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

— Approval for previously treated metastatic colorectal cancer based on results from positive, global, Phase III FRESCO-2 Trial —

— FRUZAQLA® (fruquintinib) is the first novel targeted therapy in the EU for metastatic colorectal cancer regardless of biomarker status in over a decade —

Hong Kong, Shanghai & Florham Park, NJ — Monday, June 24, 2024: HUTCHMED (China) Limited ("HUTCHMED") (Nasdaq/AIM:HCM; HKEX:13) today announces that its partner Takeda (TSE:4502/NYSE:TAK) has received notification from the European Commission ("EC") that it has approved FRUZAQLA® (fruquintinib) as a monotherapy indicated for the treatment of adult patients with metastatic colorectal cancer ("CRC") who have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents, and who have progressed on or are intolerant to treatment with either trifluridine-tipiracil or regorafenib.

"With fruquintinib being the first and only selective inhibitor of all three VEGFRs to be approved in the EU for colorectal cancer, this decision represents a significant milestone in European oncology," added **Josep Tabernero, MD, PhD, director of Vall d´Hebron Institute of Oncology (VHIO)**. "There is a clear need in Europe for patients and their clinicians to be able to access a new treatment option for previously treated metastatic colorectal cancer, and we are excited that this important step has been taken so that we can begin prescribing this new and differentiated medicine."

"We are delighted to have achieved EC approval for FRUZAQLA® and that we can now offer a new therapeutic option for patients with previously treated metastatic colorectal cancer, regardless of their biomarker status," said **Teresa Bitetti, President of the Global Oncology Business Unit at Takeda.** "Patients in Europe with metastatic colorectal cancer have long needed additional treatment options, and we are grateful to be able to meet that need thanks to our partnership with HUTCHMED."

"This is a significant milestone for HUTCHMED, as it is the first product from our research and discovery engine to be approved in Europe, achieved through our partnership with Takeda to make this possible in such a short period of time," added **Weiguo Su, PhD, Chief Executive Officer and Chief Scientific Officer of HUTCHMED**. "This novel oncology medicine is currently improving the treatment outlook in the U.S. and China, and we look forward to seeing its impact for patients across Europe."

The EC's approval has been granted following a positive opinion from the Committee for Medicinal Products for Human Use ("CHMP") in April 2024. The CHMP's opinion was primarily based on results from the Phase III multiregional FRESCO-2 trial, which supported the Marketing Authorisation Application ("MAA") that was validated and accepted for review in June 2023. Data from FRESCO-2 were published in The *Lancet* in June 2023.

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 U.S., 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 the Phase III FRESCO-2 Trial

FRESCO-2 is a multiregional clinical trial conducted in the U.S., 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.[9,10]

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 high drug exposure, sustained target inhibition, and flexibility for its 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.

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. Fruquintinib received approval in the U.S. in November 2023, where it is marketed by Takeda under the brand name FRUZAQLA®. The U.S. 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.

In addition to the submission to the EMA, a submission to the Japan Pharmaceuticals and Medical Devices Agency (PMDA) took place in September 2023.

About Fruquintinib Approval in China

Fruquintinib is approved for marketing in China, 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 approval was 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 and as of mid-2023, more than 80,000 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 marketed in the U.S. 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; **Paediatric population:** There is no relevant use of FRUZAQLA in the paediatric 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 foetal harm. Animal studies have shown reproductive toxicity, including foetal 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 foetus; **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.

- **Haemorrhagic events:** Haemorrhagic 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.

  Haematologic 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 erythrodysaesthesia 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 erythrodysaesthesia 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 haemorrhage, gastrointestinal perforation, pancreatic enzymes increased, oral pain, rash, and mucosal inflammation

Forward-Looking Statements

This announcement contains forward-looking statements within the meaning of the "safe harbor" provisions of the U.S. 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 U.S. 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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