accounting Standards. All payments due to Epizyme under this Agreement shall be made without deduction of exchange, collection or other charges. Once the amount of Net Sales paid to Epizyme in respect of a particular Calendar Quarter has been converted into Dollars, such amount of Dollars shall be used for the purpose of calculating the total amount of Net Sales during the Calendar Year that includes such Calendar Quarter.

9.10 **Methods of Payment**. All payments due to a Party under this Agreement shall be made by the other Party (and not any Affiliate of the other Party) in Dollars by wire transfer to a bank account of and designated by such Party (and not any Affiliate of such Party). In case any payment to be made by Hutchmed to Epizyme under this Agreement requires filing or approval of a Regulatory Authority under Applicable Law, including filings with relevant foreign exchange administrations in Mainland China, Hong Kong, or British Virgin Islands, Hutchmed shall take prompt actions to apply for and complete such filings or approvals in advance of the payment so that the payment can be made on a timely basis pursuant to the terms and conditions of this Agreement.

9.11 **Taxes**. Each Party shall be responsible for its own past, current, and future Taxes on such Party's income in accordance with the applicable tax regulations of any relevant tax jurisdiction. Each Party making a payment under this Agreement (a "**Payor**") shall inform the other Party (a "**Payee**") of any withholding tax obligation imposed by taxing authorities on payments due to the Payee under this Agreement as soon as it becomes aware of the withholding tax obligation. The Parties shall meet promptly thereafter to discuss how best to minimize the amount of such withholding tax obligation. The Payor shall in good faith take all reasonable and lawful steps requested by the Payee to minimize the amount of any such withholding tax obligation at the Payor's expense, and the Payee shall in good faith take all reasonable and lawful steps requested by the Payor to minimize the amount of any such withholding tax obligation at the Payee's expense. The Parties agree to cooperate in good faith to provide one another with such documents and certifications as are reasonably necessary to enable Hutchmed and Epizyme to minimize or recover any withholding tax payment. Hutchmed may withhold Taxes in the event that revenue authorities in any country require the withholding of taxes on amounts paid hereunder to Epizyme in accordance with applicable tax regulations, and Epizyme may withhold taxes in the event that revenue authorities in any jurisdiction require the withholding of taxes on amounts paid hereunder to Hutchmed in accordance with applicable tax regulation. In any such event the Payor shall deduct such taxes from such payment and such taxes shall be paid by the Payor to the proper taxing authority on behalf of the Payee (evidence of which payment to such taxing authority shall be provided promptly by the Payor to the Payee hereunder). Hutchmed shall be responsible for all customs' duties, import tariffs, freight, insurance, inspection costs and the like attributed to or for the transport and importation of any Licensed Product in or into the Territory under this Agreement. For the avoidance of doubt, (a) Hutchison China MediTech Investment Limited, a company incorporated in the British Virgin Islands, has registered its business in Hong Kong and is subject to Hong Kong Taxes, and (b) the value of this Agreement that is attributable to Hong Kong does not exceed [**] percent ([**]%) of the total value attributable of this Agreement to the Territory as a whole.

9.12 **Late Payments**. Interest shall be payable by Payor on any amounts payable to Payee under this Agreement which are not paid by the due date for payment. All interest shall accrue and be calculated on a daily basis (both before and after any judgment) at a rate per month equal to the lesser of (a) [**]

percentage points above the then-current "prime rate" in effect published in *The Wall Street Journal* or (b) the maximum rate permissible under Applicable Law, for the period from the due date for payment until the date of actual payment. The payment of such interest shall not limit Payee from exercising any other rights it may have as a consequence of the lateness of any payment.

9.13 **Invoices**. Epizyme acknowledges that Hutchmed requires invoices for all payments due under this Agreement, which invoices may be delivered by email to [**] (which email address may be changed by Hutchmed from time to time upon written notice to Epizyme). Hutchmed acknowledges that Epizyme requires invoices for all payments due under this Agreement, which invoices may be delivered by email to [**] (which email address may be changed by Epizyme from time to time upon written notice to Hutchmed).

ARTICLE 10. CONFIDENTIALITY

10.1 **Generally**. During the Term and for a period of [**] thereafter, each Recipient (a) shall maintain in confidence all Confidential Information of the Discloser; (b) shall not use such Confidential Information for any purpose except to fulfill its obligations or exercise its rights under this Agreement (for the avoidance of doubt, including, with respect to Epizyme, the right to Commercialize the Licensed Compound and Licensed Products outside of the Field or Territory (and inside of the Field and Territory after any termination of this Agreement) and to Develop and Manufacture the Licensed Compound and Licensed Products in accordance with this Agreement); and (c) shall not disclose such Confidential Information to anyone other than those of its Affiliates, directors, investors, prospective investors, lenders, prospective lenders, acquirers, prospective acquirers, licensees, prospective licensees, sublicensees, prospective sublicensees, employees, consultants, financial or legal advisors, or other agents or contractors (collectively, "**Representatives**") who are bound by written obligations of nondisclosure and non-use no less stringent than those set forth in this Article 10 and to whom such disclosure, under this Agreement, is necessary in connection with the fulfillment of such Party's obligations or exercise of such Party's rights under this Agreement or in connection with bona fide financing or acquisition activities. Each Recipient shall (i) ensure that its Representatives who receive any of the Discloser's Confidential Information comply with the obligations set forth in this Article 10 and (ii) be responsible for any breach of these obligations by any of its Representatives who receive any of the Discloser's Confidential Information. Each Recipient shall notify the Discloser promptly on discovery of any unauthorized use or disclosure of the Discloser's Confidential Information. Notwithstanding anything to the contrary in this Article 10, Epizyme may disclose Hutchmed's (or any of Hutchmed's Affiliates') Confidential Information to each Third Party counterparty under any Epizyme In-License Agreement as reasonably required to fulfill Epizyme's obligations under such Epizyme In-License Agreement, and Hutchmed acknowledges and agrees that, with respect to any such Confidential Information, such information shall be considered Epizyme's confidential information under each such Epizyme In-License Agreements and such Third Party counterparty(ies) shall be bound by the confidentiality obligations set forth in the applicable Epizyme In-License Agreement(s).

10.2 **Exceptions**. The obligations of confidentiality, non-disclosure, and non-use set forth in Section 10.1 shall not apply to, and "Confidential Information" shall exclude, any information to the extent the Recipient can demonstrate that such information: (a) was in the public domain or publicly available at the time of disclosure to the Recipient by the Discloser pursuant to this Agreement or the Confidentiality Agreement, or thereafter entered the public domain or became publicly available, in each case other than as a result of any action of the Recipient, or any of its Representatives, in breach of this Agreement or the Confidentiality Agreement; (b) was rightfully known by the Recipient (as shown by its written records) prior to the date of disclosure to the Recipient by the Discloser pursuant to this Agreement or the Confidentiality Agreement; (c) was received by the Recipient on an unrestricted basis from a Third Party rightfully in possession of such information and not under a duty of confidentiality to the Discloser; or (d) was independently developed by or for the Recipient without reference to or reliance on the Confidential Information of the Discloser (as demonstrated by written records).

10.3 **Permitted Disclosures**. Notwithstanding any other provision of this Agreement, Recipient's disclosure of the Discloser's Confidential Information shall not be prohibited if such disclosure: (a) is required by any Applicable Law, including as may be required in connection with any filings made with, or by the disclosure policies of the U.S. Securities and Exchange Commission ("**SEC**") (or similar foreign authority) or other Governmental Authority, or of a nationally or internally recognized securities exchange such as NASDAQ (as set forth in additional detail below) provided that Recipient seeking to disclose the Confidential Information of the other Party uses all reasonable efforts to inform the other Party prior to making any such disclosures and cooperate with the other Party in seeking a protective order or other appropriate remedy (including redaction) and whenever possible, requests confidential treatment of such information; (b) to prosecute or defend litigation so long as there is [**] prior written notice given by the Recipient before filing, and to enforce Patent Rights in connection with Recipient's rights and obligations pursuant to this Agreement, or (c) is to patent offices in order to seek or obtain Patent Rights as contemplated by this Agreement or to Governmental Authorities including Regulatory Authorities in order to seek or obtain approval to Develop, Manufacture, and Commercialize the Licensed Product as contemplated by this Agreement, including to conduct clinical trials or to gain Regulatory Approval with respect to the Licensed Products; provided that such disclosure may be made only to the extent reasonably necessary to seek or obtain such Patent Rights or approvals, and the Recipient (or its applicable Affiliate(s)) shall use Commercially Reasonable Efforts to obtain confidential treatment of such information.

Notwithstanding anything to the contrary set forth in this Agreement, if a Recipient is required to make a disclosure of the Discloser's Confidential Information pursuant to Section 10.3(a) or (b) above, then it will, to the extent not prohibited by Applicable Law or judicial or administrative process, except where impracticable, give reasonable advance notice to the other Party of such proposed disclosure and use reasonable efforts to secure confidential treatment of such information and will only disclose that portion of Confidential Information that is legally required to be disclosed as advised by its legal counsel. In addition, the Parties acknowledge that either or both Parties may be obligated to file a copy of this Agreement (or portions thereof or an abstract of the terms) with the SEC or other Governmental Authorities. Each Party will be entitled to make such a required filing; provided that it initially files a redacted copy of this Agreement (or portions thereof or an abstract of the terms) approved by each Party and requests confidential treatment of the terms redacted for a reasonable period of time. In the event of any such filing, each Party will permit the other Party to review and comment upon such request for confidential treatment and any subsequent correspondence with respect thereto at least [**] in advance of its submission to the SEC or other Governmental Authorities, and to the extent practicable before any filing deadline, (A) reasonably consider and incorporate the other Party's comments thereon to the extent consistent with the then-current legal requirements governing redaction of information from material agreements that must publicly filed in the applicable country, (B) promptly provide to the other Party any correspondence from or other communications with such Governmental Authority, (C) upon written request of the other Party, request an appropriate extension of the term of the confidential treatment period, where available, and (D) if such Governmental Authority requests any changes to the redactions set forth in the filed redacted copy, use reasonable efforts to support the redactions in the redacted agreement as originally filed and, to the extent reasonably practicable, not agree to any changes to the redactions without first discussing such changes with the other Party and taking the other Party's comments into consideration when deciding whether to agree to such changes.

10.4 **Publicity**. The press release attached to this Agreement as Exhibit E shall be issued by both Parties on the Effective Date. Thereafter, the Parties recognize that each Party may from time to time desire to issue press releases and make other public statements or public disclosures (each, a "**Public Statement**") in respect of this Agreement, including the Development or Commercialization of Licensed Products in the Territory. If Hutchmed desires to make a Public Statement, it shall provide Epizyme a copy of such Public Statement at least [**] prior to the date it desires to make such public disclosure. Hutchmed shall not issue a Public Statement without Epizyme's prior written approval, which advance approval shall not be

unreasonably withheld, conditioned or delayed. Epizyme shall provide to Hutchmed a preliminary draft of any Public Statement that it intends to make on a global basis with respect to Development of Licensed Products at least [**] in advance of such public disclosure and shall provide a final draft of such Public Statement at least [**] in advance of such public disclosure; provided that, if such Public Statement includes data owned by Hutchmed with respect to a Local Trial or Pre-Clinical Research conducted by Hutchmed in the Territory, Epizyme shall obtain Hutchmed's prior written approval to include such data, which approval shall not be unreasonably withheld, conditioned or delayed. Once any public statement or public disclosure has been approved in accordance with this Section 10.4, then the applicable Party may communicate information contained in such permitted statement or disclosure. Notwithstanding anything to the contrary in this Section 10.4, nothing in this Section 10.4 shall be deemed to limit either Party's rights under Section 10.3.

10.5 **Publications**. Epizyme acknowledges Hutchmed's interest in publishing certain key results of Hutchmed's Development and Commercialization of Licensed Products in the Field in the Territory. Hutchmed recognizes the mutual interest in obtaining valid patent protection and Epizyme's interest in protecting its proprietary information.

(a) By Hutchmed. Except for disclosures permitted pursuant to Sections 10.2, 10.3 or 10.4, if Hutchmed wishes to make a publication or public presentation with respect to its Development or Commercialization of Licensed Products in the Field in the Territory, Hutchmed shall deliver to Epizyme a copy of the proposed written publication or presentation; for manuscripts, at least [**] prior to submission, or for abstracts or posters, at least [**] prior to submission. Epizyme shall respond in writing in no event later than [**] after receipt of a proposed manuscript or [**] after receipt of a proposed abstract or poster. Epizyme shall have the right (i) to require modifications to the publication or presentation for patent or any other business reasons, and Hutchmed will remove all of Epizyme's Confidential Information if requested by Epizyme, and (ii) to require a reasonable delay in publication or presentation in order to protect patentable information. If Epizyme requests a delay, then Hutchmed shall delay submission or presentation for a period of [**] (or such period as may be mutually agreed by the Parties) to enable Epizyme to file patent applications protecting Epizyme's rights in such patentable information.

(b) By Epizyme. Except for disclosures permitted pursuant to Sections 10.2, 10.3 or 10.4, if Epizyme wishes to make a publication or public presentation with respect to its Development or Commercialization of Joint Combination Therapies or the results of any Joint Global Trial, Epizyme shall deliver to Hutchmed a copy of the proposed written publication or presentation; for manuscripts, at least [**] prior to submission, or for abstracts or posters, at least [**] prior to submission. Hutchmed shall respond in writing in no event later than [**] after receipt of a proposed manuscript or [**] after receipt of a proposed abstract or poster. Hutchmed shall have the right (i) to require modifications to the publication or presentation for patent or any other business reasons, and Epizyme will remove all of Hutchmed's Confidential Information if requested by Hutchmed, and (ii) to require a reasonable delay in publication or presentation in order to protect patentable information. If Hutchmed requests a delay, then Epizyme shall delay submission or presentation for a period of [**] (or such period as may be mutually agreed by the Parties) to enable Hutchmed or Epizyme to file patent applications protecting the Parties' rights in such patentable information. In addition, unless prohibited by confidentiality obligations to any Third Party, Epizyme shall provide Hutchmed with a draft of any other publication pertaining to Licensed Products reasonably in advance of submission for publication.

10.6 **Injunctive Relief**. Each Party acknowledges and agrees that there may be no adequate remedy at law for any breach of its obligations under this Article 10, that any such breach may result in irreparable harm to the other Party and, therefore, that upon any such breach or any threat thereof, such other Party may seek appropriate equitable relief in addition to whatever remedies it might have at law, without the necessity of showing actual damages.

10.7 **Information Security**. During the Term, each Party will maintain safety and facility procedures, data security procedures and other safeguards against the disclosure, destruction, loss, or alteration of the other Party's information in its possession.

ARTICLE 11. INTELLECTUAL PROPERTY

11.1 **Ownership and Disclosure**.

(a) Ownership; Notice. As between the Parties, ownership of any Epizyme IP, Epizyme Combination Therapy IP, and Epizyme Manufacturing IP (individually and collectively, the "**Licensed IP**") Controlled by Epizyme as of the Effective Date shall remain vested at all times in Epizyme, and ownership of any Hutchmed IP Controlled by Hutchmed as of the Effective Date shall remain vested at all times in Hutchmed.

Except as expressly set forth in this Agreement, including in 11.1(b) and (c), and subject to the terms and conditions of this Agreement, (i) each Party will own all rights, title, and interests in and to any and all Know-How that is conceived, identified, discovered, authored, developed, or reduced to practice by or on behalf of such Party in connection with the performance of such Party's activities conducted under this Agreement or during the Term and any and all Patent Rights Covering any such Know-How, and (ii) the Parties will jointly own any and all Know-How that is conceived, identified, discovered, authored, developed, or reduced to practice jointly by or behalf of the Parties in connection with the performance of the Parties' activities conducted under this Agreement or during the Term, and any and all Patent Rights Covering any such Know-How. Inventorship shall be determined according to United States patent laws.

Hutchmed shall promptly disclose to Epizyme in writing any inventions (whether or not patentable) or discoveries conceived, identified, discovered, authored, developed, or reduced to practice during the Term solely or jointly by or on behalf of any Hutchmed Entity and included in Epizyme Combination Therapy Know-How, Epizyme Know-How, or Epizyme Manufacturing Know-How, and any inventions (whether or not patentable) or discoveries included in Hutchmed Know-How upon becoming aware thereof, but in any event no later than [**] after the conception, identification, discovery, authorship, development or reduction to practice thereof.

Epizyme shall promptly disclose to Hutchmed in writing any inventions (whether or not patentable) or discoveries conceived, identified, discovered, authored, developed, or reduced to practice during the Term solely or jointly by or on behalf of any Epizyme Entity and included in Epizyme Combination Therapy Know-How, Epizyme Know-How, or Epizyme Manufacturing Know-How and any inventions (whether or not patentable) or discoveries included in Epizyme Know-How, upon becoming aware thereof, but in any event no later than [**] after the conception, identification, discovery, authorship, development or reduction to practice thereof.

(b) Assignment to Epizyme. Epizyme shall own all Epizyme Combination Therapy IP, Epizyme IP, and Epizyme Manufacturing IP. Unless prohibited by Applicable Law, Hutchmed will assign and hereby does assign to Epizyme, and Epizyme hereby accepts such assignment of, all of Hutchmed's rights, title and interests in and to any and all inventions or discoveries conceived, identified, discovered, authored, developed, or reduced to practice solely or jointly by or on behalf of any Hutchmed Entity, and any Patent Rights thereon, included in (i) Epizyme Combination Therapy IP, (ii) Epizyme IP, and (iii) Epizyme Manufacturing IP. In the case of such assignment, Hutchmed shall, with Epizyme bearing Hutchmed's reasonable Out-of-Pocket Costs for such assignment, obtain all necessary assignment documents for Epizyme, render all signatures that shall be necessary for the relevant patent filings and assist Epizyme in all other reasonable ways that are necessary for the Prosecution of the Patent Rights assigned to Epizyme pursuant to this Section 11.1(b). In the event that (A) Applicable Law prohibits the assignment to Epizyme

of inventions, discoveries, or Patent Rights included in Epizyme Combination Therapy IP, Epizyme IP, or Epizyme Manufacturing IP, then in lieu of the assignment of such inventions, discoveries, or Patent Rights to Epizyme, Hutchmed will grant and hereby grants to Epizyme, without cost to Epizyme, as broad, exclusive and unrestricted license to, with the broadest enforcement rights with respect to, such inventions, discoveries, or Patent Rights as allowable under Applicable Law, or (B) despite the good faith efforts of Hutchmed to obtain an assignment obligation from a Hutchmed Entity (other than Hutchmed), the Hutchmed Entity (other than Hutchmed) does not agree to an assignment to Epizyme of inventions, discoveries, or Patent Rights included in Epizyme Combination Therapy IP, Epizyme IP, or Epizyme Manufacturing IP (other than intellectual property rights constituting improvements to such Hutchmed Entity's background intellectual property), then in lieu of the assignment of such inventions, discoveries, or Patent Rights to Epizyme, Hutchmed will obtain from the Hutchmed Entity the rights necessary to grant to Epizyme and Hutchmed will grant and hereby grants to Epizyme, without cost to Epizyme, as broad, exclusive and unrestricted a license to, with the broadest enforcement rights with respect to, such inventions, discoveries, or Patent Rights (other than intellectual property rights constituting improvements to such Hutchmed Entity's background intellectual property) as agreed with such Hutchmed Entity. In each case ((A) and (B)), such inventions and discoveries (other than intellectual property rights constituting improvements to such Hutchmed Entity's background intellectual property) shall be deemed Epizyme Combination Therapy Know-How, Epizyme Know-How, or Epizyme Manufacturing Know-How, as applicable, and such Patent Rights shall be deemed Epizyme Combination Therapy Patent Rights, Epizyme Patent Rights or Epizyme Manufacturing Patent Rights, as applicable, hereunder, and Hutchmed shall provide to Epizyme any necessary or reasonably requested documentation reflecting such licenses and shall assist Epizyme in all other reasonable ways that are necessary for Epizyme to enjoy and exploit or enforce any such Know-How and Patent Rights. For clarity, all such Epizyme Combination Therapy IP, Epizyme IP, and Epizyme Manufacturing IP assigned to Epizyme by Hutchmed shall be included in the applicable licenses granted by Epizyme to Hutchmed under Section 2.1.

Hutchmed will take, and cause the Hutchmed Entities to take, with Epizyme bearing Hutchmed's reasonable Out-of-Pocket Costs with respect to, all action reasonably requested by Epizyme to evidence such assignment and to assist Epizyme in obtaining Patent Rights and other intellectual property protection for Know-How within the Epizyme Combination Therapy IP, Epizyme IP, or Epizyme Manufacturing IP, including rendering all signature that shall be necessary for the relevant patent filings and assisting Epizyme in all other reasonable ways that are necessary for the Prosecution of any such Patent Rights by Epizyme as set forth in Section 11.2.

(c) Joint Combination Therapy IP. The Parties shall jointly own any Joint Combination Therapy IP except that, as between the Parties, Epizyme shall own any Joint Combination Therapy IP that is Controlled by Epizyme as of the Effective Date or is Controlled by Epizyme during the Term under any Epizyme In-License Agreement, and Hutchmed shall own any Joint Combination Therapy IP that is Controlled by Hutchmed as of the Effective Date or is Controlled by Hutchmed during the Term under any Hutchmed In-License Agreement. Each Party shall promptly disclose in writing to the other Party any inventions (whether or not patentable) or discoveries conceived, identified, discovered, authored, developed, or reduced to practice during the Term solely or jointly by or behalf of Epizyme or Hutchmed Entity and included in Joint Combination Therapy Know-How upon becoming aware thereof, but in any event no later than [**] after the conception, identification, discovery, authorship, development or reduction to practice thereof. Each Party will assign and does hereby assign to the other Party, subject to the licenses granted in Sections 2.1 and 2.2, a one-half undivided interest in all of such Party's rights, title and interests in and to any and all inventions, discoveries or Patent Rights included in Joint Combination Therapy IP. Each Party shall, without cost to the other Party, obtain all necessary assignment documents for the other Party to give effect to the one-half undivided ownership described above, render all signatures that shall be necessary for the relevant patent filings and assist the other Party in all other reasonable ways that are necessary for the Prosecution of the Joint Combination Therapy Patent Rights by the other Party as set forth in Section

11.2(c). Subject to the terms and conditions of this Agreement, including Sections 2.5 and 2.8 and the licenses granted herein, each Party is entitled to practice any Joint Combination Therapy IP for all purposes on a worldwide basis and to license such Joint Combination Therapy IP through multiple tiers without consent of the other Party (where consent is required by Applicable Law, such consent is deemed hereby granted) and without a duty of accounting to the other Party.

(d) Joint IP. Subject to the terms and conditions of this Agreement, including Sections 2.5 and 2.8 and the licenses granted herein, each Party is entitled to practice any Joint IP for all purposes on a worldwide basis and to license such Joint IP through multiple tiers without consent of the other Party (where consent is required by Applicable Law, such consent is deemed hereby granted) and without a duty of accounting to the other Party. Each Party will cooperate with the other Party if the Parties determine to apply for US or foreign patent protection for any Joint Know-How as mutually agreed by the Parties and will join in any action to enforce the Joint IP (if joinder is required in order for the action to proceed), at the enforcing Party's reasonable request and cost.

(e) Each Party shall be solely responsible for payments due under Applicable Laws regarding inventor remuneration to each inventor as to any Patent Right described in the foregoing Section 11.1(a)-(d) to which such Party is assigned an ownership interest by such inventor.

11.2 **Prosecution of Patent Rights**.

(a) Licensed Patent Rights. Subject to the terms of each Epizyme In-License Agreement:

(i) As between the Parties, Epizyme shall have the sole right, but not the obligation, to Prosecute all Epizyme Combination Therapy Patent Rights, Epizyme Patent Rights, and Epizyme Manufacturing Patent Rights (individually and collectively, the "**Licensed Patent Rights**") and their foreign counterparts worldwide. Hutchmed shall reimburse Epizyme, on a Calendar Quarter basis, for all Out-of-Pocket Costs incurred by Epizyme or any of its Affiliates after the Effective Date in the Territory in Prosecuting the Licensed Patent Rights (for the avoidance of doubt, including amounts paid by Epizyme after the Effective Date to any Third Party counterparty under any Epizyme In-License Agreement with respect to such Third Party counterparty's Prosecution of applicable Licensed Patent Rights in the Territory), within [**] after receiving an invoice therefor.

(ii) Epizyme shall consult with Hutchmed on the Prosecution of the Licensed Patent Rights in the Territory, and shall take into consideration the commercial and patent strategy for Licensed Products in the Territory. Epizyme shall furnish Hutchmed with copies of each document relevant to such Prosecution in the Territory at least [**] prior (or such shorter period prior if it is not reasonably practicable to provide such copies [**] prior) to filing such document or making any payment due thereunder to allow for review and comment Hutchmed and shall consider in good faith timely comments from Hutchmed thereon. Epizyme shall also furnish Hutchmed with copies of all final filings and responses made to any patent authority in the Territory with respect to the Licensed Patent Rights being Prosecuted by Epizyme in a timely manner following submission thereof. Hutchmed shall execute such documents and perform such acts as may be reasonably necessary for Epizyme to perform its actions under this Section 11.2(a).

(b) Hutchmed Patent Rights. Subject to the terms of each Hutchmed In-License Agreement:

(i) Hutchmed shall have the sole right, but not the obligation, to Prosecute all Hutchmed Patent Rights, at its sole expense, worldwide.

(ii) Hutchmed shall consult with Epizyme on the Prosecution of such Hutchmed Patent Right, and shall take into consideration the commercial and patent strategy for Licensed Products of Epizyme globally. Hutchmed shall furnish Epizyme with copies of each document relevant to such Prosecution at least [**] prior (or such shorter period prior if it is not reasonably practicable to provide such copies [**] prior) to filing such document or making any payment due thereunder to allow for review and comment by such other Party and shall consider in good faith timely comments from such other Party thereon. Hutchmed shall also furnish Epizyme with copies of all final filings and responses made to any patent authority with respect to the Hutchmed Patent Rights being Prosecuted by Hutchmed in a timely manner following submission thereof.

(c) Joint Combination Therapy Patent Rights. Subject to the terms of each Epizyme In-License Agreement and Hutchmed In-License Agreement:

(i) Epizyme shall have the first right, but not the obligation, to Prosecute all Joint Combination Therapy Patent Rights outside the Territory, and Hutchmed shall have the first right, but not the obligation, to Prosecute all Joint Combination Therapy Patent Rights in the Territory The Parties shall [**] of all Out-of-Pocket Costs incurred by the Prosecuting Party after the Effective Date in Prosecuting such Joint Combination Therapy Patent Rights in and outside the Territory. The non-Prosecuting Party shall reimburse its share of such costs on a [**] basis within [**] after receiving an invoice from the Prosecuting Party therefor. If the Prosecuting Party elects not to, or is unable to, Prosecute any Joint Combination Therapy Patent Rights in any country anywhere in the world, or intends to allow a Joint Combination Therapy Patent Right to lapse or become abandoned without having first filed a substitute, the Prosecuting Party shall give the non-Prosecuting Party prompt notice and shall permit the non-Prosecuting Party at the non-Prosecuting Party's own expense to take such actions itself in such country.

(ii) The Party Prosecuting a Joint Combination Therapy Patent Right in accordance with Section 11.2(c)(i) shall consult with the other Party on the Prosecution of all Joint Combination Therapy Patent Rights, and shall take into consideration the commercial and patent strategies for Joint Combination Therapies of (A) if the Party Prosecuting is Epizyme, in the Territory, and (B) if the Party Prosecuting is Hutchmed, globally. The Party Prosecuting shall furnish the other Party with copies of each document relevant to such Prosecution at least [**] prior (or such shorter period prior if it is not reasonably practicable to provide such copies [**] prior) to filing such document or making any payment due thereunder to allow for review and comment by the other Party and shall consider in good faith timely comments from the other Party thereon. The Party Prosecuting shall also furnish the other Party with copies of all final filings and responses made to any patent authority with respect to the Joint Combination Therapy Patent Rights in a timely manner following submission thereof. The other Party shall execute such documents and perform such acts as may be reasonably necessary for the Prosecuting Party to perform such actions.

(iii) In preparing, filing, prosecuting and maintaining Joint Combination Therapy Patent Rights, in no event shall Hutchmed take any position that is contrary to or detrimental to the scope or enforceability of any Epizyme Patent Rights or any Patent Rights owned or otherwise controlled by Epizyme that are counterparts to any Epizyme Patent Rights without the express written consent of Epizyme.

(d) Patent Liaisons. Promptly (but in no event later than [**]) following the Effective Date, the Parties shall each designate a representative to consult with the other Party's representative with respect to the Prosecution of the Licensed Patent Rights, Hutchmed Patent Rights, and Joint Combination Therapy Patent Rights (such representatives, the "**Patent Liaisons**"). The Patent Liaisons shall discuss and provide input to each other, at such times, places and frequencies as mutually agreed, on all material issues with

respect to the Prosecution of such Patent Rights; *provided* that all final decisions related to the Prosecution, enforcement or defense of the Licensed Patent Rights, Hutchmed Patent Rights, and Joint Combination Therapy Patent Rights shall be made by the Party with the right to control such Prosecution, enforcement or defense, as applicable as set forth in this Article 11.

11.3 **Enforcement and Defense**. Subject to the terms of each Epizyme In-License Agreement:

(a) If either Party becomes aware of any Third Party activity, including any Development activity (whether or not an exemption from infringement liability for such Development activity is available under Applicable Law), that materially infringes (or that is directed to the Development of a product that would infringe) a Licensed Patent Right, Hutchmed Patent Right or a Joint Combination Therapy Patent Right, or that misappropriates any Epizyme Combination Therapy Know-How, Epizyme Know-How, or Epizyme Manufacturing Know-How (individually or collectively the "**Licensed Know-How**"), Hutchmed Know-How, or Joint Combination Therapy Know-How, or of any Third Party Patent Right that, if issued or enforced, is reasonably likely to materially affect the scope, claims, validity, or other material element of a Licensed Patent Right, Hutchmed Patent Right or a Joint Combination Therapy Patent Right then the Party becoming aware of such activity shall give prompt written notice to the other Party regarding such alleged infringement or misappropriation (collectively, "**Infringement Activity**").

(b) Epizyme shall have the first right, but not the obligation, to attempt to resolve any Infringement Activity involving Licensed Patent Rights, Licensed Know-How, Joint Combination Therapy Patent Rights, or Joint Combination Therapy Know-How outside the Territory at its own expense, including the filing of an infringement or misappropriation suit using counsel of its own choice, and Hutchmed shall have the first right, but not the obligation, to attempt to resolve any Infringement Activity involving Licensed Patent Rights, Licensed Know-How, Epizyme Marks, Joint Combination Therapy Patent Rights, or Joint Combination Therapy Know-How in the Territory by commercially appropriate steps at its own expense, including the filing of an infringement or misappropriation suit using counsel of its own choice. If (i) Hutchmed fails to resolve such Infringement Activity in the Territory, or (ii) solely with respect to Joint Combination Therapy Patent Rights, Epizyme fails to resolve such Infringement Activity outside the Territory, but solely (in the case of this clause (ii)) where the allegedly infringing product is or would be competitive with Hutchmed's Other Combination Drug(s) that form(s) part of a Joint Combination Therapy covered by such Joint Combination Therapy Patent Rights, or, in either case ((i) or (ii)), to initiate a suit with respect thereto by the date that is [**] before any deadline for taking action to avoid any loss of material enforcement rights or remedies, then, upon written notice to the non-enforcing Party, such Party shall have the right, but not the obligation, to attempt to resolve such Infringement Activity by commercially appropriate steps at its own expense, including the filing of an infringement or misappropriation suit using counsel of its own choice.

(c) Any amounts recovered by a Party as a result of an action pursuant to Section 11.3(b), whether by settlement or judgment, shall be allocated as follows: (i) first to pay to each Third Party counterparty under any Epizyme In-License Agreement or Hutchmed In-License Agreement any amounts owed to such Third Party counterparty with respect to such enforcement action, then (ii) to reimburse the Parties for their costs and expenses of the enforcement action (which amounts will be allocated pro rata if insufficient to cover the totality of such expenses), and (iii) any remaining amount shall be shared between the Parties, with the enforcing Party retaining [**] percent ([**]%) of such amount and the other Party retaining [**] percent ([**]%) of such amount. In the event that any action pursuant to this Section 11.3 does not result in the recovery of any amounts (e.g., payments to a Third Party, expenses for invalidation proceedings for Third Party Patent Rights that a Party reasonably believes may infringe a Licensed Patent Right, Hutchmed Patent Right or a Joint Combination Therapy Patent Right), then unless otherwise provided by this Agreement, such expenses shall be borne equally by the Parties and the Party not incurring such expenses

shall reimburse the incurring Party within [**] after receipt of an invoice reasonably documenting such expenses.

(d) If a Third Party in the context of an enforcement action under this Section 11.3 asserts that a Licensed Patent Right or Joint Combination Therapy Patent Right is invalid or unenforceable, then the Party responsible for such enforcement action will be responsible for defending against such assertion. If a Third Party outside of an enforcement action under this Section 11.3 asserts that a Licensed Patent Right is invalid or unenforceable, then Epizyme shall have the sole right, but not the obligation, to defend against such assertion. If a Third Party outside of an enforcement action under this Section 11.3 asserts that a Joint Combination Therapy Patent Right is invalid or unenforceable, then Epizyme shall have the sole right, but not the obligation, outside the Territory, and Hutchmed shall have the first right, but not the obligation, within the Territory, to defend against such assertion (such Party with a sole or first right to defend being known as the "**First Defending Party**") and, at the First Defending Party's request and expense, the other Party shall provide reasonable assistance in defending against such Third Party assertion. The First Defending Party shall (i) keep the other Party reasonably informed regarding such assertion and such defense (including by providing such other Party with drafts of each filing a reasonable period before the deadline for such filing and promptly providing such other Party with copies of all final filings and correspondence), (ii) consult with the other Party on such defense, and (iii) consider in good faith all comments from the other Party regarding such defense. The non-defending Party shall have the right to join as a party to such defense and participate with its own counsel at its sole expense; provided, however, that the First Defending Party shall retain control of such defense. Should Epizyme (with respect to Licensed Patent Rights or Joint Combination Therapy Patent Rights outside the Territory, including in the context of an applicable enforcement action) or Hutchmed (with respect to Joint Combination Therapy Patent Rights within the Territory or in the context of an applicable enforcement action) decide that it is not, or is no longer, interested in controlling such defense with respect to a Joint Combination Therapy Patent Right, it shall promptly (and in any event by the date that is [**] before any deadline for taking action to avoid any loss of material rights) provide the other Party written notice of this decision. The other Party may, upon written notice to such first Party, assume such defense at such other Party's sole expense.

(e) In any event, at the request and expense of the Party bringing an infringement or misappropriation action under Section 11.3(b) or defending an action under Section 11.3(d), the other Party shall provide reasonable assistance in any such action (including entering into a common interest agreement if reasonably deemed necessary by any Party) and be joined as a party to the suit if necessary for the initiating or defending Party to bring or continue such suit. Neither Party may settle any action or proceeding brought under Section 11.3(b) or 11.3(d), or knowingly take any other action in the course thereof, in a manner that materially adversely affects the other Party's interest in any Licensed Patent Rights or Joint Combination Therapy Patent Rights or counterpart Patent Rights outside of the Territory without the written consent of such other Party. Each Party shall always have the right to be represented by counsel of its own selection and its own expense in any suit or other action instituted by the other Party pursuant to Section 11.3(b) or 11.3(d). The Party enforcing a Licensed Patent Right or Joint Combination Therapy Patent Right will keep the other Party reasonably informed with respect to the status of such enforcement and will consider in good faith all comments provided by the non-enforcing Party with respect to such enforcement.

11.4 **Defense of Third Party Infringement and Misappropriation Claims**. Subject to the terms of each Epizyme In-License Agreement:

(a) If a Third Party asserts that a Patent Right or other right controlled by it in the Territory is infringed or misappropriated by a Party's activities under this Agreement or a Party becomes aware of a Patent Right or other right that might form the basis for such a claim, the Party first obtaining knowledge of such a claim or such potential claim shall immediately provide the other Party with notice thereof and

the related facts in reasonable detail. Subject to Section 13.1, the Parties shall discuss what commercially appropriate steps, if any, to take to avoid infringement or misappropriation of said Third Party Patent Right or other right controlled by such Third Party in the Territory.

(b) If a Third Party asserts that a Patent Right or other right controlled by it in the Territory is infringed or misappropriated by a Party's activities under this Agreement, then, subject to Section 13.1, such Party shall have the first right, but not the obligation, to defend against such assertion and, at such Party's request and expense, the other Party will provide reasonable assistance in defending against such Third Party assertion. Such Party shall keep the other Party reasonably informed regarding such assertion and such defense.

11.5 **Patent Linkage**. To the extent required by Applicable Law, Hutchmed shall use Commercially Reasonable Efforts to promptly, accurately and completely list, with the applicable Regulatory Authorities in the Territory, all applicable Patents for any Licensed Product that Hutchmed intends to, or has begun to, Commercialize and that have become the subject of an application for Regulatory Approval submitted to Regulatory Authorities in the Territory. Prior to such listings, the Parties shall meet to evaluate and identify all applicable Patents, and Hutchmed shall retain final decision-making authority as to the listing of all applicable Patents for such Licensed Product in the Territory, regardless of which Party owns such Patent.

11.6 **Patent Term Extensions**. Subject to the terms of each Epizyme In-License Agreement, the Parties shall discuss and select the appropriate Licensed Patent Rights or Joint Combination Therapy Patent Rights for filing to obtain patent term extensions, including supplementary protection certificates and any other extensions that are now available or become available in the future, based on Regulatory Approvals for Licensed Products in the Field in the Territory. If the Parties are unable to reach mutual agreement, as between the Parties, Hutchmed shall have the right to make the final decision as to such Patent Rights. In such cases, Epizyme shall consult with Hutchmed with respect to such decisions and shall consider the comments and concerns of the other Party in good faith. Hutchmed shall cooperate with Epizyme in gaining any such patent term extensions, including by signing all necessary papers.

ARTICLE 12. REPRESENTATIONS, WARRANTIES, AND COVENANTS

12.1 **Mutual Representations and Warranties**. Each of Hutchmed and Epizyme hereby represents and warrants to the other Party as of the Effective Date that:

(a) it is a corporation or entity duly organized and validly existing under the Applicable Laws of the nation, state, municipality, province, administrative division or other jurisdiction of its incorporation or formation;

(b) the execution, delivery and performance of this Agreement by it has been duly authorized by all requisite corporate action;

(c) it has the power and authority to execute and deliver this Agreement and to perform its obligations hereunder, and such performance does not conflict with or constitute a breach of any of its agreements with any Third Party;

(d) it has the right to grant the rights and licenses described in this Agreement;

(e) it has not made any commitment to any Third Party in conflict with the rights granted by it hereunder;

(f) its, and its Affiliates' employees have executed agreements requiring automatic assignment to such Party of all inventions (whether or not patentable) or other Know-How identified, discovered, authored, developed, conceived or reduced to practice during the course of and as the result of their employment with such Party or its Affiliates, and all intellectual property rights therein (other than intellectual property rights constituting improvements to any such employee's background intellectual property), and obligating the relevant individual or entity to maintain as confidential such Party's confidential information related to any Licensed Compound or Licensed Product as well as confidential information of other parties (including Epizyme and any other Epizyme Entity or Hutchmed and any other Hutchmed Entity, as applicable) which such individual or entity may receive, to the extent required to support such Party's obligations under this Agreement;

(g) to its knowledge, no consent, approval or agreement of any person or Governmental Authority is required to be obtained in connection with the execution and delivery of this Agreement; and

(h) it has not been debarred by the FDA, is not the subject of a conviction described in Section 306 of the FD&C Act, has not been excluded by the Office of Inspector General ("**OIG**"), and is not subject to any similar sanction of any other Governmental Authority outside of the U.S., including revocation or suspension of any business license or relevant pharmaceutical enterprise permits or approvals by the State Administration of Market Regulation (SAMR), the NMPA, or other Regulatory Authority in Mainland China, as applicable or otherwise "blacklisted" by such Regulatory Authority in Mainland China, and neither it nor any of its Affiliates has used, in any capacity, any person or entity who either has been debarred by the FDA, is the subject of a conviction described in Section 306 of the FD&C Act, excluded by the OIG, or is subject to any such similar sanction inside or outside of the U.S.

12.2 **Mutual Covenants**. Each of Hutchmed and Epizyme hereby covenants to the other Party during the Term that:

(a) it will not engage, in any capacity in connection with this Agreement or any ancillary agreement, any person or entity who has been debarred by the FDA, excluded by the OIG, is the subject of a conviction described in Section 306 of the FD&C Act or is subject to any similar sanction inside or outside of the U.S., and such Party shall inform the other Party in writing promptly if such Party or any person or entity engaged by such Party who is performing services under this Agreement, or any ancillary agreement, is debarred or is the subject of a conviction described in Section 306 of the FD&C Act or any similar sanction inside or outside of the U.S., or if any action, suit, claim, investigation or legal or administrative proceeding is pending or, to such Party's knowledge, is threatened, relating to any such debarment or conviction of a Party, any of its Affiliates or any such person or entity performing services hereunder or thereunder;

(b) it and its Affiliates' employees, upon their employment by such Party or any of its Affiliates, will execute agreements requiring automatic assignment to such Party of all inventions (whether or not patentable) or other Know-How identified, discovered, authored, developed, conceived or reduced to practice during the course of and as the result of their employment with such Party or its Affiliates, and all intellectual property rights therein (other than intellectual property rights constituting improvements to any such person's or entity's background intellectual property), and obligating the relevant individual or entity to maintain as confidential such Party's confidential information related to any Licensed Compound or Licensed Product as well as confidential information of other parties (including Epizyme and any other Epizyme Entity or Hutchmed and any other Hutchmed Entity, as applicable) which such individual or entity may receive, to the extent required to support such Party's obligations under this Agreement; it will not make any commitment to any Third Party in conflict with the rights granted by it hereunder or that would materially adversely affect the rights granted by it hereunder; and

(c) it will comply with all Applicable Laws in performing its activities hereunder.

12.3 **Additional Epizyme Warranties**. Epizyme hereby represents and warrants to Hutchmed as of the Effective Date that:

(a) Exhibit B contains a list of all Patent Rights that are Controlled by Epizyme as of the Effective Date in the Territory and Cover or are otherwise reasonably necessary or useful for (i) the Development or Commercialization of the Licensed Products as they exist on the Effective Date in the Field in the Territory or (ii) the Manufacture in the Territory of the Licensed Compound and Licensed Product as they exist on the Effective Date, in each case ((i) and (ii)) in accordance with this Agreement;

(b) Epizyme does not own or have license rights to any intellectual property rights that would constitute Licensed IP Controlled by Epizyme but for Epizyme not having the right to sublicense such intellectual property rights to Hutchmed to the extent set forth in this Agreement;

(c) Epizyme has not granted any license or other right under the Licensed IP inconsistent with the terms of this Agreement or the Eisai Agreement;

(d) all of the issued Patent Rights on Exhibit B are in full force and effect, and, to Epizyme's knowledge, are not invalid or unenforceable, in whole or in part;

(e) Epizyme has complied with Applicable Law, including any duties of candor to applicable patent offices, in connection with the filing, prosecution, and maintenance of the Patent Rights on Exhibit B. All Patent Rights on Exhibit B have been duly filed and maintained in the Territory and are being diligently prosecuted in the Territory;

(f) with respect to the Licensed IP that is solely-owned by Epizyme as of the Effective Date, Epizyme has obtained assignments from the inventors of all inventorship rights relating to all Patents included in such Licensed IP, and all such assignments of inventorship rights relating to such Patents have been properly executed and recorded in the relevant U.S. and foreign patent offices;

(g) Epizyme and its Affiliates have taken commercially reasonable measures consistent with industry practices to protect the secrecy, confidentiality and value of all Licensed Know-How that constitutes trade secrets under Applicable Law (including requiring all employees, consultants and independent contractors to execute binding and enforceable agreements requiring all such employees, consultants and independent contractors to maintain the confidentiality of such Licensed Know-How and, to Epizyme's Knowledge, such Licensed Know-How has not been disclosed to any Third Party by Epizyme except pursuant to such confidentiality agreements and to Epizyme's Knowledge there has not been a breach by any party to such confidentiality agreements;

(h) no Licensed IP owned by Epizyme or its Affiliates, and, to Epizyme's knowledge, no Licensed IP otherwise Controlled by Epizyme or its Affiliates, is subject to any funding agreement with any government or governmental agency;

(i) Epizyme is unaware of any challenge in the Territory to the validity or enforceability of any of the Licensed Patent Rights listed in Exhibit B;

(j) other than as set forth on Schedule 12.3, to Epizyme's knowledge, no Third Party is infringing or misappropriating any Licensed IP in the Field in the Territory;

(k) Epizyme and its Affiliates have not, prior to the Effective Date, assigned, transferred, conveyed or otherwise encumbered their right, title and interest in any Licensed IP within the Territory, other than with respect to the activities set forth on Schedule 2.8(b) and as set forth on Schedule 12.3;

(l) to Epizyme's knowledge, the research, development, manufacture, use, sale or import of Licensed Products in the Territory will not infringe or misappropriate the Patent Rights or Know-How owned or controlled by such Third Party;

(m) to Epizyme's knowledge, no Third Party has a valid basis upon which to claim that the research, development, manufacture, use, sale or import of Licensed Products in the Field and in the Territory, in each case as contemplated by this Agreement, would infringe or misappropriate such Third Party's Patent Rights or Know-How;

(n) Epizyme, its Affiliates, and, to Epizyme's knowledge, Third Parties acting on its or their behalf, have conducted all Development of all Licensed Compounds and Licensed Products in the Territory in accordance with Applicable Laws, including all applicable GLP, GVP and GCP promulgated or endorsed by any applicable Regulatory Authority in the Territory;

(o) Epizyme has not received written notice of any investigations, inquiries, actions or other proceedings pending before or threatened by any Regulatory Authority or other Governmental Authority in the Territory with respect to the Licensed Products in the Territory arising from any action or default by Epizyme or any of its Affiliates or a Third Party acting on behalf of Epizyme in the discovery or Development of the Licensed Products; and

(p) The Eisai Agreement is the only Epizyme In-License Agreement in effect as of the Effective Date; and Epizyme and its Affiliates (i) have been in compliance with all material terms and conditions of the Eisai Agreement as of the Effective Date and, to the knowledge of Epizyme, Eisai has been in compliance with all material terms and conditions of the Eisai Agreement as of the Effective Date; (ii) have not received any written notice that alleges breach or default by Epizyme or any of its Affiliates of, requests a material amendment of, or termination of the Eisai Agreement; and (iii) are not aware of any material breach or default of the Eisai Agreement.

12.4 **Additional Epizyme Covenants**. Epizyme hereby covenants to Hutchmed during the Term that Epizyme and its Affiliates (a) shall remain in compliance with all material terms and conditions of the Epizyme In-License Agreements; (b) shall ensure that the Epizyme In-License Agreements are in full force and effect for so long as any Licensed IP licensed to Epizyme under such Epizyme In-License Agreement is necessary or reasonably useful for the Development, Manufacture or Commercialization of Licensed Compound or Licensed Products in the Field and in the Territory; (c) shall provide prompt notice to Hutchmed of its receipt of any written notice that alleges breach or default by Epizyme of, requests a material amendment of, or termination of any Epizyme In-License Agreement and provide to Hutchmed a copy of each of the foregoing; (d) not Develop, Manufacture, or Commercialize Licensed Products outside or inside the Territory in a manner that could be reasonably expected to materially adversely affect Hutchmed's Development, Manufacture, or Commercialization of the Licensed Products in the Territory hereunder; and (e) shall not amend any Epizyme In-License Agreement in a manner that would adversely affect the rights granted to Hutchmed hereunder without Hutchmed's prior written consent.

12.5 **Additional Hutchmed Warranties**. Hutchmed hereby represents and warrants to Epizyme that as of the Effective Date:

(a) other than Regulatory Approval for the Licensed Products, Hutchmed possesses any required, material permits and licenses to Develop, obtain Regulatory Approval and Reimbursement Approval (if applicable) for, Manufacture (after Manufacturing Technology Transfer) and Commercialize Licensed Products in the Field and Territory as contemplated in this Agreement, and has passed all annual inspections by Governmental Authorities relevant to the activities under this Agreement;

(b) neither Hutchmed nor any of its Affiliates is (i) state-owned, (ii) subject to any state-owned assets administrations or other authorities with respect to the registration of state-owned assets or ownership of scientific data or (iii) under collective ownership;

(c) neither Hutchmed nor any of its Affiliates is a relevant scientific research institution or higher-level educational school under the Notice of the General Office of the State Council on Issuing the Measures for the Management of Scientific Data, Guo Ban Fa (2018) No. 17, as such law exists as of the Effective Date, or otherwise subject to any obligations to disclose to or share with any Regulatory Authority Confidential Information hereunder other than for the purposes intended under this Agreement;

(d) Hutchmed or a Hutchmed Affiliate is a legally registered institution in Mainland China and has the technical expertise and familiarity with the relevant Applicable Laws to act as Epizyme's Authorized Regulatory Agent as required by this Agreement;

(e) to Hutchmed's knowledge, Hutchmed has not received written notice of any investigations, inquiries, actions or other proceedings pending before or threatened by any Regulatory Authority or other Governmental Authority in the Territory with respect to the Licensed Products in the Territory arising from any action or default by Hutchmed or any of its Affiliates or a Third Party acting on behalf of Hutchmed; and

(f) there are no Hutchmed In-License Agreements as of the Effective Date and no Hutchmed IP as of the Effective Date.

12.6 **Additional Hutchmed Covenants**. Hutchmed hereby covenants to Epizyme during the Term that:

(a) Hutchmed will obtain and maintain valid permits and licenses to Develop, Manufacture (after Manufacturing Technology Transfer) and Commercialize Licensed Products in the Field and Territory as contemplated in this Agreement;

(b) neither Hutchmed nor any of its Affiliates will become a relevant scientific research institution or higher-level educational school under the Notice of the General Office of the State Council on Issuing the Measures for the Management of Scientific Data, Guo Ban Fa (2018) No. 17, as such law exists as of the Effective Date, or otherwise subject to any obligations to disclose to or share with any Regulatory Authority Confidential Information hereunder other than for the purposes intended under this Agreement;

(c) Hutchmed and its Affiliates (a) shall remain in compliance with all material terms and conditions of the Hutchmed In-License Agreements; (b) shall ensure that the Hutchmed In-License Agreements are in full force and effect for so long as any Hutchmed IP licensed to Hutchmed under such Hutchmed In-License Agreement is necessary or reasonably useful for the Development, Manufacture or Commercialization of Licensed Compound or Licensed Products in the Field and in the Territory; (c) shall provide prompt notice to Epizyme of its receipt of any written notice that alleges breach or default by Hutchmed of, requests a material amendment of, or termination of any Hutchmed In-License Agreement and provide to Epizyme a copy of each of the foregoing; (d) not Develop, Manufacture, or Commercialize Licensed Products inside the Territory in a manner that could be reasonably expected to materially adversely affect Epizyme's Development, Manufacture, or Commercialization of the Licensed Products outside the Territory; and (e) shall not amend any Hutchmed In-License Agreement in a manner that would adversely affect the rights granted to Epizyme hereunder without Hutchmed's prior written consent; and

(d) the Development to be undertaken under this Agreement will not be funded by the government of Mainland China and the government of Mainland China shall obtain no rights to any Licensed IP.

12.7 **Anti-Corruption**.

(a) Anti-Corruption Provisions. Each Party represents and warrants to the other Party that such Party has not, directly or indirectly, offered, promised, paid, authorized or given, and each Party agrees that such Party will not, in the future, offer, promise, pay, authorize or give, money or anything of value, directly or indirectly, to any Government Official (as defined below) or Other Covered Party (as defined below) for the purpose, pertaining to this Agreement, of: (i) influencing any act or decision of such Government Official or Other Covered Party; (ii) inducing such Government Official or Other Covered Party to do or omit to do an act in violation of a lawful duty; (iii) securing any improper advantage; or (iv) inducing such Government Official or Other Covered Party to influence the act or decision of a Governmental Authority, in order to obtain or retain business, or direct business to, any person or entity, in any way related to this Agreement.

(b) For purposes of this Agreement: (A) "Government Official" means any official, officer, employee or representative of: (1) any Governmental Authority; (2) any public international organization (such as the International Monetary Fund, World Bank or the United Nations) or any department or agency thereof; or (3) any company or other entity owned or controlled by any Governmental Authority (including state-owned enterprises); and (B) "Other Covered Party" means any political party or party official, or any candidate for political office.

(c) Anti-Corruption Compliance.

(i) In performing under this Agreement, each Party, on behalf of itself, its respective Affiliates and (in the case of Epizyme) other Epizyme Entities and (in the case of Hutchmed) other Hutchmed Entities, agrees to materially comply with all anti-corruption or anti-bribery Applicable Laws, including the Foreign Corrupt Practices Act of 1977, as amended from time to time ("**FCPA**"), and all anti-corruption Laws of the Territory including relevant anti-corruption and anti-bribery provisions under the Criminal Law and Drug Administration law, Anti-Unfair Competition Law, Interim Regulations on Prohibiting Commercial Bribery Activities and other anti-corruption Laws and regulations in the Territory, each as may be enacted or amended from time to time (the "**Anti-Corruption Laws**").

(ii) Each Party represents and warrants to the other Party that such Party is not aware of any Government Official or Other Covered Party having any financial interest in the subject matter of this Agreement or in any way personally benefiting, directly or indirectly, from this Agreement.

(iii) No Party, nor any Affiliate of any Party (and (in the case of Epizyme) no other Epizyme Entity and (in the case of Hutchmed) no other Hutchmed Entity), shall give, offer, promise or pay any political contribution or charitable donation at the request of any Government Official or Other Covered Party that is in any way related to this Agreement or any related activity.

(iv) Each Party, its Affiliates and third party contractors shall in all cases, refrain from engaging in any activities or conduct which would cause the other Party, its Affiliates or third party contractors to be in violation of any Anti-Corruption Law. To the extent allowed by Applicable Law, if any Party (or its Affiliates or third party contractors) proposes to provide any information, data or documentation to any governmental or regulatory authority in respect of the Licensed Product that relates to or may result in a violation of the Anti-Corruption Laws, it shall first obtain the prior written approval of the other Party, which will not be unreasonably withheld, or shall provide such information, data or documentation in accordance with the other Party's written instructions.

(v) Hutchmed agrees that an executive of Hutchmed will, at the request of Epizyme, no more frequently than [**], provide Epizyme with a certification in the form hereto attached and incorporated by reference as Schedule 12.7(c).

(vi) Hutchmed agrees that should it learn or have reason to know of: (i) any payment, offer, or agreement to make a payment to a foreign official or political party for the purpose of obtaining or retaining business or securing any improper advantage for Epizyme under this Agreement, or (ii) any other development during the Term that in any way makes inaccurate or incomplete the representations, warranties and certifications of Hutchmed hereunder given or made as of the date hereof or at any time during the Term, relating to the Anti-Corruption Laws, Hutchmed will immediately advise Epizyme in writing of such knowledge or suspicion and the entire basis known to Hutchmed therefor.

(vii) Hutchmed covenants it shall maintain records (financial and otherwise) and supporting documentation related to the subject matter of this Agreement in order to document or verify compliance with the provisions of this Section, and upon request of Epizyme, upon reasonable advance notice, shall provide a Third Party auditor mutually acceptable to the Parties with access to such records for purposes of verifying compliance with the provisions of this Section. Acceptance of a proposed Third Party auditor may not be unreasonably withheld, delayed, or conditioned by Hutchmed. It is expressly agreed that the costs related to the Third Party auditor shall be fully paid by Epizyme, and that any auditing activities may not unduly interfere with the normal business operations of Hutchmed. The Hutchmed may require the Third Party auditor to enter into a reasonable confidentiality agreement in connection with such an audit.

(viii) In the event that a Party violates any Anti-Corruption Law, or breaches any provision in this Section 12.7, the other Party shall have the right to unilaterally terminate this Agreement pursuant to Section 14.4, except that the cure period set forth therein shall not apply.

12.8 **Disclaimer**. EXCEPT AS EXPRESSLY SET FORTH HEREIN, THE INTELLECTUAL PROPERTY RIGHTS PROVIDED BY ONE PARTY TO THE OTHER PARTY HEREIN ARE PROVIDED "AS IS" AND WITHOUT WARRANTY. EXCEPT AS EXPRESSLY SET FORTH HEREIN, EACH OF THE PARTIES EXPRESSLY DISCLAIMS ANY AND ALL WARRANTIES OF ANY KIND, EXPRESS OR IMPLIED, INCLUDING THE WARRANTIES OF DESIGN, MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE, VALIDITY OR ENFORCEABILITY OF THEIR RESPECTIVE INTELLECTUAL PROPERTY RIGHTS, AND NONINFRINGEMENT OF THE INTELLECTUAL PROPERTY RIGHTS OF THIRD PARTIES.

12.9 **Limitation of Liability**. NEITHER PARTY SHALL BE ENTITLED TO RECOVER FROM THE OTHER PARTY ANY SPECIAL, INCIDENTAL, EXEMPLARY, INDIRECT, CONSEQUENTIAL OR PUNITIVE DAMAGES OR DAMAGES FOR LOSS OF PROFIT OR LOST OPPORTUNITY IN CONNECTION WITH THIS AGREEMENT, ITS PERFORMANCE OR LACK OF PERFORMANCE HEREUNDER, OR ANY LICENSE GRANTED HEREUNDER. THE FOREGOING SHALL NOT LIMIT (a) ANY INDEMNIFICATION OBLIGATIONS HEREUNDER, OR (b) REMEDIES AVAILABLE TO EITHER PARTY WITH RESPECT TO A BREACH OF Article 10 OR SECTION 2.8 OR FRAUD COMMITTED BY THE OTHER PARTY

ARTICLE 13. INDEMNIFICATION

13.1 **Indemnification by Epizyme**. Epizyme shall indemnify, hold harmless and defend Hutchmed and its Affiliates, and their respective directors, officers, consultants, agents, contractors and employees (the "**Hutchmed Indemnitees**") from and against any and all Third Party suits, claims, actions, demands,

liabilities, expenses, costs, damages, deficiencies, obligations or losses (including reasonable attorneys' fees, court costs, witness fees, damages, judgments, fines and amounts paid in settlement) ("**Losses**") to the extent that such Losses arise out of (a) any breach of this Agreement by Epizyme, (b) any act or failure to act by any Epizyme Entity that causes a breach of any Epizyme In-License Agreement or Hutchmed In-License Agreement, (c) the Development, Manufacture or Commercialization of the Licensed Compound or any Licensed Product by or on behalf of any Epizyme Entity, (d) any act or omission by Hutchmed in its capacity as Authorized Regulatory Agent, or (e) the gross negligence or willful misconduct of any Epizyme Indemnitee, except, in each case of clauses (a) through (e), for those Losses for which Hutchmed has an obligation to indemnify Epizyme pursuant to Section 13.2, as to which Losses each Party shall indemnify the other to the extent of their respective liability for the Losses.

13.2 **Indemnification by Hutchmed**. Hutchmed shall indemnify, hold harmless and defend Epizyme and its Affiliates, and their respective directors, officers, consultants, agents, contractors and employees (the "**Epizyme Indemnitees**") from and against any and all Losses, to the extent that such Losses arise out of (a) any breach of this Agreement by Hutchmed, (b) any act or failure to act by any Hutchmed Entity that causes a breach of any Epizyme In-License Agreement or Hutchmed In-License, (c) the Development, Manufacture, or Commercialization of the Licensed Compound or any Licensed Product by or on behalf of any Hutchmed Entity, other than to the extent arising out of the practice of the Licensed IP, Epizyme Marks, or Epizyme Domains in accordance with this Agreement, or (d) the gross negligence or willful misconduct of any Hutchmed Indemnitee, except, in each case of clauses (a), through (d), for those Losses for which Epizyme has an obligation to indemnify Hutchmed pursuant to Section 13.1, as to which Losses each Party shall indemnify the other to the extent of their respective liability for the Losses.

13.3 **Procedure**. In the event of a claim by a Third Party against a Hutchmed Indemnitee or Epizyme Indemnitee entitled to indemnification under this Agreement ("**Indemnified Party**"), the Indemnified Party shall promptly notify the Party obligated to provide such indemnification ("**Indemnifying Party**") in writing of the claim and the Indemnifying Party shall undertake and solely manage and control, at its sole expense, the defense of the claim and its settlement. The Indemnified Party shall cooperate with the Indemnifying Party. The Indemnified Party may, at its option and expense, be represented in any such action or proceeding by counsel of its choice. The Indemnifying Party shall not be liable for any litigation costs or expenses incurred by the Indemnified Party without the Indemnifying Party's written consent. The Indemnifying Party shall not settle any such claim unless such settlement fully and unconditionally releases the Indemnified Party from all liability relating thereto and does not impose any obligations on the Indemnified Party, unless the Indemnified Party otherwise agrees in writing. No Indemnified Party may settle any claim for which it is being indemnified under this Agreement without the Indemnifying Party's prior written consent.

13.4 **Insurance**. Hutchmed shall, at its own expense, obtain and maintain insurance with a reputable insurance carrier with respect to the Hutchmed Entities' Development, Manufacture and Commercialization of Licensed Products in the Field in the Territory under this Agreement in such type and amount and subject to such deductibles and other limitations as biopharmaceutical companies in the Territory customarily maintain with respect to the Development, Manufacture and Commercialization of similar products, but in any event no less than (a) prior to the First Commercial Sale of the first Licensed Product in the Territory, [**] Dollars ($[**]) per incident and (b) following the First Commercial Sale of the first Licensed Product in the Territory, [**] Dollars ($[**]) per incident and [**] Dollars ($[**]) annual aggregate. Such insurance policy shall provide product liability coverage and broad form contractual liability coverage for Hutchmed's indemnification obligations under this Agreement. Hutchmed shall provide a copy of such insurance policy to Epizyme upon reasonable request by Epizyme. Hutchmed shall provide Epizyme with written notice at least [**] prior to any cancellation, non-renewal or material change in such insurance. This Section 13.4 shall survive expiration or termination of this Agreement and last until [**] after the last sale of any Licensed Product in the Field in the Territory by any Hutchmed Entity.

ARTICLE 14. TERM AND TERMINATION

14.1 **Term**. The term of this Agreement shall commence on the Effective Date and, unless earlier terminated in accordance with the terms of this Article 14, will expire, on a Licensed Product-by-Licensed Product basis, upon the expiration of the Royalty Term for such Licensed Product in the Territory (the "**Term**").

14.2 **Termination at Will by Hutchmed**. Hutchmed may terminate this Agreement at any time for any or no reason upon giving twelve (12) months' written notice to Epizyme.

14.3 **Termination for Patent Right Challenge**. In the event that either Party or its Affiliates challenges, or assists any individual or entity in challenging, the validity, patentability or enforceability of any Patent Right that (a) is owned by or licensed to the non-challenging Party or any of its Affiliates and (b) licensed or sublicensed, as the case may be, to the challenging Party under this Agreement, or otherwise opposes the validity, patentability or enforceability of any such Patent Right (except, in each case, as required by Applicable Law) then, to the extent consistent with Applicable Law, the non-challenging Party may terminate this Agreement by providing [**] written notice thereof to the challenging Party; provided, however, that the non-challenging Party's termination right under this Section shall not apply if (i) such challenge is stayed, withdrawn, or otherwise terminated during such [**] period, (ii) the applicable challenging Party is a sublicensee of the challenging Party's rights hereunder, and promptly after notice of such challenge from the non-challenging Party, the challenging Party terminates such sublicensee's rights to the Licensed Compound and Licensed Products in accordance with the terms of the applicable sublicense agreement(s), (iii) such challenge is asserted defensively as response, counterclaim, or cross-claim to a suit by the non-challenging Party or its Affiliates alleging that the challenging Party has infringed or misappropriated such Patent Rights, or (iv) such challenge is initiated by an Acquirer or a Third Party that the challenging Party acquires, in either case, prior to the effective date of such acquisition.

14.4 **Termination for Breach**. Subject to the terms and conditions of this Section 14.4, a Party (the "**Non-Breaching Party**") shall have the right, in addition to any other rights and remedies available to such Party at law or in equity, to terminate this Agreement in the event the other Party (the "**Breaching Party**") is in material breach of this Agreement. The Non-Breaching Party shall first provide written notice to the Breaching Party, which notice shall identify with particularity the alleged breach (the "**Breach Notice**"). With respect to material breaches of any payment provision hereunder, the Breaching Party shall have a period of [**] after such Breach Notice is provided to cure such breach. Except as expressly set forth in this Agreement, with respect to all other breaches, the Breaching Party shall have a period of [**] after such Breach Notice is provided to cure such breach; provided that if such breach is not a payment breach and is not reasonably capable of being cured within such [**] period, then such cure period shall be extended for an additional period not to exceed an addition [**] for so long as the Breaching Party is continuing diligent efforts to cure such breach; and provided further, that such cure period shall be tolled during the pendency of any good faith dispute as to whether such material breach has occurred or been cured. If such breach is not cured within the applicable period set forth above, the Non-Breaching Party may, at its election, terminate this Agreement upon written notice to the Breaching Party. The waiver by either Party of any breach of any term or condition of this Agreement shall not be deemed a waiver as to any subsequent or similar breach.

14.5 **Alternative Remedy in Lieu of Termination**. If Hutchmed has the right to terminate this Agreement pursuant to Section 14.4 based on an uncured material breach by Epizyme, then Hutchmed may elect either (a) terminate this Agreement and have the consequences of termination described in Section 14.7 apply, or (b) elect, in lieu of terminating this Agreement, for the rights and obligations of the Parties under this Agreement to continue, including the licenses and rights granted by Epizyme to Hutchmed under Section 2.1; provided that, (i) Hutchmed shall become solely responsible for one hundred percent (100%) of all

payments payable to the relevant Third Party on account of the sublicense to Hutchmed to Third Party IP under any Epizyme In-License Agreement, (ii) notwithstanding anything to the contrary herein (including Section 9.6(b)(iv)), Hutchmed's financial obligations to Epizyme (other than as provided under subsection (i) above) under Sections 9.4, 9.5, and 9.6 thereafter will be reduced to [**] percent ([**]%) of the excess of such financial obligations (as calculated without regard for this Section 14.5) over the amounts payable by Hutchmed pursuant to subsection (i) above, and (iii) if Hutchmed initiates an action seeking damages from Epizyme resulting from such material breach, then any payment reductions taken by Hutchmed pursuant to subsection (ii) will be applied to reduce the damages (if any) awarded to Hutchmed by a final decision of a court of competent jurisdiction.

14.6 **Termination for Bankruptcy and Rights in Bankruptcy**.

(a) To the extent permitted under Applicable Law, if, at any time during the Term, an Event of Bankruptcy (as defined below) relating to either Party (the "**Bankrupt Party**") occurs, the other Party shall have, in addition to all other legal and equitable rights and remedies available to such Party, the option to terminate this Agreement upon [**] written notice to the Bankrupt Party. It is agreed and understood that, if the other Party does not elect to terminate this Agreement upon the occurrence of an Event of Bankruptcy, except as may otherwise be agreed with the trustee or receiver appointed to manage the affairs of the Bankrupt Party, the other Party shall continue to make all payments required of it under this Agreement as if the Event of Bankruptcy had not occurred, and the Bankrupt Party shall not have the right to terminate any license granted herein. The term "**Event of Bankruptcy**" means: (a) filing in any court or agency pursuant to any statute or regulation of any state or country, a petition in bankruptcy or insolvency or for reorganization or for an arrangement or for the appointment of a receiver or trustee of the Bankrupt Party or of its assets or (b) being served with an involuntary petition against the Bankrupt Party, filed in any insolvency proceeding, where such petition is not dismissed within [**] after the filing thereof.

(b) All rights and licenses granted under or pursuant to this Agreement by Hutchmed and Epizyme are and shall otherwise be deemed to be, for purposes of Section 365(n) of the U.S. Bankruptcy Code or any analogous provisions in any other country or jurisdiction, licenses of right to "intellectual property" as defined under Section 101 of the U.S. Bankruptcy Code. The Parties agree that the Parties, as licensees of such rights under this Agreement, shall retain and may fully exercise all of their rights and elections under the U.S. Bankruptcy Code or any analogous provisions in any other country or jurisdiction. The Parties further agree that, in the event of the commencement of a bankruptcy proceeding by or against either Party under the U.S. Bankruptcy Code or any analogous provisions in any other country or jurisdiction, the Party hereto that is not a Party to such proceeding shall be entitled to a complete duplicate of (or complete access to, as appropriate) any such intellectual property and all embodiments of such intellectual property, which, if not already in the non-subject Party's possession, shall be promptly delivered to it (i) upon any such commencement of a bankruptcy proceeding upon the non-subject Party's written request therefor, unless the Party subject to such proceeding elects to continue to perform all of its obligations under this Agreement or (ii) if not delivered under clause (i) above, following the rejection of this Agreement by or on behalf of the Party subject to such proceeding upon written request therefor by the non-subject Party.

14.7 **Effects of Termination**. In the event of any termination (but not expiration) of this Agreement, the terms of this Section 14.7 shall apply:

(a) Except as provided in this Section 14.7, (i) all license grants in this Agreement from Epizyme to Hutchmed shall terminate as of the effective date of termination and (ii) in the event of termination by Hutchmed pursuant to Section 14.3, 14.4 or 14.6, all license grants from Hutchmed to Epizyme shall terminate as of the effective date of termination; provided, however, that, notwithstanding anything to the contrary in this Agreement and to the extent permitted by any applicable Epizyme In-License Agreement or Hutchmed In-License Agreement, any existing sublicense granted by the terminated Party in accordance

with Article 2 shall, upon the written request of any Sublicensee within [**] following the effective date of termination, remain in full force and effect, *provided* that such Sublicensee is not then in breach of its sublicense agreement, and in the event of termination by a Party for material breach by the other Party under Section 14.4, that such Sublicensee did not cause the material breach that gave rise to such termination, if applicable. Promptly following such written request from such Sublicensee, the terminating Party shall enter into a direct license agreement with such Sublicensee, whereby such Sublicensee agrees in writing to be bound to the terminating Party under the same terms and conditions of this Agreement, on terms that are substantially the same terms as the applicable terms of this Agreement; provided that, the terminating Party shall not in any event be obligated to agree to any obligations under any such direct license agreement that are greater than those in this Agreement;

(b) The ROFN (including for clarity the right to receive royalties) granted to Epizyme under Section 8.1 will survive in the event of termination by Hutchmed under Section 14.2, or termination by Epizyme under Section 14.3, 14.4, or 14.6.

(c) Upon termination by Hutchmed under Section 14.2:

(i) Hutchmed shall continue to use Commercially Reasonable Efforts to perform all of its obligations hereunder with respect to the completion all ongoing Joint Global Trials and Rejected Global Trials in the Territory (including patient enrollment and follow-up), in the case of Joint Global Trials, at Hutchmed's cost, subject to Section 9.3(c), and in the case of Rejected Global Trials, at Epizyme's cost;

(ii) Simultaneously with providing Epizyme a notice of termination under Section 14.2, Hutchmed shall provide to Epizyme a list of all Local Trials that are ongoing at such time. During the [**] period after Hutchmed notifies Epizyme that Hutchmed is terminating this Agreement under Section 14.2, Hutchmed shall continue to use Commercially Reasonable Efforts to perform all Local Trials at Hutchmed's cost; provided, however, that, at any time during such [**] period, Epizyme may provide [**] prior written notice to Hutchmed identifying (i) which Local Trials Epizyme elects to have transferred to an Epizyme Entity and (ii) which Local Trials Epizyme elects not to have transferred to an Epizyme Entity and which Hutchmed shall wind-down (each such Local Trial a "**Rejected Local Trial**"). Hutchmed shall promptly wind down all Rejected Local Trials in compliance with all Applicable Laws at Hutchmed's sole expense, subject to subsection (iii) below.

(iii) For all Local Trials that are not Rejected Local Trials, all costs during the [**] period in subsection (ii) above shall, as between the Parties, be borne by Hutchmed and all costs after the [**] period in subsection (ii) above shall, as between the Parties, be borne by Epizyme. Hutchmed shall, if requested by Epizyme and subject to availability of Hutchmed's or its Permitted Subcontractor CMO's Manufacturing capacity, supply each applicable Epizyme Entity with Other Combination Drug(s), and in the event Manufacturing Technology Transfer Completion has occurred prior to the notice of termination by Hutchmed, all Licensed Product required to conduct any Local Trial being conducted by such Epizyme Entity, before the effective date of termination under Section 14.2 and for a period not to exceed [**] after the effective date of termination. Such supply shall be at Hutchmed's Fully-Burdened Cost.

(d) Upon termination by Epizyme under Section 14.3, 14.4. or 14.6, to the extent permitted under Applicable Law, Hutchmed shall, as requested by Epizyme on a clinical trial-by-clinical trial basis: (i) promptly wind down any clinical trial then being conducted with respect to any Licensed Product in the Territory or (ii) transfer any clinical trial then being conducted with respect to any Licensed Product in the Territory to any Epizyme Entity or a Third Party as specified by Epizyme, at Hutchmed's expense; provided

that Hutchmed shall be permitted to take all reasonable steps necessary to minimize liability and harm to patients in this process. Upon termination by Hutchmed under Section 14.3, 14.4. or 14.6, Hutchmed shall promptly wind down any clinical trial then being conducted with respect to any Licensed Product in the Territory; provided that Hutchmed shall be permitted to take all reasonable steps necessary to minimize liability and harm to patients in this process.

(e) Hutchmed shall cease using the Licensed IP and, subject to a sell-off period not to exceed six (6) months after the effective date of termination, return all inventory of the Licensed Compound and Licensed Product (including Drug Substance and Drug Product) to Epizyme after such [**] period, together with all copies of the Licensed Know-How and other Confidential Information of Epizyme in the possession or control of Hutchmed or any of its Representatives, and if termination is by Hutchmed under Section 14.3, 14.4 or 14.6, Epizyme shall refund Hutchmed the applicable Clinical Supply Price or Commercial Supply Price for such Licensed Compound and Licensed Product returned to Epizyme;

(f) Hutchmed shall, at Epizyme's written request, to the extent reasonably feasible under Applicable Law, promptly: (i) assign and transfer to Epizyme all of the Hutchmed Entities' right, title, and interest in and to all Hutchmed Regulatory Documents (including Regulatory Filings and Regulatory Approvals), clinical trial agreements (to the extent assignable), confidentiality and other agreements, and materials and Know-How solely relating to any Licensed Product, and solely to the extent in any Hutchmed Entity's possession or control, and (ii) disclose to Epizyme all documents embodying the foregoing that are in any Hutchmed Entity's possession or control or that any Hutchmed Entity is able to obtain using reasonable efforts;

(g) at Epizyme's request, Hutchmed shall promptly take all action that may be reasonably required to transfer to Epizyme or a Third Party designated by Epizyme all portions of customer lists, promotional materials and any other information it has generated for selling the Commercialization of the Licensed Products in the Territory that are (i) solely related to the Licensed Products and (ii) not subject to any confidentiality obligations to any Third Parties or other restrictions on sharing such information with Epizyme;

(h) Except as otherwise provided in this Agreement, including in connection with clinical trials pursuant to Sections 14.7(c) and 14.7(d) and Hutchmed's sell-down right in Section 14.7(e), Hutchmed shall also cease immediately the use of any Internet website solely relating to any Licensed Product as well as any Epizyme Mark;

(i) The Manufacturing Technology Transfer Agreement shall terminate as of the effective date of termination of this Agreement;

(j) The Hutchmed Entities' Out-of-Pocket Costs associated with the activities set forth in this Section 14.7 shall be borne by (i) Hutchmed, if this Agreement is terminated by Epizyme pursuant to Section 14.3, Section 14.4, Section 14.6 or Section 17.1, or by Hutchmed pursuant to Section 14.2, or (ii) Epizyme, if this Agreement is terminated by Hutchmed pursuant to Section 14.3, 14.4, 14.6, or 17.1;

(k) If Epizyme does not obtain the right to sublicense Third Party IP to Hutchmed in the Territory pursuant to Section 2.7(a) (and as a result is not permitted to enter into any agreement with respect to such Third Party IP that includes any grant of rights in the Field in the Territory) and Hutchmed obtains rights (with the right to sublicense) to such Third Party IP in the Field in the Territory, then at Epizyme's written election, the Parties shall negotiate in good faith the commercially reasonable terms under which Hutchmed would grant Epizyme a non-exclusive license under such Third Party IP; and

(l) Notwithstanding any expiration or termination of this Agreement, the Safety Data Exchange Agreement (with respect to Hutchmed's obligations thereunder) shall continue in accordance with its terms.

14.8 **Survival; Accrued Rights**. The following articles and sections of this Agreement shall survive expiration or early termination for any reason: Article 1, Section 2.3, Section 2.5, Section 2.6(b), Section 2.7 (solely to the extent applicable to a Party's exercise of any rights, or performance of any obligations, retained by such Party hereunder following the applicable expiration or termination), Section 4.10, Section 4.13, Section 5.3, Section 5.5, Section 5.6, Section 5.7, Section 6.6 (second sentence only), Section 7.5 (solely with respect to any Licensed Product sold following expiration or early termination of this Agreement in accordance with Section 14.7(e)), Article 9 (solely with respect to any payment obligations incurred prior to expiration or termination), Article 10, Section 11.1, Section 11.2 (with respect to Joint Combination Therapy Patent Rights), Section 11.3 (with respect to Joint Combination Therapy Patent Rights), Section 12.7, Section 12.8, Section 12.9, Article 13, Section 14.6, Section 14.7, this Section 14.8, Article 15, Section 16.1, Section 16.2, and Article 17. In any event, expiration or termination of this Agreement shall not relieve either Party of any liability which accrued hereunder prior to the effective date of such expiration or termination nor preclude either Party from pursuing all rights and remedies it may have hereunder or at law or in equity with respect to any breach of this Agreement, nor prejudice either Party's right to obtain performance of any obligation.

ARTICLE 15. DISPUTE RESOLUTION; GOVERNING LAW

15.1 **Arbitration**. Other than any dispute that relates to the validity or enforceability of a Patent Right, which shall be resolved in accordance with Section 15.1(c) or a dispute that relates to Net Sales, which shall be resolved in accordance with Section 1.139, any dispute, claim or controversy in connection with this Agreement, including any question regarding its formation, existence, validity, enforceability, performance, interpretation, breach or termination, that is not resolved in accordance with Article 3 and is not subject to a Party's final decision-making authority in accordance with Article 3 (each, a "**Dispute**") shall be referred to and finally resolved by binding arbitration under the International Chamber of Commerce ("**ICC**") Rules of Arbitration (the "**Rules**"), which Rules are deemed to be incorporated by reference into this Section 15.1, in the manner described below:

(a) Arbitration Request. If a Party intends to begin an arbitration to resolve a Dispute arising under this Agreement, such Party shall provide written notice (the "**Arbitration Request**") to the other Party of such intention and the issues for resolution. Within [**] after the receipt of an Arbitration Request, the other Party may, by written notice, add additional issues for resolution. Any such Dispute shall be resolved in accordance with Section 15.1(b).

(b) General Arbitration Procedure for Disputes. The seat of arbitration will be in London, England unless another venue is agreed upon by Parties, and it will be conducted in the English language. The arbitrators may not decide based on equity. Unless agreed by the Parties to choose a single common arbitrator, the arbitration will be conducted by three arbitrators, one appointed by each Party, according to the Rules. The two arbitrators appointed by the Parties will by mutual agreement appoint the third arbitrator, who will preside over the arbitration. Any dispute or omission regarding the appointment of the arbitrators by the Parties, as well as the choice of the third arbitrator, will be resolved by the ICC. The arbitral award shall be final, definitive and binding on the Parties and their successors. The Parties reserve the right to apply to a competent judicial court to obtain urgent remedies to protect rights before establishment of the arbitration panel, without such recourse being considered as a waiver of arbitration. Except as otherwise determined by the arbitrators, the Parties shall each bear half of the fees and expenses of the arbitrators and the ICC, and each Party shall bear the costs and fees of its attorneys. Nothing in this Agreement shall be deemed as preventing either Party from seeking injunctive relief (or any other provisional remedy) from any court having jurisdiction over the Parties and the subject matter of the dispute

as necessary to protect either Party's name, Confidential Information, Know-How, intellectual property rights or any other proprietary right or otherwise to avoid irreparable harm. If the issues in dispute involve scientific or technical matters, any arbitrators chosen hereunder shall have educational training or experience sufficient to demonstrate a reasonable level of knowledge in the field of biotechnology and pharmaceuticals. Judgment on the award rendered by the arbitrator may be entered in any court having jurisdiction thereof. The Parties intend that each award rendered by an arbitrator hereunder shall be entitled to recognition and enforcement under the United Nations Convention on the Recognition and Enforcement of Arbitral Awards (New York, 1958).

(c) Intellectual Property Disputes. Unless otherwise agreed by the Parties, a dispute between the Parties relating to the validity or enforceability of any Patent Right shall not be subject to arbitration and shall be submitted to a court or patent office of competent jurisdiction in the relevant country or jurisdiction in which such patent was issued or, if not issued, in which the underlying patent application was filed. For the avoidance of doubt, in addition to any remedies available to Epizyme hereunder, Epizyme shall have the right to seek injunctive relief from any court of competent jurisdiction in the Territory against Hutchmed for any infringement by Hutchmed of Licensed Patent Rights.

15.2 **Choice of Law**. This Agreement and all amendments, modifications, alterations, or supplements hereto, and the rights of the Parties hereunder, shall be construed under and governed by the laws of the State of New York, exclusive of its conflicts of laws principles.

15.3 **Language**. This Agreement has been prepared in the English language and the English language shall control its interpretation. Except as explicitly provided otherwise in this Agreement, all consents, notices, and reports, to be delivered or provided by a Party under this Agreement shall be in the English language, and in the event of any conflict between the provisions of any such consent, notice, or report and the English language translation thereof, the terms of the English language translation shall control.

ARTICLE 16. ASSIGNMENT AND CHANGE OF CONTROL

16.1 **Assignment**.

(a) Neither this Agreement nor any of the rights, interests or obligations hereunder shall be assigned by either Party (and, for these purposes, a merger, sale of assets, operation of law or other transaction shall be deemed an assignment) without the prior written consent of the other Party. Notwithstanding the foregoing, either Party may, without the other Party's written consent, assign this Agreement and its rights and obligations hereunder in whole or in part to (i) an Affiliate of such Party for so long as such Affiliate remains an Affiliate of such Party or (ii) a Third Party that acquires, by or otherwise in connection with, a merger, sale of assets or otherwise, all or substantially all of the business of such Party to which the subject matter of this Agreement relates; provided that the assignee agrees in writing to assume all of such Party's obligations under this Agreement. The assigning Party will remain responsible for the performance by its assignee of this Agreement or any obligations hereunder so assigned.

(b) The terms of this Agreement will be binding upon and will inure to the benefit of the successors, heirs, administrators and permitted assigns of the Parties. Any purported assignment in violation of this Section 16.1 will be null and void ab initio.

16.2 **Consequences of a Party becoming an Acquired Party**.

(a) Each Party agrees that, in the event that a Party or any of its Affiliates (the "**Acquired Party**") is acquired through a Change in Control by one or more persons or entities (collectively, the "**Acquirer**"), the Acquired Party shall be deemed not to "Control" for purposes of this Agreement, and the non-Acquired

Party shall not obtain any rights or access under this Agreement to, any Know-How or Patent Rights owned by or licensed to such Acquirer, or any of such Acquirer's Affiliates that were not Affiliates of the Acquired Party immediately prior to the consummation of such Change in Control, that were not already within Licensed IP (if the Acquired Party is Epizyme or any of its Affiliates) or Hutchmed IP (if the Acquired Party is Hutchmed or any of its Affiliates) or Joint Combination Therapy IP immediately prior to the consummation of such Change in Control or that such Acquirer develops following the consummation of such Change in Control without access to or use of the Acquired Party's information or intellectual property. Each Party shall notify the other Party promptly after any Change in Control of such Party or any of its Affiliates. The Acquired Party will notify the other Party of the Change of Control within [**] after closing of the Change of Control.

(b) If, during the Term, either Party or any of its Affiliates becomes an Acquired Party, then, such Change of Control shall not alter or diminish Hutchmed's diligence obligations hereunder. If, during the Term, a Party or any of its Affiliates becomes an Acquired Party and the Acquirer or an Affiliate of the Acquirer has a Competing Product, then unless otherwise agreed by the other Party, the Acquired Party or such Affiliate will notify the other Party in writing within [**] after the closing date of the Change of Control that the Acquirer or such Affiliate will, at its election:

(i) divest, whether by license, divestiture of assets or otherwise, its interest in such Competing Product, as applicable, in the Territory to a Third Party, to the extent necessary to be in compliance with Section 2.8, as applicable, provided that the Acquirer or its applicable Affiliate may retain an economic interest through such a license, divestiture of assets or other transaction as long as the Acquirer or its applicable Affiliate does not retain any other material rights as to such Competing Product, as applicable, in the Territory beyond a passive economic interest; or

(ii) terminate the Development, Manufacture and Commercialization of such Competing Product, as applicable, in the Territory, to the extent necessary to be in compliance with Section 2.8, as applicable; or

(iii) implement reasonable measures to keep the Acquirer's and its applicable Affiliates' activities relating to any Competing Product(s) of the Acquirer or its Affiliates in the Territory separated from the Acquirer's and its applicable Affiliates' activities relating to the Licensed Products in the Territory, and subject to the Acquirer and its applicable Affiliates implementing such measures, the Acquirer's and its applicable Affiliates' Development, Manufacture and Commercialization of such Competing Product(s) shall be deemed not to violate Section 2.8.

If the Acquired Party or any of its Affiliates notifies the other Party in writing that it or its relevant Affiliate intends to divest such Competing Product, as applicable, or terminate the Development, Manufacture and Commercialization of the Competing Product, as applicable, in the Territory as provided in clause (i) or clause (ii) of this Section 16.2(b), then the Acquired Party or its relevant Affiliate will effect such divestiture or termination within [**] after the date of the relevant acquisition or other event, subject to compliance with Applicable Law, and will confirm to the other Party in writing when such divestiture or termination has been completed. The Acquired Party will keep the other Party reasonably informed of its and its Affiliates' efforts and progress in effecting such divestiture or termination until it is completed. Until such divestiture or termination occurs, the Acquired Party shall (1) keep its and its Affiliates' activities with respect to such Competing Product, as applicable, separate from their activities with respect to the Licensed Products, and (2) continue to fully perform all of their obligations hereunder with respect to Licensed Products, including their applicable diligence obligations with respect to the Development and Commercialization of Licensed Products hereunder.

16.3 **Consequences of a Party Acquiring a Third Party**.

(a) Without altering or diminishing Hutchmed's diligence obligations hereunder, if, during the Term, either Party or any of its Affiliates acquires a Third Party (whether by way of a purchase of assets, merger, consolidation, Change in Control or otherwise) that is, at such time, Developing, Manufacturing or Commercializing a Competing Product in a manner that, if performed by the acquiring Party or any of its Affiliates, would violate Section 2.8, then the acquiring Party or its applicable Affiliate will notify the non-acquiring Party of the closing of the relevant acquisition within [**]. Unless otherwise agreed by the non-acquiring Party, the acquiring Party or such Affiliate will notify the non-acquiring Party in writing within [**] of the closing date that the acquiring Party or such Affiliate will:

(i) divest, whether by license, divestiture of assets or otherwise, its interest in such Competing Product, as applicable, in the Territory to a Third Party, to the extent necessary to be in compliance with Section 2.8, as applicable, provided that the acquiring Party or its applicable Affiliate may retain an economic interest through such a license, divestiture of assets or other transaction as long as the acquiring Party does not retain any other material rights as to such Competing Product, as applicable, in the Territory beyond a passive economic interest;

(ii) with respect to Hutchmed as the acquiring Party, terminate this Agreement in accordance with Section 14.2; or

(iii) terminate the Development, Manufacture and Commercialization of such Competing Product, as applicable, in the Territory, to the extent necessary to be in compliance with Section 2.8, as applicable.

If the acquiring Party or any of its Affiliates notifies the non-acquiring Party in writing that it or its relevant Affiliate intends to divest such Competing Product, as applicable, or terminate the Development, Manufacture and Commercialization of the Competing Product, as applicable, in the Territory as provided in this Section 16.3, then the acquiring Party or its relevant Affiliate will effect such divestiture or termination within [**] after the date of the relevant acquisition or other event, subject to compliance with Applicable Law, and will confirm to the non-acquiring Party in writing when such divestiture or termination has been completed. The acquiring Party will keep the non-acquiring Party reasonably informed of its and its Affiliates' efforts and progress in effecting such divestiture or termination until it is completed. Until such divestiture or termination occurs, the acquiring Party shall keep its and its Affiliates' activities with respect to such Competing Product, as applicable, separate from their activities with respect to the Licensed Products and shall continue to fully perform all of their obligations hereunder with respect to Licensed Products, including their applicable diligence obligations with respect to the Development and Commercialization of Licensed Products hereunder.

ARTICLE 17. MISCELLANEOUS

17.1 **Force Majeure**. If either Party shall be delayed, interrupted in or prevented from the performance of any obligation hereunder by reason of a force majeure event, which may include any act of God, fire, flood, earthquake, public disaster, war (declared or undeclared), act of terrorism, epidemic or pandemic, government action, strike or labor differences, or lack of or inability to obtain raw materials, fuel, or power, in each case outside of such Party's reasonable control, and whether or not such force majeure event is foreseeable as of the Effective Date, such Party shall not be liable to the other therefor, and the time for performance of such obligation shall be extended for a period equal to the duration of the force majeure event which occasioned the delay, interruption or prevention. The Party invoking the force majeure rights of this Section 17.1 must notify the other Party by courier or overnight dispatch (e.g., Federal Express) within a period of [**] of both the first and last day of the force majeure event unless the force majeure

renders such notification impossible, in which case notification will be made as soon as possible. During the pendency of any force majeure event, the Party subject to such force majeure shall use Commercially Reasonable Efforts to terminate such force majeure or to mitigate the effects of such force majeure so that such Party can still perform its obligations under this Agreement. If the delay resulting from the force majeure event exceeds [**], the other Party may terminate this Agreement immediately upon written notice to the Party.

17.2 **Entire Agreement**. This Agreement, together with the exhibits and schedules attached hereto, constitutes the entire agreement between Epizyme or any of its Affiliates, on the one hand, and Hutchmed or any of its Affiliates, on the other hand, with respect to the subject matter hereof, supersedes all prior understandings and writings between Epizyme or any of its Affiliates, on the one hand, and Hutchmed or any of its Affiliates, on the other hand relating to such subject matter, including the Confidentiality Agreement, and, subject to Section 4.3, shall not be modified, amended or (subject to Article 14) terminated, except by another agreement in writing executed by the Parties.

17.3 **Severability**. If, under Applicable Law, any provision of this Agreement is invalid or unenforceable, or otherwise directly or indirectly affects the validity of any other material provision of this Agreement (such invalid or unenforceable provision, a "**Severed Clause**"), it is mutually agreed that this Agreement shall endure except for the Severed Clause. The Parties shall consult one another and use their reasonable efforts to agree upon a valid and enforceable provision that is a reasonable substitute for the Severed Clause in view of the intent of this Agreement.

17.4 **Notices**. Any notice required or permitted to be given under this Agreement shall be in writing and shall be mailed by internationally recognized express delivery service, or sent by facsimile or email and confirmed by mailing, as follows (or to such other address as the Party to whom notice is to be given may have furnished to the other Party in writing in accordance herewith):

If to Epizyme:
Epizyme, Inc.
400 Technology Square
Cambridge, MA 02139 USA
Attention: General Counsel
Facsimile:

with a copy to (which shall not constitute notice for purposes of this Agreement):

WilmerHale LLP
60 State Street
Boston, Massachusetts 02109 USA
Attention: Steven D. Barrett, Esq.
Facsimile: (617) 526-5000

If to Hutchmed:
Hutchison China MediTech Investment Limited
Level 18 Metropolis Tower
10 Metropolis Drive
Hung Hom
Kowloon
Hong Kong
Attention: Christian Hogg, Director

with copy to (which shall not constitute notice for purposes of this Agreement):

Hutchison China MediTech Investment Limited
Vistra Corporate Services Centre
Wickhams Cay II, Road Town, Tortola, VG1110
British Virgin Islands

with copy to (which shall not constitute notice for purposes of this Agreement):

Ropes & Gray LLP
Prudential Tower
800 Boylston Street
Boston, Massachusetts 02199 USA
Attn: Marc A. Rubenstein

Any such notice shall be deemed to have been given (a) when delivered if personally delivered, (b) on receipt if sent by overnight courier or (c) on receipt if sent by mail.

17.5 **Interpretation**. (a) Whenever any provision of this Agreement uses the word "including," "include," "includes," or "e.g.," such word shall be deemed to mean "including without limitation" and "including but not limited to"; (b) "herein," "hereby," "hereunder," "hereof" and other equivalent words shall refer to this Agreement in its entirety and not solely to the particular portion of this Agreement in which any such word is used; (c) a capitalized term not defined herein but reflecting a different part of speech from that of a capitalized term which is defined herein shall be interpreted in a correlative manner; (d) wherever used herein, any pronoun or pronouns shall be deemed to include both the singular and plural and to cover all genders; (e) the recitals set forth at the start of this Agreement, along with the schedules and the exhibits to this Agreement, and the terms and conditions incorporated in such recitals and schedules and exhibits, shall be deemed integral parts of this Agreement and all references in this Agreement to this Agreement shall encompass such recitals and schedules and exhibits and the terms and conditions incorporated in such recitals and schedules and exhibits; provided that, in the event of any conflict between the terms and conditions of the body of this Agreement and any terms and conditions set forth in the recitals, schedules or exhibits, the terms of the body of this Agreement shall control; (f) in the event of any conflict between the terms and conditions of this Agreement and any terms and conditions that may be set forth on any order, invoice, verbal agreement or otherwise, the terms and conditions of this Agreement shall govern; (g) this Agreement shall be construed as if both Parties drafted it jointly, and shall not be construed against either Party as principal drafter; (h) unless otherwise provided, all references to Sections, Articles and Schedules in this Agreement are to Sections, Articles, Exhibits and Schedules of and to this Agreement; (i) any reference to any Applicable Law shall mean such Applicable Law as in effect as of the relevant time, including all rules and regulations thereunder and any successor Applicable Law in effect as of the relevant time, and including the then-current amendments thereto; (j) wherever used, the word "shall" and the word "will" are each understood to be imperative or mandatory in nature and are interchangeable with one another; (k) references to a particular person or entity include such person's or entity's successors and assigns to the extent not prohibited by this Agreement; (l) references to a Party's knowledge shall be taken to refer to the actual knowledge of such Party's senior management team as of the Effective Date; (m) the captions and table of contents used herein are inserted for convenience of reference only and shall not be construed to create obligations, benefits or limitations; (n) the word "year" means any consecutive twelve (12) month period, unless otherwise specified; and (o) the term "or" shall be interpreted in the inclusive sense commonly associated with the term "and/or" where applicable.

17.6 **Agency**. Other than to the extent Hutchmed serves as an Authorized Regulatory Agent as provided in this Agreement, neither Party is, nor will be deemed to be a partner, employee, agent or representative of the other Party for any purpose. Each Party is an independent contractor of the other Party. Neither Party shall have the authority to speak for, represent or obligate the other Party in any way without prior written authority from the other Party.

17.7 **No Waiver**. Any omission or delay by either Party at any time to enforce any right or remedy reserved to it, or to require performance of any of the terms, covenants or provisions hereof, by the other Party, shall not constitute a waiver of such Party's rights to the enforcement of any of its rights under this Agreement. Any waiver by a Party of a particular breach or default by the other Party shall not operate or be construed as a waiver of any subsequent breach or default by the other Party.

17.8 **Cumulative Remedies**. Except as may be expressly set forth herein, no remedy referred to in this Agreement is intended to be exclusive, but each shall be cumulative and in addition to any other remedy referred to in this Agreement or otherwise available under law or in equity.

17.9 **No Third Party Beneficiary Rights**. This Agreement is not intended to and shall not be construed to give any Third Party any interest or rights (including any third party beneficiary rights) with respect to or in connection with any agreement or provision contained herein or contemplated hereby, other than (a) to the extent provided in Section 2.4, Epizyme, (b) to the extent provided in Section 13.1, the Hutchmed Indemnitees, and (c) to the extent provided in Section 13.2, the Epizyme Indemnitees.

17.10 **Performance by Affiliates, Sublicensees, or Permitted Subcontractors**. To the extent that this Agreement imposes any obligation on any Hutchmed Entity, Hutchmed shall cause such Hutchmed Entity to perform such obligation. Subject to Section 9.10, either Party may use one or more of its Affiliates to perform its obligations and duties hereunder; provided that such Party so notifies the other Party in writing and provided, further, that such Party shall remain liable hereunder for the prompt payment and performance of all of its obligations hereunder.

17.11 **Counterparts**. This Agreement may be executed in counterparts, all of which taken together shall be regarded as one and the same instrument.

[*Signature page follows*]

IN WITNESS WHEREOF, the Parties have executed this Agreement through their duly authorized representatives to be effective as of the Effective Date.

EPIZYME, INC.

By: /s/ Robert Bazemore

Name: Robert Bazemore

Title: President & Chief Executive Officer

HUTCHISON CHINA MEDITECH INVESTMENT LIMITED

By: /s/ Christian Hogg

Name: Christian Hogg

Title: Director

Exhibit 4.16

[DATE] **PRIVATE & CONFIDENTIAL**

[NAME]

Present

Dear NAME,

This is to confirm our offer of employment (the "Agreement") to you as [TITLE]. You will be employed by Hutchison MediPharma (US), Inc. ("the Company") under the following terms and conditions with effect from [DATE] (the "Effective Date") :-

1. **Basic Salary**

   Your basic salary will be [XX] Dollars (US$[XX]) per month payable in arrears ("Basic Salary"). This is an exempt position in the Company and in accordance with federal or New Jersey State law, is not eligible for overtime pay.

2. **Annual Bonus**

   For each calendar year completed from the Effective Date of this Agreement, pro-rated for a partial initial year, you will be eligible to receive an annual performance bonus, which target amount for calendar year [XX] is set at [XX] Dollars (US$[XX]) or [XX]% of your base annual salary ("Bonus"). This Bonus, which is payable at the discretion of the Company, will depend on the Company's business results and your performance, and you must be employed on the date of any Bonus payment in order to receive it.

3. **Share Options/Long Term Incentive Award**

   On commencement of your employment, subject to any necessary approvals and trading window restrictions, Hutchison China MediTech Limited ("HCML") will consider granting you shares of HCML pursuant to the rules of the HCML Share Option Scheme as well as an award which provides for a performance related right to cash or shares of HCML pursuant to the vesting and other rules of the HCML Long Term Incentive Award Scheme.

4. **Benefits**

You and your eligible dependents will have the opportunity to participate in the Company's benefits program, subject to the terms and conditions of such benefit programs. As of this date, the Company's benefit program includes medical, life, long-term disability and group travel accident programs as well as a 401-K savings plan.

5. **Transfer of Furniture & Personal Effects**

You will be entitled to an allowance ("Relocation Allowance") of up to US$[XX] for the purposes of transporting personal effects from your home town to New Jersey and/or purchase of furniture locally. To the extent determined by the Company, the Relocation Allowance will be provided on a pre-tax basis in accordance with Internal Revenue Service rules.

6. **Taxation**

All payments made by the Company under this Agreement shall be reduced by any tax or other amounts required to be withheld by the Company under applicable law.

7. **Business Travel**

As the Company, its subsidiaries and associated companies are involved in a regional business and have business interests and dealings overseas, you may therefore be required from time to time to travel overseas in the performance of your duties of employment with the Company, its subsidiaries or associated companies.

For all business purposes you will be entitled to travel economy class except in those instances when total elapsed travel time from point of departure to destination (including in-transit time at airports enroute to destination) is in excess of 6 hours. In such cases, Business Class travel will be permitted.

8. **Vacation and Holidays**

During the term of this employment, you will be entitled to three (3) weeks of paid time off (15 days) during the first full calendar year of employment and each subsequent year. Additionally, you will receive ten (10) paid holidays and five (5) sick days in addition to the paid time off mentioned. Unused vacation does not carry over from year-to-year

unless approved by your line manager, and no amounts will be paid with respect to unused vacation upon your termination of employment.

9. **Expenses**

The Company will reimburse authorised expenses incurred by you on Company business, subject to the Company's policies from time to time in force relating to expenses. A guiding principle in settling expenses is that there should neither be financial loss nor gain to you as a result of any reasonable expense incurred on Company business.

All claims for expenses must be approved by the Company. No employee is allowed to approve or authorise payment for his/her own expenses.

10. **Conflict of Interest**

You will not (without the prior written consent of the Company or any one of its subsidiaries or associated companies) during your employment hereunder, directly or indirectly be interested in any other businesses, or engage in, be concerned with, or provide services to, any other person, company, business entity or other organisation whatsoever (whether as an employee, officer, director, agent, partner, consultant or otherwise). You will devote your whole time and attention to servicing the Company, its subsidiaries and associated companies.

Without prejudice to the provisions of the preceding paragragh, you agree to declare all your business interests and provide requisite details of such interests to the Company, whether or not they are similar to or in conflict with the business or activities of the Company, its subsidiaries or associated companies, at the date hereof and in future.

11. **Confidentiality**

Your employment terms and conditions are strictly confidential between you and the Company. Any disclosure of such employment terms and conditions to other employees or outside parties constitute a breach of this contract and may result in disciplinary action.

You will neither during the employment hereunder (except in the proper performance of your duties) nor at any time (without limit) after the termination thereof, howsoever arising, directly or indirectly:

(a) use for your own purposes or those of any other person, company, business entity or other organisation whatsoever; or

(b) disclose to any person, company, business entity or other organisation whatsoever;

any trade secrets or confidential information relating or belonging to the Company or any of its subsidiaries or associated companies including but not limited to information relating to customers, customer lists or requirements, price lists or pricing structures, marketing and sales information, business plans or dealings, employees or officers, financial information or plans, designs, formulae, product lines, information relating to drug research and clinical development activities, any document marked "confidential" or any information which you have been advised is "confidential" or which you might reasonably except the Company would regard as "confidential" or any information which has been given to the Company or any of its subsidiaries or associated companies in confidence by customers, suppliers or other persons.

You will not at any time during the continuance of your employment with the Company make any notes or memoranda relating to any matter within the scope of the Company's business, dealings or affairs otherwise than for the benefit of the Company or its subsidiaries or associated companies.

You will not make or communicate any statement (whether written or oral) to any representative of the press, television, radio, file or other media and shall not write any article for the press or otherwise for publication on any matter connected with or relating to the business of the Company or any of its subsidiaries or associated companies without obtaining the written approval of the Company unless permitted under the Group Policy on the Media.

Forthwith upon the termination of your employment hereunder, and/or at any other time if the Company shall so request, you shall deliver to the Company all documents (including correspondence, lists of customers, notes, memoranda, plans, drawings and other documents of whatsoever nature) in whatever forms, including magnetic media, models or samples made or compiled by or delivered to you or in your possession concerning the business, finances or affairs of the Company or any of its subsidiaries or associated companies. For the avoidance of doubt, it is hereby declared that the property in all such document as aforesaid shall at all times be vested in the Company or its subsidiaries or associated companies.

12. **Reasonableness of Restrictions**

12.1 You recognise that, whilst performing your duties hereunder, you will have access to and come into contact with trade secrets and confidential information belonging to the Company or any of its subsidiaries or associated companies and will obtain personal knowledge of and influence over its or their customers and/or employees. You therefore agree that the restrictions contained in Clauses 10 and 11 are resonable and necessary to protect the legitimate business interests of the Company or any of its subsidiaries or associated companies both during and after the termination of such employment.

12.2 Without prejudice to the foregoing, if any part of any such restrictions is found to be wholly or partly void, invalid, or otherwise unenforceable then such part shall be deemed eliminated or modified to the extent to which it is necessary so that the restrictions in that part shall become valid or enforceable.

13. **Code of Conduct**

At all times, you are expected to observe the highest standards of ethical, personal and professional conduct.

You must not act dishonourably nor abuse the trust placed in you by the Company. All improper business practices must be rejected.

Whether working in the United States or overseas, you should adhere to the Company's policies, procedures and regulations which are applicable to you from time to time during your employment and you must comply with all legal requirements. Failure to comply with the Company's policies, procedures and regulations or any legal requirements may result in appropriate disciplinary actions taken against you and/or termination of your employment.

14. **Termination Notice**

14.1 You will be engaged on an at-will basis. You may terminate your employment with the Company by providing 3 months' advance notice in writing. This period of notice can commence from any day of the month.

14.2 In the event that your employment is terminated by the Company without Cause, and prior to the notice of termination you have completed at least 12 months of continuous service with the Company, subject to your signing and returning to the

Company a timely and effective customary general release of claims in the form provided by the Company by no later than the 30th calendar day following the termination of employment, you will be entitled to receive 6 months' Basic Salary (in equal periodic instalments consistent with the Company's standard payroll practices) and an annual target bonus prorated for the calendar year up to the date of termination (pay together with the 6th instalments of the severance payments) subject to the following applying during the period of 6 months while the severance payments are paid to you:

a) you shall continue to comply with the terms of Conflict of Interest, Confidentiality and Code of Conduct contained in clauses 10, 11 and 13 herein respectively and in particular you will make no public statements regarding the Company or its affiliates;
b) you will not either directly or indirectly solicit or encourage employees of the Company or its affiliates to terminate their employment with the Company or its affiliates;
c) you will not directly or indirectly engage in, become financially interested in, be employed by, provide services to or otherwise have any connection with any business or venture that is engaged in activities which compete with the drug candidates/products of Hutchison MediPharma Limited.

For the purposes of this Clause, **"Cause"** means your termination of employment by the Company means your termination of employment due to (i) your willful or grossly negligent failure to perform your duties to the Company, (ii) your commission of any felony or any other crime involving moral turpitude; (iii) your committing any act of fraud or a material act of dishonesty in connection with the performance of your duties to the Company, (iv) your use of narcotics, alcohol, or illegal drugs in a manner that has a detrimental effect on the performance of your duties, (v) your material breach of your obligations hereunder.

15. **References**

This offer of employment is subject to satisfactory references, which the Company will take up upon receipt of your acceptance of our offer of employment.

16. **Alterations To Contract**

This letter constitutes the written terms and conditions governing your employment with the Company and supersedes any prior written or verbal agreements. Any changes in your terms and conditions of employment will be notified to you.

17. **Governing Law**

This letter shall be governed by and construed in accordance with the laws of New Jersey State without regard to principles of conflicts of law.

19. **Successors and Assigns**

This letter shall be binding upon the Company and any successors and assigns of the Company, including any corporation with which, or into which, the Company may be merged or which may succeed to the Company's assets or business. Neither this letter nor any right or obligation hereunder may be assigned by you.

If the terms and conditions of this offer of employment are satisfactory, please accept the offer by signing and returning an executed copy of this offer employment letter herein.

Yours sincerely,

[NAME]

[TITLE]

****

If you agree with the terms herein, please signify your acceptance by signing and returning to me the duplicate copy of this contract.

Signed : _____

Name : _____

Date : _____

Exhibit 4.17

CONFIDENTIAL
OFFER OF EMPLOYMENT-Hutchison MediPharma International Inc.

[DATE]

[NAME]

Dear [NAME],

We are pleased to offer you a position with Hutchison Medipharma International Inc. (the "Company") as [TITLE], effective [DATE].

This offer of at-will employment is conditioned upon your satisfactory completion of certain requirements fully outlined below in this letter. Your employment is subject to the terms and conditions set forth in this letter, which override anything said to you during your interview or any other discussions about your employment with the Company.

Base Salary
You will be paid an annual salary of $[XX] payable in accordance with the Company's standard payroll practices, and subject to all withholdings and deductions as required by law.

Bonus
You will also be eligible for an annual bonus at a target level of [XX]% ($[XX]), which is payable at the discretion of the Company, and is dependent on the Company's business results and your performance, provided that you remain employed by the Company on the date of the payment of any annual bouns.

Share Options/Long term Incentive Award
Upon commencement of your employment, subject to any necessary approvals and trading window restrictions, Hutchison China Medi Tech Limited ("HCML") will consider granting you shares of HCML Share Option Scheme as well as an award which provides for a performance related right to cash or shares of HCML pursuant to the vesting and other rules of the HCML Long Term Incentives Award Scheme.

Benefits
You will be eligible to participate in the Company's benefits plans and programs in effect, subject to the terms and conditions of such benefits programs, including: group medical, dental, vision, and life/travel accident insurance, short-term and long-term disability and eligibility to participate in the 401K plan upon 3months of employment.

Vacation and Holidays
You will be entitled to 18 days paid time off during the first full calendar year of employment. Additionally, you will receive eight (8) paid holidays and five (5) sick days. The office is also closed for the holiday between December 25 — January 1, [XX].

Business Travel

You may be required to travel for business in the performance of your duties of employment with the Company, its subsidiaries or associated companies.

Termination Notice

You will be employed on an at-will basis. In the case of a termination for Cause by the Company (as defined below) or by you with Good Reason (as defined below), no notice of termination needs to be provided by either party.

In the event of a termination by the Company without Cause or by you without Good Reason, either party may terminate your employment with the Company by providing 3 months' advance notice in writing; however, in lieu of notice of a termination without Cause, the Company may provide you with your base salary for all or any portion of the notice period. This period of notice can commence from any day of the month. In the event that your employment is terminated by the Company without Cause or by you with Good Reason, and prior to the notice of termination you have completed at least 12 months of continuous service with the Company, subject to your signing and returning to the Company a timely and effective customary general release of claims in the form provided by the Company by no later than 30th calender day following the termination of employment, you will be entitled to receive i) 6 months Basic Salary (in equal installments consistent with the Company's standard payroll practices); ii) an annual target bonus prorated for the calender year up to the date of termination (pay together with the 6th installments of the severance payments); iii) a continuation of coverage under the Company's health plan at the same levels of coverage and contribution to premiums by the parties as in effect immediately preceding the termination notice, subject to the following applying during the period of 6 months while severance payments are paid to you:

1) You shall continue to comply with the terms of Conflict of Interest, Confidentiality and Code of Conduct policy
2) You will not either directly or indirectly solicit or encourage employees of the Company or its affiliates to terminate their employment with the Company or its affiliates;
3) You will not directly or indirectly engage in, become financially interested in, be employed by, provide services to or otherwise have any connection with any business or venture that is engaged in activities which compete with the drug candidates/products of Hutchison MediPharma International Inc.

For the purpose of **"Cause"** this means your termination of employment by the Company means your termination of employment is due to your willful or grossly negligent failure to perform your duties to the Company, your committing any act of fraud or a material act of dishonesty in connection with the performance of your duties to the Company and/or your material breach of your obligations hereunder.

For the purpose of **"Good Reason"** this shall mean that one or more of the following has occurred without your written consent: i) a material reduction in the scope of your duties and responsibilities; ii) a material reduction in your annual level of target compensation, including base salary and incentive compensation; iii) the Company's breach of any of its material obligations hereunder.

You will be subject to all applicable employment and other policies of the Company, as outlined in the Hutchison MediPharma International Inc. Employee Handbook and elsewhere. **Your employment will be at-will, meaning that you or the Company may terminate the employment relationship at any time, with or without cause, and with or without notice, except as otherwise stated herein.**

This offer is contingent upon:

a) Verification of your right to work in the United States, as demonstrated by your completion of the I-9 form upon hire and your submission of acceptable documentation (as noted on the I-9 form) verifying your identity and work authorization within three days of starting employment. For your convenience, a copy of the I-9 Form's List of Acceptable Documents is enclosed for your review;

b) Satisfactory completion of a background investigation, for which the required notice and consent forms are enclosed with this letter; and

c) Satisfactory completion of a drug screening, for which the required notice and consent forms are enclosed with this letter.

This offer will be withdrawn if any of the above condition are not satisfied. Please do not resign from your current job until you have confirmation from the Company that these conditions have been satisfied.

By accepting this offer, you confirm that you are able to accept this job and carry out the work that it would involve without breaching any legal restrictions on your activities, such as restrictions imposed by a current or former employer. You also confirm that you will inform the Company about any such restrictions and provide the Company with as much information about them as possible, including any agreements between you and your current or former employer describing such restrictions on your activities.

You further confirm that you will not remove or take any document or proprietary data or materials of any kind, electronic or otherwise, with you from your current or former employer to the Company without written authorization from your current or former employer, nor will you use or disclose any such confidential information during the course and scope of your employment with the Company. If you have any questions about the ownership of particular documents or other information, discuss such questions with your former employer before removing or copying the documents or information.

All of us at Hutchison MediPharma International Inc. are excited at the prospect of you joining our team. If you have any questions about the above details, please call me immediately. If you wish to accept this position, please sign below and return this letter agreement to [NAME] within 7 business days. This offer is open for you to accept until [DATE] at which time it will be deemed to be withdrawn.

Yours sincerely,

[NAME]

[TITLE]

ACCEPTED AND AGREED

[NAME]

Signed _____
Date _____

Exhibit 8.1

List of Significant Subsidiaries of HUTCHMED (China) Limited

HUTCHMED Limited (PRC)

HUTCHMED International Corporation (U.S.)

Hutchison Whampoa Sinopharm Pharmaceuticals (Shanghai) Company Limited (PRC)

Hutchison Hain Organic (Hong Kong) Limited (Hong Kong)

Hutchison Healthcare Limited (PRC)

HUTCHMED Science Nutrition Limited (Hong Kong)

Shanghai Hutchison Pharmaceuticals Limited (PRC)*

*non-consolidated entity

Exhibit 12.1

CERTIFICATION

I, Christian Lawrence Hogg, certify that:

1. I have reviewed this annual report on Form 20-F of HUTCHMED (China) Limited (the "Company");

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the Company as of, and for, the periods presented in this report;

4. The Company's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the Company and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the Company, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (c) Evaluated the effectiveness of the Company's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the Company's internal control over financial reporting that occurred during the period covered by the annual report that has materially affected, or is reasonably likely to materially affect, the Company's internal control over financial reporting; and

5. The Company's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the Company's auditors and the audit committee of the Company's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the Company's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the Company's internal control over financial reporting.

Date: March 3, 2022

By: /s/Christian Lawrence Hogg
Christian Lawrence Hogg
Chief Executive Officer

Exhibit 12.2

CERTIFICATION

I, Chig Fung Cheng, Johnny, certify that:

1. I have reviewed this annual report on Form 20-F of HUTCHMED (China) Limited (the "Company");

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the Company as of, and for, the periods presented in this report;

4. The Company's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the Company and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the Company, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (c) Evaluated the effectiveness of the Company's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the Company's internal control over financial reporting that occurred during the period covered by the annual report that has materially affected, or is reasonably likely to materially affect, the Company's internal control over financial reporting; and

5. The Company's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the Company's auditors and the audit committee of the Company's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the Company's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the Company's internal control over financial reporting.

Date: March 3, 2022

By: /s/Chig Fung Cheng, Johnny
Chig Fung Cheng, Johnny
Chief Financial Officer

Exhibit 13.1

906 Certification

Securities and Exchange Commission
100 F Street, N.E.
Washington, D.C. 20549

Ladies and Gentlemen:

In connection with the annual report of HUTCHMED (China) Limited (the "Company") on Form 20-F for the year ended December 31, 2021 as filed with the Securities and Exchange Commission (the "Report"), I, Christian Lawrence Hogg, the Chief Executive Officer of the Company, hereby certify as of the date hereof, solely for purposes of Title 18, Chapter 63, Section 1350 of the United States Code, that to the best of my knowledge:

1. The Report fully complies with the requirements of Section 13(a) or 15(d), as applicable, of the Securities Exchange Act of 1934; and

2. The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company at the dates and for the periods indicated.

This Certificate has not been, and shall not be deemed, "filed" with the Securities and Exchange Commission.

Date: March 3, 2022

By: /s/Christian Lawrence Hogg
Christian Lawrence Hogg
Chief Executive Officer

Exhibit 13.2

906 Certification

Securities and Exchange Commission
100 F Street, N.E.
Washington, D.C. 20549

Ladies and Gentlemen:

In connection with the annual report of HUTCHMED (China) Limited (the "Company") on Form 20-F for the year ended December 31, 2021 as filed with the Securities and Exchange Commission (the "Report"), I, Chig Fung Cheng, Johnny, the Chief Financial Officer of the Company, hereby certify as of the date hereof, solely for purposes of Title 18, Chapter 63, Section 1350 of the United States Code, that to the best of my knowledge:

1. The Report fully complies with the requirements of Section 13(a) or 15(d), as applicable, of the Securities Exchange Act of 1934; and

2. The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company at the dates and for the periods indicated.

This Certificate has not been, and shall not be deemed, "filed" with the Securities and Exchange Commission.

Date: March 3, 2022

By: /s/Chig Fung Cheng, Johnny
Chig Fung Cheng, Johnny
Chief Financial Officer

Exhibit 15.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in the Registration Statements on Form S-8 (No. 333-240180, No. 333-224391 and No.333-212406) and Form F-3 (No. 333-237574) of HUTCHMED (China) Limited (formerly known as "Hutchison China MediTech Limited") of our report dated March 3, 2022 relating to the financial statements and the effectiveness of internal control over financial reporting, which appears in this Form 20-F.

/s/ PricewaterhouseCoopers Zhong Tian LLP
Shenzhen, the People's Republic of China
March 3, 2022

Exhibit 15.2

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in the Registration Statements on Form S-8 (No. 333-240180, No. 333-224391 and No.333-212406) and Form F-3 (No. 333-237574) of HUTCHMED (China) Limited (formerly known as "Hutchison China MediTech Limited") of our report dated March 4, 2021 relating to the financial statements, which appears in this Form 20-F.

/s/ PricewaterhouseCoopers
Hong Kong
March 3, 2022

Exhibit 15.3

CONSENT OF INDEPENDENT ACCOUNTANTS

We hereby consent to the incorporation by reference in the Registration Statements on Form S-8 (No. 333-240180, No. 333-224391 and No.333-212406) and Form F-3 (No. 333-237574) of HUTCHMED (China) Limited (formerly known as "Hutchison China MediTech Limited") of our report dated March 3, 2022 relating to the consolidated financial statements of Shanghai Hutchison Pharmaceuticals Limited, which appears in this Annual Report on Form 20-F of HUTCHMED (China) Limited.

/s/ PricewaterhouseCoopers Zhong Tian LLP
Shanghai, the People's Republic of China
March 3, 2022

Exhibit 15.4

CONSENT OF INDEPENDENT ACCOUNTANTS

We hereby consent to the incorporation by reference in the Registration Statements on Form S-8 (No. 333-240180, No. 333-224391 and No.333-212406) and Form F-3 (No. 333-237574) of HUTCHMED (China) Limited (formerly known as "Hutchison China MediTech Limited") of our report dated December 7, 2021 relating to the consolidated financial statements of Hutchison Whampoa Guangzhou Baiyunshan Chinese Medicine Company Limited, which appears in this Annual Report on Form 20-F of HUTCHMED (China) Limited.

/s/ PricewaterhouseCoopers Zhong Tian LLP
Guangzhou, the People's Republic of China
March 3, 2022

Exhibit 15.5

March 3, 2022

Matter No.: 835165
Doc Ref: 107790896
(852) 2842 9595
Felicity.Lee@conyers.com

HUTCHMED (China) Limited
48th Floor, Cheung Kong Center
2 Queen's Road Central
Hong Kong

Dear Sirs,

Re: HUTCHMED (China) Limited (the "Company")
Annual Report on Form 20-F

We hereby consent to the filing of this letter as an exhibit to the Company's annual report on Form 20-F for the year ended 31 December 2021 with the U.S. Securities and Exchange Commission and to the inclusion therein of the reference to our name on page 217 of the annual report under the heading "Taxation – Overview of Tax Implications of Various Other Jurisdictions – Cayman Islands Taxation" in the form and context in which they appear. In giving such consent, we do not thereby admit that we come within the category of persons whose consent is required under Section 7 of the Securities Act, or the Rules and Regulations of the U.S. Securities and Exchange Commission thereunder.

Yours faithfully,

/s/ Conyers Dill & Pearman
Conyers Dill & Pearman