HUTCHMED Announces that Takeda Receives U.S. FDA Approval of FRUZAQLA™ (fruquintinib) for Previously Treated Metastatic Colorectal Cancer

— FRUZAQLA is the first targeted therapy approved in the U.S. for metastatic colorectal cancer regardless of biomarker status or prior types of therapies in more than a decade —

— U.S. approval of FRUZAQLA triggers first milestone payment from Takeda of US$35 million and royalties on net sales —

Hong Kong, Shanghai & Florham Park, NJ — Thursday, November 9, 2023: HUTCHMED (China) Limited (Nasdaq/AIM:HCM, HKEX:13) ("HUTCHMED") today announced that its partner Takeda received approval from the U.S. Food and Drug Administration ("FDA") for FRUZAQLA™ (fruquintinib), an oral targeted therapy for adults with metastatic colorectal cancer ("CRC") who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-vascular endothelial growth factor ("VEGF") therapy, and, if RAS wild-type and medically appropriate, an anti-epidermal growth factor receptor (EGFR) therapy. FRUZAQLA is the first and only selective inhibitor of all three VEGF receptor kinases approved in the U.S. for previously treated metastatic CRC regardless of biomarker status.[1,2] This approval was received under Priority Review more than 20 days ahead of the scheduled Prescription Drug Users Fee Act (PDUFA) date of November 30, 2023.

"This is a landmark moment for metastatic colorectal cancer patients in the U.S., who will soon have a much-needed new treatment option that improves survival rates without negatively impacting their quality of life," said **Weiguo Su, PhD, Chief Executive Officer and Chief Scientific Officer of HUTCHMED**. "It is also a landmark moment for HUTCHMED, as we see our first medicine approved outside of our home market, where we have been improving patient outcomes with our novel oncology medicines for the last 5 years. In late 2022 we launched a partnership strategy for globalizing our innovative drug candidates and we are pleased to see early delivery of this new approach just a year later. This initial success is thanks to our partner Takeda, who saw the value in fruquintinib, shared our vision for taking it global, and worked hard with us to secure U.S. approval. We look forward to continuing our work with Takeda in an effort to bring FRUZAQLA to patients across the globe."

Takeda has the exclusive worldwide license to further develop, commercialize, and manufacture fruquintinib outside of mainland China, Hong Kong and Macau. The FDA approval of FRUZAQLA triggers a US$35 million milestone payment from Takeda. HUTCHMED will receive royalties on net sales, and is also eligible to receive potential payments relating to other regulatory, development and commercial sales milestones. Fruquintinib is developed and marketed in China by HUTCHMED following approval in September 2018, under the brand name ELUNATE™, in partnership with Eli Lilly and Company.

"For more than a decade there has been limited innovation for patients with metastatic colorectal cancer, one of the leading causes of cancer death in the U.S.," said **Teresa Bitetti, President of the Global Oncology Business Unit at Takeda**. "We are proud that our partnership with HUTCHMED enabled us to bring forth a new option to this patient population and we look forward to continuing our work for patients with this underserved cancer."

The approval of FRUZAQLA is based on data from two large Phase III trials: the multi-regional FRESCO-2 trial, data from which were published in *The Lancet*, along with the FRESCO trial conducted in China, data from which were published in JAMA, The Journal of the American Medical Association. The trials investigated FRUZAQLA plus best supportive care versus placebo plus best supportive care in patients with previously treated mCRC. Both FRESCO and FRESCO-2 met their primary and key secondary efficacy endpoints and showed consistent benefit among a total of 734 patients treated with FRUZAQLA. Safety profiles were consistent across trials.

"Metastatic colorectal cancer patients often present with inoperable disease. As cancer care providers, we must evaluate and consider treatment options that will improve overall survival without compromising quality of life," said **Cathy Eng, M.D., FACP, at Vanderbilt University Medical Center**. "A selective oral anti-VEGF agent with proven benefit in overall survival and demonstrated a manageable safety profile would be advantageous for patients by continuing the treatment paradigm of anti-VEGF therapy at home."

In the U.S., approximately 153,000 new cases of CRC will be diagnosed in 2023, representing 7.8% of all new cancer cases.[3,4] Approximately 70% of patients with CRC will experience metastatic disease, whether at diagnosis or after treatment. Metastases are the main cause of CRC-related mortality.[5,6]

The data from FRESCO and FRESCO-2 also supported the marketing authorization application ("MAA") for fruquintinib, which was validated and accepted for review by the European Medicines Agency ("EMA") in June 2023. A submission to the Japan Pharmaceuticals and Medical Devices Agency ("PMDA") also took place in September 2023.

About FRUZAQLA (fruquintinib)

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

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 https://takeda.info/Fruzaqla-Prescribing-Information.

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.[7] 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 2023.[3] In Europe, CRC was the second most common cancer in 2020, with approximately 520,000 new cases and 245,000 deaths. In Japan, CRC was the most common cancer, with an estimated 148,000 new cases and 60,000 deaths in 2020.[7] 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.[8,9,10,11,12]

About the Phase III FRESCO-2 Trial

The FRESCO-2 study is a multi-regional clinical trial conducted in the U.S., Europe, Japan and Australia investigating FRUZAQLA (fruquintinib) plus best supportive care vs placebo plus best supportive care in patients with previously treated metastatic CRC (NCT04322539). The study met its primary and key secondary endpoints, demonstrating that treatment with FRUZAQLA resulted in statistically significant and clinically meaningful improvement in overall survival (OS) and progression-free survival (PFS). The safety profile of FRUZAQLA in FRESCO-2 was consistent with previously reported FRUZAQLA studies. Results from the study were presented at the European Society for Medical Oncology (ESMO) Congress in September 2022 and subsequently published in *The Lancet*.[13,14]

The Phase III FRESCO and FRESCO-2 trials supported the MAA from the EMA for fruquintinib, which was validated and accepted for review in June 2023. A submission to the PMDA also took place in September 2023.

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 oncology drugs now approved and marketed in China. 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 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 approval of a NDA for fruquintinib for the treatment of CRC with the EMA and the PMDA and the timing of such approvals, the therapeutic potential of fruquintinib for the treatment of 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 timing and outcome of clinical studies and the sufficiency of clinical data to support NDA approval of fruquintinib for the treatment of patients with CRC or other indications in the E.U., Japan or other jurisdictions, its potential to gain approvals from regulatory authorities on an expedited basis or at all; the efficacy and 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; Takeda's ability to successfully develop, manufacture and commercialize fruquintinib; and the impact of COVID-19 on general economic, regulatory and political conditions. In addition, as certain studies rely on the use of other drug products such as paclitaxel as combination therapeutics with fruquintinib, such risks and uncertainties include assumptions regarding the safety, efficacy, supply and continued regulatory approval of these therapeutics. Such forward-looking statements include, without limitation, statements regarding the plan to develop, manufacture and commercialize fruquintinib under the license agreement; potential payments under the license agreement, including any milestone or royalty payments; potential benefits of the license agreement; and HUTCHMED's strategy, goals and anticipated milestones, business plans and focus. 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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References

1. Xu X, et al. Efficacy and safety of regorafenib and fruquintinib as third-line treatment for colorectal cancer: a narrative review. Transl Cancer Res 2022;11(1):276-287. doi: 10.21037/tcr-20-3539.
2. Sun Q, et al. (2014) Discovery of fruquintinib, a potent and highly selective small molecule inhibitor of VEGFR 1, 2, 3 tyrosine kinases for cancer therapy, Cancer Biol Ther. 2014 15:12, 1635-1645. doi: 10.4161/15384047.2014.964087.
3. Siegel RL, et al. Colorectal cancer statistics, 2023 [published online ahead of print, 2023 Mar 1]. CA Cancer J Clin. 2023; 73(3):233-254. doi:10.3322/caac.21772.
4. National Cancer Institute. Available at: https://seer.cancer.gov/statfacts/html/colorect.html (accessed May 2023).
5. Atreya CE, Yaeger R, Chu E. Systemic therapy for metastatic colorectal cancer: from current standards to future molecular targeted approaches. Am Soc Clin Oncol Educ Book. 2017;37:246-256. doi:10.1200/EDBK_175679.
6. Vatandoust S, et al. Colorectal cancer: Metastases to a single organ. World J Gastroenterol. 2015;21(41):11767-76. doi:10.3748/wjg.v21.i41.11767.
7. Sung H, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-249. doi:10.3322/caac.21660.
8. Bando H, et al. Therapeutic landscape and future direction of metastatic colorectal cancer. Nat Rev Gastroenterol Hepatol 2023; 20(5)306-322. doi:10.1038/s41575-022-00736-1.
9. D'Haene N, et al. Clinical application of targeted next-generation sequencing for colorectal cancer patients: a multicentric Belgian experience. Oncotarget. 2018;9(29):20761-20768. Published 2018 Apr 17. doi:10.18632/oncotarget.25099.
10. Venderbosch, et al. Mismatch repair status and braf mutation status in metastatic colorectal cancer patients: A pooled analysis of the Cairo, Cairo2, coin, and Focus Studies. Clinical Cancer Res.,2014; 20(20):5322–5330. doi:10.1158/1078-0432.ccr-14-0332.
11. Koopman, M., et al. Deficient mismatch repair system in patients with sporadic advanced colorectal cancer. Br J Cancer. 209;100(2), 266–273. doi:10.1038/sj.bjc.6604867.
12. Ahcene Djaballah S, et al. HER2 in Colorectal Cancer: The Long and Winding Road From Negative Predictive Factor to Positive Actionable Target. Am Soc Clin Oncol Educ Book. 2022;42:1-14. doi:10.1200/EDBK_351354.
13. Dasari NA, et al. LBA25 – FRESCO-2: A global phase 3 multiregional clinical trial (MRCT) evaluating the efficacy and safety of fruquintinib in patients with refractory metastatic colorectal cancer. Ann Oncol. 2022 Sep;33(suppl_7): S1391-S1392. doi:10.1016/j.annonc.2022.08.021.
14. Dasari NA, et al. Fruquintinib versus placebo in patients with refractory metastatic colorectal cancer (FRESCO-2): an international, multicentre, randomised, double-blind, phase 3 study [published online ahead of print, 2023 Jun 15]. Lancet. 2023. doi: 10.1016/S0140-6736(23)00772-9.