Press Release

HUTCHMED to Receive Milestone Payment from Takeda following First European Reimbursement for FRUZAQLA® (fruquintinib)

— US$10 million milestone payment to HUTCHMED follows first national reimbursement in Europe —

— Follows June 2024 European approval of FRUZAQLA® (fruquintinib), the first novel oral targeted therapy in the EU for metastatic colorectal cancer regardless of biomarker status in over a decade —

Hong Kong, Shanghai & Florham Park, NJ — Friday, December 13, 2024: HUTCHMED (China) Limited ("HUTCHMED") (Nasdaq/AIM:HCM; HKEX:13) today announces that it will receive a US$10 million milestone payment by its partner Takeda (TSE:4502/NYSE:TAK). Takeda received a national reimbursement recommendation for FRUZAQLA® (fruquintinib) for patients with previously treated metastatic colorectal cancer ("CRC") in Spain in December 2024, the first national reimbursement recommendation in Europe. CRC is the second most common cause of cancer-related deaths in Europe.

FRUZAQLA® was approved by the European Commission ("EC") of the European Union ("EU") in June 2024. Takeda has the exclusive worldwide license to further develop, commercialize and manufacture fruquintinib outside of mainland China, Hong Kong and Macau.

"We are delighted for both our partner, Takeda, and patients in Spain who will now be able to receive reimbursement for this innovative treatment. This is an important step forward in improving patient access across Europe more broadly," said **Dr Weiguo Su, Chief Executive Officer and Chief Scientific Officer of HUTCHMED.** "It also underscores our ongoing collaboration with Takeda and reinforces our shared commitment to addressing the needs of patients with metastatic colorectal cancer."

The approvals by the EC were primarily based on results from the Phase III multiregional FRESCO-2 trial. Data from FRESCO-2 were published in The *Lancet* in June 2023. FRUZAQLA® was approved in the US in November 2023, in the EU in June 2024, in Switzerland in August 2024, in Canada, Japan and the United Kingdom in September 2024 and in Argentina, Australia and Singapore in October 2024. Regulatory applications are progressing in many other jurisdictions.

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 Europe, CRC was the second most common cancer in 2022, with approximately 538,000 new cases and 248,000 deaths.[1,2] 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.[3] In Japan, CRC was the most common cancer, with an estimated 146,000 new cases and 60,000 deaths, in 2022.[2] 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.[4,5,6,7,8]

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.

About Fruquintinib Approvals

Global regulatory submissions are based on data from two large, randomized, controlled Phase III trials, the global, 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. Results from

the FRESCO-2 trial were published in *The Lancet* in June 2023, [9] while results from the FRESCO trial were published in The Journal of the American Medical Association, *JAMA*.[10]

In mainland China, Hong Kong and Macau, fruquintinib 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. Since its launch in China, over 100,000 patients with colorectal cancer have been treated with fruquintinib.

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 approved in the US, Europe and Japan. For more information, please visit: www.hutch-med.com or follow us on LinkedIn.

E.U. IMPORTANT SAFETY INFORMATION

Please consult the FRUZAQLA (fruquintinib) Summary of Product Characteristics (SmPC) before prescribing.

Guidance for use: FRUZAQLA should be initiated by a physician experienced in the administration of anticancer therapy. Patients should be given the package leaflet.

CONTRAINDICATIONS: Hypersensitivity to the active substance or to any of the excipients.

SPECIAL POPULATIONS: Renal impairment: No dose adjustment is required for patients with mild, moderate, or severe renal impairment; **Hepatic impairment:** No dose adjustment is required for patients with mild or moderate hepatic impairment. FRUZAQLA is not recommended for use in patients with severe hepatic impairment as FRUZAQLA has not been studied in this population; **Elderly:** No dose adjustment is required in patients aged 65 years or above; **Pediatric population:** There is no relevant use of FRUZAQLA in the pediatric population for the indication of metastatic colorectal cancer; **Women of childbearing potential / Contraception in females:** Women of childbearing potential should be advised to use highly effective contraception during treatment and for at least 2 weeks following the last dose of FRUZAQLA; **Pregnancy:** There are no clinical data available on the use of FRUZAQLA in pregnant women. Based on its mechanism of action, FRUZAQLA has the potential to cause fetal harm. Animal studies have shown reproductive toxicity, including fetal malformations. FRUZAQLA should not be used during pregnancy unless the clinical condition of the woman requires treatment with FRUZAQLA. If FRUZAQLA is used during pregnancy or if the patient becomes pregnant while on treatment, the patient must be informed of the potential hazard to the fetus; **Breast-feeding:** The safe use of FRUZAQLA during breast-feeding has not been established. It is not known whether FRUZAQLA or its metabolites are excreted in human milk. There are no animal data on the excretion of FRUZAQLA in animal milk. A risk to the breastfeeding newborns/infants cannot be excluded. Breastfeeding should be discontinued during treatment and for 2 weeks after the last dose; **Fertility:** There are no data on the effects of FRUZAQLA on human fertility. Results from animal studies indicate that FRUZAQLA may impair male and female fertility.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

- **Hypertension:** Hypertension, including hypertensive crisis, has been reported in patients treated with FRUZAQLA. Pre-existing hypertension should be monitored and adequately controlled in accordance with standard medical practices before starting FRUZAQLA treatment.

  Hypertension should be medically managed with antihypertensive medicinal products and adjustment of the FRUZAQLA dose, if necessary. FRUZAQLA should be permanently discontinued for hypertension that cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis.

- **Hemorrhagic events:** Hemorrhagic events have been reported in patients treated with FRUZAQLA, including gastrointestinal (GI) tract events. Serious and sometimes fatal bleeding events have been reported in patients after treatment with FRUZAQLA.

  Hematologic and coagulation profiles should be monitored in accordance with standard medical practices in patients at risk for bleeding, including those treated with anticoagulants or other concomitant medicinal

products that increase the risk of bleeding. In the event of severe bleeding requiring immediate medical intervention, FRUZAQLA should be permanently discontinued.

- **Gastrointestinal perforation:** GI perforation events, including fatal events, have been reported in patients treated with FRUZAQLA.

  Symptoms of GI perforation should be periodically monitored during treatment with FRUZAQLA.

  FRUZAQLA should be permanently discontinued in patients developing GI perforation.

- **Proteinuria:** Proteinuria events have occurred in patients treated with FRUZAQLA.

  Proteinuria should be monitored before initiation and during treatment with FRUZAQLA in accordance with standard medical practices. If urine dipstick proteinuria ≥ 2 g / 24 hours is detected, dose interruptions, adjustments, or discontinuation may be necessary. FRUZAQLA should be permanently discontinued in patients developing nephrotic syndrome.

- **Palmar-plantar erythrodysesthesia syndrome (PPES):** PPES is the most frequently reported dermatological adverse reaction.

  If Grade ≥2 skin reactions are detected, dose interruptions, adjustments, or discontinuation may be necessary.

- **Posterior reversible encephalopathy syndrome (PRES):** PRES has been reported in 1 patient (0.1%) treated with FRUZAQLA in clinical studies. PRES is a rare neurologic disorder that can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). In patients developing PRES, discontinuation of FRUZAQLA, along with control of hypertension and supportive medical management of other symptoms, are recommended.

- **Impaired wound healing:** Impaired wound healing has been reported in 1 patient (0.1%) treated with FRUZAQLA in clinical studies.

  Patients are recommended to withhold FRUZAQLA for at least 2 weeks prior to surgery. FRUZAQLA should not be resumed for at least 2 weeks after surgery, as clinically indicated when there is evidence of adequate wound healing.

- **Arterial and venous thromboembolic events:** It is recommended to avoid starting treatment with FRUZAQLA in patients with a history of thromboembolic events (including deep vein thrombosis and pulmonary embolism) within the past 6 months or if they have a history of stroke and/or transient ischemic attack within the last 12 months. If arterial thrombosis is suspected, FRUZAQLA should be discontinued immediately.

INTERACTIONS

Effects of other medicinal products on the pharmacokinetics of FRUZAQLA

CYP3A inducers

Co-administration of FRUZAQLA with rifampicin (a strong CYP3A inducer) 600 mg once daily decreased FRUZAQLA AUC_{inf} by 65% and decreased C_{max} by 12%. The concomitant use of FRUZAQLA with strong and moderate CYP3A inducers should be avoided.

CYP3A inhibitors

Co-administration of FRUZAQLA with itraconazole (a strong CYP3A inhibitor) 200 mg twice daily did not result in clinically meaningful changes in the area under the concentration-time curve (AUC) and C_{max} of FRUZAQLA. No dose adjustment of FRUZAQLA is needed during concomitant use with CYP3A inhibitors.

Gastric acid lowering agents

Co-administration of FRUZAQLA with rabeprazole (a proton pump inhibitor) 40 mg once daily did not result in clinically meaningful changes in the AUC of FRUZAQLA. No dose adjustment of FRUZAQLA is needed during concomitant use with gastric acid lowering agents.

Effect of FRUZAQLA on the pharmacokinetics of other medicinal products

Medicinal products that are substrates of P-glycoprotein (P-gp)

Co-administration of a single dose of dabigatran etexilate 150 mg (a P-gp substrate) with a single dose of FRUZAQLA 5 mg decreased AUC of dabigatran by 9%. No dose adjustment is recommended for P-gp substrates during concomitant use with FRUZAQLA.

Medicinal products that are substrates of breast cancer resistance protein (BCRP)

Co-administration of a single 10 mg dose of rosuvastatin (a BCRP substrate) with a single 5 mg dose of FRUZAQLA decreased AUC of rosuvastatin by 19%. No dose adjustment is recommended for BCRP substrates during concomitant use with FRUZAQLA.

UNDESIRABLE EFFECTS: The **most commonly reported adverse reactions** with FRUZAQLA are:

Very common (frequency ≥1/10)	Thrombocytopenia, hypothyroidism, anorexia, hypertension, dysphonia, diarrhoea, stomatitis, aspartate aminotransferase increased, total bilirubin increased, alanine aminotransferase increased, palmar-plantar erythrodysesthesia syndrome, musculoskeletal discomfort, arthralgia, proteinuria, asthenia, and fatigue
Common (≥1/100 to <1/10)	Pneumonia, upper respiratory tract infection, bacterial infections, leukopenia, neutropenia, hypokalemia, epistaxis, throat pain, gastrointestinal hemorrhage, gastrointestinal perforation, pancreatic enzymes increased, oral pain, rash, and mucosal inflammation

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

For Japan Prescribing Information:
https://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/400256_42910H0M1028_1_01

For EU Prescribing Information:
https://www.ema.europa.eu/en/documents/product-information/fruzaqla-epar-product-information_en.pdf

Forward-Looking Statements

This press release 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 jurisdictions such as Europe, 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, The Stock Exchange of Hong Kong Limited and on AIM. HUTCHMED undertakes no obligation to update or revise the information contained in this press release, whether as a result of new information, future events or circumstances or otherwise.

Medical Information

This press release 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.

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