HUTCHMED Announces Japan Approval for FRUZAQLA® (fruquintinib) Received by Takeda

— Approval based on results from global Phase III FRESCO-2 trial in patients with previously treated metastatic colorectal cancer —

— Fruquintinib already approved in several regions including the United States, Europe and China —

Hong Kong, Shanghai & Florham Park, NJ — Tuesday, September 24, 2024: HUTCHMED (China) Limited ("HUTCHMED") (Nasdaq/AIM:HCM; HKEX:13) today announces that its partner Takeda (TSE:4502/NYSE: TAK) has received approval from the Japanese Ministry of Health, Labour and Welfare ("MHLW") to manufacture and market FRUZAQLA® (fruquintinib) for previously treated metastatic colorectal cancer ("CRC"). FRUZAQLA® is the first novel targeted therapy in Japan to be approved for metastatic CRC, regardless of biomarker status, in over a decade. CRC is the most prevalent type of cancer in Japan, with an estimated 161,000 new cases and 54,000 deaths in 2023, according to the National Cancer Center's statistics.[1]

FRUZAQLA® has been approved for the treatment of advanced or recurrent CRC that is neither curable nor resectable and that has progressed after chemotherapy.

"Takeda has now obtained approval in Japan for FRUZAQLA®, demonstrating the strength of our global data package and the potential of this novel medicine to provide a much-needed treatment option to patients with metastatic CRC," said **Dr Weiguo Su, Chief Executive Officer and Chief Scientific Officer of HUTCHMED**. "Takeda has been a leader in metastatic CRC treatment in Japan for over a decade and we are confident that it is well placed to bring FRUZAQLA® to patients in Japan."

Dr. Takayuki Yoshino, Deputy Director of Hospital, Head, Division for the Promotion of Drug and Diagnostic Development, and Chief, Department of Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan, added**:** "The approval of FRUZAQLA® in Japan is significant news for patients with metastatic colorectal cancer, who have long needed additional effective treatment options. The global FRESCO-2 study demonstrated the impact that this treatment can have on patients in the clinic. The increasing availability of screening and effective therapies in Japan has been driving patient outcomes in colorectal cancer, and we hope the introduction of FRUZAQLA® will offer new hope to those with the condition."

The approval by the Japanese MHLW was primarily based on results from the Phase III FRESCO-2 trial conducted in the US, Europe, Japan and Australia. Data from FRESCO-2 were published in The *Lancet* in June 2023. Takeda has the exclusive worldwide license to further develop, commercialize, and manufacture fruquintinib outside of mainland China, Hong Kong and Macau. FRUZAQLA® was approved in the US in November 2023 and in Europe in June 2024.

About CRC

CRC is a cancer that starts in either the colon or rectum. According to the International Agency for Research on Cancer/World Health Organization, CRC is the third most prevalent cancer worldwide, associated with more than 1.9 million new cases and 900,000 deaths in 2022. In Japan, CRC was the most common cancer, with an estimated 146,000 new cases and 60,000 deaths, in 2022.[2] In Europe, CRC was the second most common cancer in 2022, with approximately 538,000 new cases and 248,000 deaths.[2,3] In the US, it is estimated that 153,000 patients will be diagnosed with CRC and 53,000 deaths from the disease will occur in 2024.[4] Although early-stage CRC can be surgically resected, metastatic CRC remains an area of high unmet need with poor outcomes and limited treatment options. Some patients with metastatic CRC may benefit from personalized therapeutic strategies based on molecular characteristics; however, most patients have tumors that do not harbor actionable mutations.[5,6,7,8,9]

About the Phase III FRESCO-2 Trial

FRESCO-2 is a multiregional clinical trial conducted in the US, Europe, Japan and Australia investigating fruquintinib plus best supportive care ("BSC") versus placebo plus BSC in patients with previously treated metastatic CRC (NCT04322539). FRESCO-2 met all of its primary and key secondary endpoints, demonstrating statistically significant and clinically meaningful improvement in overall survival (OS) and

progression-free survival (PFS), with consistent benefit among patients treated with fruquintinib, regardless of the prior types of therapies they received. Fruquintinib demonstrated a manageable safety profile in FRESCO-2, consistent with previously reported fruquintinib monotherapy studies. Adverse reactions leading to treatment discontinuation occurred in 20% of patients treated with fruquintinib plus BSC versus 21% of those treated with placebo plus BSC. Results from the study were presented at the European Society for Medical Oncology Congress (ESMO) in September 2022 and subsequently published in *The Lancet* in June 2023.[10,11]

About Takeda and FRUZAQLA®

Takeda has the exclusive worldwide license to further develop, commercialize, and manufacture fruquintinib outside of mainland China, Hong Kong and Macau, and markets under the brand name FRUZAQLA®. FRUZAQLA® received approval in the US in November 2023, in the EU in June 2024, in Switzerland in August 2024 and in Canada, Japan and the United Kingdom in September 2024. The US approval was based on data from two large, randomized, controlled Phase III trials, the multi-regional FRESCO-2 trial and the FRESCO trial conducted in China, showing consistent benefit among a total of 734 patients treated with fruquintinib. Safety profiles were consistent across trials. Regulatory applications are progressing in many other jurisdictions.

About Fruquintinib Approval in China

Fruquintinib is approved for marketing in mainland China, Hong Kong and Macau, where it is co-marketed by HUTCHMED and Eli Lilly and Company under the brand name ELUNATE®. It was included in the China National Reimbursement Drug List (NRDL) in January 2020. The approvals were based on data from the FRESCO study, a Phase III pivotal registration trial of fruquintinib in 416 patients with metastatic colorectal cancer in China, which were published in The Journal of the American Medical Association, *JAMA*. Since its launch in China, over 100,000 patients with colorectal cancer have been treated with fruquintinib.

About Fruquintinib

Fruquintinib is a selective oral inhibitor of all three VEGF receptors (VEGFR-1, -2 and -3). VEGFR inhibitors play a pivotal role in inhibiting tumor angiogenesis. Fruquintinib was designed to have enhanced selectivity that limits off-target kinase activity, allowing for drug exposure that achieves sustained target inhibition and flexibility for potential use as part of a combination therapy. Fruquintinib has demonstrated a manageable safety profile and is being investigated in combinations with other anti-cancer therapies.

JAPAN IMPORTANT SAFETY INFORMATION

Please consult the FRUZAQLA (fruquintinib) Japan package insert (J-PI) before prescribing.

WARNING: FRUZAQLA should be administered only to patients for whom the use of FRUZAQLA is considered appropriate under the supervision of a physician with sufficient knowledge of and experience in cancer chemotherapy at a medical institution where adequate emergency care can be provided. Prior to treatment initiation, the efficacy and risks should be fully explained to the patient and/or his/her family and informed consent should be obtained; Severe gastrointestinal hemorrhage, including fatal cases, has been reported. Patients should be carefully monitored, and if any abnormalities are observed, administration of FRUZAQLA should be withheld and appropriate measures should be taken. If severe hemorrhage occurs, FRUZAQLA should not be re-administered; Gastrointestinal perforation has been reported with some fatal cases. Patients should be carefully monitored, and if any abnormalities are observed, administration of FRUZAQLA should be withheld and appropriate measures should be taken. If gastrointestinal perforation occurs, FRUZAQLA should not be re-administered.

CONTRAINDICATIONS: Patients with a history of hypersensitivity to any of the ingredients of FRUZAQLA.

IMPORTANT PRECAUTIONS: Hypertension, including hypertensive crisis, may occur. Blood pressure should be measured prior to the initiation of FRUZAQLA treatment and periodically during this treatment; Proteinuria may occur. Urinary protein should be monitored prior to the initiation of FRUZAQLA treatment and periodically during this treatment; If a surgical procedure is to be performed, patients are recommended to withhold FRUZAQLA before the surgery because wound healing may be delayed. Treatment resumption after the surgical procedure should be determined depending on the patient's condition upon confirmation of adequate wound healing.

PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS: Patients with hypertension: Hypertension may worsen; **Patients with bleeding diathesis or abnormal coagulation system:** Hemorrhagic events may occur; **Patients with hemorrhage such as gastrointestinal hemorrhage:** Hemorrhage may be enhanced; **Patients with a complication of intra-abdominal inflammation in the gastrointestinal tract, etc.:** Gastrointestinal perforation may occur; **Patients with current or a history of thromboembolism:** Transient ischaemic attack, thrombotic microangiopathy, pulmonary embolism, portal vein thrombosis, deep vein thrombosis, etc. may occur; **Patients with severe hepatic impairment (Child-Pugh Class C):** Since FRUZAQLA is metabolized mainly in the liver, blood concentrations may be increased. There have been no clinical studies conducted in patients with severe hepatic impairment; **Patients with Reproductive Potential:** Women of childbearing potential should be advised to use adequate contraception during treatment with FRUZAQLA and for 2 weeks after the last dose; **Pregnant Women:** FRUZAQLA can be administered to women who are or may be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with this treatment. In a rat embryo-fetal toxicity study, fetal abnormalities and teratogenic effects consisting of fetal external, visceral, and skeletal malformations and visceral and skeletal variations were observed at exposure levels approximately 0.05 times the exposure level (AUC) of FRUZAQLA at the maximum clinical dose (5 mg/day); **Breast-feeding Women:** It is advisable not to breastfeed. FRUZAQLA may pass into breast milk, and infants may experience serious adverse reactions if they are ingested through breast milk; **Pediatric Use:** There have been no clinical studies conducted in pediatric patients.

ADVERSE REACTIONS:

Any of the adverse reactions listed below may occur. Patients should be closely monitored, and if any such abnormalities are observed, appropriate measures should be taken, including treatment discontinuation. Clinically Significant Adverse Reactions are follows.

Hypertension: Hypertension or hypertensive crisis may occur. If an increase in blood pressure is observed, appropriate treatment such as antihypertensive drug administration should be given as necessary, and if necessary, the dose of fruquintinib should be reduced, or fruquintinib administration should be interrupted. If severe or persistent hypertension, or hypertension that cannot be controlled by routine antihypertensive therapy occurs or if a hypertensive crisis occurs, fruquintinib administration should be discontinued; **Skin disorder:** Skin disorder including palmar-plantar erythrodysesthesia syndrome and rash may occur; **Hemorrhage:** Hemorrhage including epistaxis, hematuria, gastrointestinal hemorrhage and hemoptysis may occur. Fatal outcomes have been reported; **Gastrointestinal perforation:** Fatal outcomes have been reported; **Arterial thromboembolic events:** Arterial thromboembolic events including transient ischemic attack and thrombotic microangiopathy may occur; **Venous thromboembolism events:** Venous thromboembolism such as pulmonary embolism, portal vein thrombosis, and deep vein thrombosis may occur; **Posterior reversible encephalopathy syndrome:** If headaches, convulsions, lethargy, confusion, changes in mental function, blindness or other visual disturbances, or neurological impairment are observed, fruquintinib administration should be discontinued, and appropriate measures should be taken, including blood pressure control; **Arterial dissection:** Arterial dissection including aortic dissection may occur.

For US Prescribing Information:
https://www.fruzaqla.com/sites/default/files/resources/fruzaqla-prescribing-information.pdf

For European Union Summary of Product Characteristics:
https://www.ema.europa.eu/en/medicines/human/EPAR/fruzaqla

About HUTCHMED

HUTCHMED (Nasdaq/AIM:HCM; HKEX:13) is an innovative, commercial-stage, biopharmaceutical company. It is committed to the discovery and global development and commercialization of targeted therapies and immunotherapies for the treatment of cancer and immunological diseases. It has approximately 5,000 personnel across all its companies, at the center of which is a team of about 1,800 in oncology/immunology. Since inception it has focused on bringing cancer drug candidates from in-house discovery to patients around the world, with its first three medicines marketed in China, the first of which is also marketed in the US and Europe. For more information, please visit: www.hutch-med.com or follow us on LinkedIn.

Forward-Looking Statements

This announcement contains forward-looking statements within the meaning of the "safe harbor" provisions of the US Private Securities Litigation Reform Act of 1995. These forward-looking statements reflect HUTCHMED's current expectations regarding future events, including its expectations regarding the therapeutic potential of fruquintinib for the treatment of such patients with CRC and the further clinical development of fruquintinib in this and other indications. Forward-looking statements involve risks and uncertainties. Such risks and uncertainties include, among other things, assumptions regarding the sufficiency of clinical data to support approval of fruquintinib for the treatment of patients with CRC or other indications in other jurisdictions such as Japan, its potential to gain approvals from regulatory authorities, the safety profile of fruquintinib, HUTCHMED and/or Takeda's ability to fund, implement and complete its further clinical development and commercialization plans for fruquintinib, the timing of these events, each party's ability to satisfy the terms and conditions under the license agreement; actions of regulatory agencies, which may affect the initiation, timing and progress of clinical trials or the regulatory pathway for fruquintinib; and Takeda's ability to successfully develop and commercialize fruquintinib. In addition, as certain studies rely on the use of other drug products as combination therapeutics with fruquintinib, such risks and uncertainties include assumptions regarding the safety, efficacy, supply and continued regulatory approval of these therapeutics. Existing and prospective investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof. For further discussion of these and other risks, see HUTCHMED's filings with the US Securities and Exchange Commission, on AIM and on The Stock Exchange of Hong Kong Limited. HUTCHMED undertakes no obligation to update or revise the information contained in this announcement, whether as a result of new information, future events or circumstances or otherwise.

Medical Information

This announcement contains information about products that may not be available in all countries, or may be available under different trademarks, for different indications, in different dosages, or in different strengths. Nothing contained herein should be considered a solicitation, promotion or advertisement for any prescription drugs including the ones under development.

Inside Information

This announcement contains inside information for the purposes of Article 7 of Regulation (EU) No 596/2014 (as it forms part of retained EU law as defined in the European Union (Withdrawal) Act 2018).

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