HUTCHMED (China) Limited

和黃醫藥（中國）有限公司

(Incorporated in the Cayman Islands with limited liability)

(Stock Code: 13)

INSIDE INFORMATION

HUTCHMED Announces Positive CHMP Opinion for Fruquintinib in Previously Treated Metastatic Colorectal Cancer Received by Takeda

— If approved in the European Union, fruquintinib will be the first novel targeted therapy for metastatic colorectal cancer regardless of biomarker status in over a decade —

— Positive opinion based on results from FRESCO-2 Phase III clinical trial —

This announcement is made by HUTCHMED (China) Limited ("HUTCHMED") pursuant to Rule 13.09(2)(a) of the Rules Governing the Listing of Securities on The Stock Exchange of Hong Kong Limited and the Inside Information Provisions under Part XIVA of the Securities and Futures Ordinance (Cap. 571).

HUTCHMED today announces that its partner Takeda (TSE:4502/NYSE:TAK) received notification that the Committee for Medicinal Products for Human Use ("CHMP") of the European Medicines Agency ("EMA") has recommended the approval of fruquintinib for the treatment of adult patients with previously treated metastatic colorectal cancer ("CRC").

The European Commission (EC) will consider the CHMP positive opinion when determining the potential marketing authorization for fruquintinib for metastatic CRC throughout the European Union ("EU"), Norway, Liechtenstein and Iceland. If approved, fruquintinib will be the first and only selective inhibitor of all three vascular endothelial growth factor receptors ("VEGFR") approved in the EU for previously treated metastatic CRC.[1,2] Takeda has the exclusive worldwide license to further develop, commercialize, and manufacture fruquintinib outside of mainland China, Hong Kong and Macau.

"Through our partnership with HUTCHMED, we have made strides in expanding access to fruquintinib to eligible patients. With this positive CHMP opinion for fruquintinib, we are one step closer to potentially offering patients in the EU an oral, chemotherapy-free option that can provide a significant survival benefit," said Awny Farajallah, M.D., Chief Medical Officer, Oncology at Takeda. "We look forward to the European Commission's official decision in the near future."

"HUTCHMED has a strong track record of developing innovative oncology medicines for patients in need. People living with metastatic CRC in the EU currently have limited treatment options available to them, which can lead to poor outcomes. We are pleased with our partner Takeda's progress toward redefining the treatment landscape and helping to address a significant unmet need for those affected by metastatic CRC in Europe," said Weiguo Su, PhD, Chief Executive Officer and Chief Scientific Officer of HUTCHMED. "This novel oncology medicine has had a profound impact for patients in China over the last five years. Since entering our partnership with Takeda we have seen this impact extended with its approval and launch in the U.S. and, pending approval by the European Commission, we look forward to the medicine having a positive effect for patients in Europe too."

The CHMP's positive opinion was primarily based on results from the Phase III multi-regional FRESCO-2 trial, which supported the Marketing Authorisation Application ("MAA"). The MAA was validated and accepted for review by the EMA 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, CRC is the third most prevalent cancer worldwide, associated with more than 935,000 deaths in 2020. In Europe, CRC was the second most common cancer in 2020, with approximately 520,000 new cases and 245,000 deaths.[3] 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.[4] In Japan, CRC was the most common cancer, with an estimated 148,000 new cases and 60,000 deaths, in 2020.[3] 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 multi-regional 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 mCRC (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 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 Fruquintinib

Fruquintinib is a selective oral inhibitor of 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 colorectal cancer patients 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.

U.S. IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- Hypertension occurred in 49% of 911 patients with mCRC treated with FRUZAQLA, including Grade 3-4 events in 19%, and hypertensive crisis in three patients (0.3%). Do not initiate FRUZAQLA unless blood pressure is adequately controlled. Monitor blood pressure weekly for the first month and at least monthly thereafter as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue FRUZAQLA based on severity of hypertension.
- Hemorrhagic Events including serious, fatal events can occur with FRUZAQLA. In 911 patients with mCRC treated with FRUZAQLA, 6% of patients experienced gastrointestinal hemorrhage, including 1% with a Grade ≥3 event and 2 patients with fatal hemorrhages. Permanently discontinue FRUZAQLA in patients with severe or life-threatening hemorrhage. Monitor the International Normalized Ratio (INR) levels in patients receiving anticoagulants.
- Infections. FRUZAQLA can increase the risk of infections, including fatal infections. In 911 patients with mCRC treated with FRUZAQLA, the most common infections were urinary tract infections (6.8%), upper respiratory tract infections (3.2%) and pneumonia (2.5%); fatal infections included pneumonia (0.4%), sepsis (0.2%), bacterial infection (0.1%), lower respiratory tract infection (0.1%), and septic shock (0.1%). Withhold FRUZAQLA for Grade 3 or 4 infections, or worsening infection of any grade. Resume FRUZAQLA at the same dose when the infection has resolved.
- Gastrointestinal Perforation occurred in patients treated with FRUZAQLA. In 911 patients with mCRC treated with FRUZAQLA, 1.3% experienced a Grade ≥3 gastrointestinal perforation, including one fatal event. Permanently discontinue FRUZAQLA in patients who develop gastrointestinal perforation or fistula.
- Hepatotoxicity. FRUZAQLA can cause liver injury. In 911 patients with mCRC treated with FRUZAQLA, 48% experienced increased ALT or AST, including Grade ≥3 events in 5%, and fatal events in 0.2% of patients. Monitor liver function tests (ALT, AST, and bilirubin) before initiation and periodically throughout treatment with FRUZAQLA. Temporarily hold and then reduce or permanently discontinue FRUZAQLA depending on the severity and persistence of hepatotoxicity as manifested by elevated liver function tests.
- Proteinuria. FRUZAQLA can cause proteinuria. In 911 patients with mCRC treated with FRUZAQLA, 36% experienced proteinuria and 2.5% of patients experienced Grade ≥3 events. Monitor for proteinuria before initiation and periodically throughout treatment with FRUZAQLA. For proteinuria ≥2g/24 hours, withhold FRUZAQLA until improvement to ≤Grade 1 proteinuria and resume FRUZAQLA at a reduced dose. Discontinue FRUZAQLA in patients who develop nephrotic syndrome.
- Palmar-Plantar Erythrodysesthesia (PPE) occurred in 35% of 911 patients treated with FRUZAQLA, including 8% with Grade 3 events. Based on severity of PPE, withhold FRUZAQLA and then resume at the same or reduced dose.
- Posterior Reversible Encephalopathy Syndrome (PRES), a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, occurred in one of 911 patients treated with FRUZAQLA. Perform an evaluation for PRES in any patient presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Discontinue FRUZAQLA in patients who develop PRES.
- Impaired Wound Healing. In 911 patients with mCRC treated with FRUZAQLA, 1 patient experienced a Grade 2 event of wound dehiscence. Do not administer FRUZAQLA for at least 2 weeks prior to major surgery. Do not administer FRUZAQLA for at least 2 weeks after major surgery and until adequate wound healing. The safety of resumption of FRUZAQLA after resolution of wound healing complications has not been established.
- Arterial Thromboembolic Events. In 911 patients with mCRC treated with FRUZAQLA, 0.8% of patients experienced an arterial thromboembolic event. Initiation of FRUZAQLA in patients with a recent history of thromboembolic events should be carefully considered. In patients who develop arterial thromboembolism, discontinue FRUZAQLA.
- Allergic Reactions to FD&C Yellow No. 5 (Tartrazine) and No. 6 (Sunset Yellow FCF). FRUZAQLA 1 mg capsules contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. FRUZAQLA 1 mg contains FD&C Yellow No. 6 (sunset yellow FCF), which may cause allergic reactions.
- Embryo-Fetal Toxicity. Based on findings in animal studies and its mechanism of action, FRUZAQLA can cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to a fetus. Advise females of childbearing potential and males with female partners of childbearing potential to use effective contraception during treatment with FRUZAQLA and for 2 weeks after the last dose.

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥20%) following treatment with FRUZAQLA included hypertension, palmar-plantar erythrodysesthesia (hand-foot skin reactions), proteinuria, dysphonia, abdominal pain, diarrhea, and asthenia.

DRUG INTERACTIONS: Avoid concomitant administration of FRUZAQLA with strong or moderate CYP3A inducers.

USE IN SPECIFIC POPULATIONS

- Lactation: Advise women not to breastfeed during treatment with FRUZAQLA and for 2 weeks after the last dose.

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals at 1-844-662-8532 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see FRUZAQLA (fruquintinib) full Prescribing Information.

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 review of a MAA for fruquintinib for the treatment of patients with CRC with the EMA and the timing of such review, 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 MAA approval of fruquintinib for the treatment of patients with CRC or other indications in the EU or other jurisdictions such as Japan, its potential to gain approvals from regulatory authorities, the safety profile of fruquintinib, HUTCHMED'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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By Order of the Board

Edith Shih
Non-executive Director and Company Secretary

Hong Kong, April 26, 2024

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

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

Non-executive Directors:
Dr Dan ELDAR
Ms Edith SHIH
Ms Ling YANG

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