**INTRODUCTION**

Patients with metastatic colorectal cancer (mCRC) have limited treatment options following progression on standard therapies. The current standard of care after patients progress on fluoriduracil/safenex (TAS-102) or regorafenib is to rechallenge with previous systemic treatments, enroll in a clinical trial or pursue best supportive care (BSC).

Fruquintinib (HMP-010) is a novel, potent and highly selective oral kinase inhibitor of vascular endothelial growth factor receptors 1, 2, and 3.1 Fruquintinib was approved in China for patients with refractory metastatic colorectal cancer (mCRC) in September 2018 based on results of the FRESCO trial NCT02314819, a phase 3 study in patients with refractory mCRC in the 1st or later setting. Results showed fruquintinib significantly improved median overall survival (mOS) and median progression-free survival (mPFS) compared to placebo.

**METHODS**

A phase 1b/2 dose-confirmation study was conducted in the US. Results were previously confirmed and the established RP2D in China with similar PK characteristics,2 and showed preliminary efficacy and safety in patients with refractory mCRC who had progressed on TAS-102 and/or regorafenib.3 At the time FRESCO was conducted in China, the SOC for patients with mCRC differed from that outside of China. Here we present an ongoing, global, multicenter, randomized, placebo-controlled phase 3 trial (FRESCO-2; NCT0219-013-GLOBL; NCT04322539) being conducted to investigate the efficacy and safety of fruquintinib plus BSC to placebo plus BSC in patients with refractory mCRC.

**KEY INCLUSION CRITERIA**

- Historically or cytologically documented metastatic colorectal adenocarcinoma, RAS, B-Raf, and dMMR are not mutably instable (MSI)/mismatch repair (MMR) status must be documented.
- Patients must have progressed on or been intolerant to all standard chemotherapies, relevant laboratory tests, when compared to placebo: mOS: 9.30 vs. 6.57 months (HR=0.65, p<0.001); mPFS: 3.71 vs. 1.84 months (HR=0.26, p<0.001).
- The toxicities of fruquintinib were manageable.

**KEY EXCLUSION CRITERIA**

- Absolute neutrophil count (ANC) <1.5×10^9/L, platelet count <100×10^9/L, or hemoglobin <10 g/dL.
- Total serum bilirubin ≥1.5, the upper limit of normal (ULN).
- Patients with Gilbert syndrome, bilirubin >2×ULN, and normal AST/LAT are excluded.
- Fruquintinib was approved in China for patients with refractory metastatic colorectal cancer (mCRC). In September 2018 based on results of the FRESCO trial NCT02314819, a phase 3 study in patients with refractory mCRC in the 1st or later setting. Results showed fruquintinib significantly improved median overall survival (mOS) and median progression-free survival (mPFS) compared to placebo.

**OBJECTIVES**

- Determine the safety and tolerability of fruquintinib in combination of BSC.
- Evaluate the anti-fractionary activity of fruquintinib in combination of BSC.
- Evaluate the relationship between fruquintinib exposure and antitumor effects.
- Evaluate the effects of fruquintinib on PFS.
- Assess the impact of fruquintinib on health-related quality of life.
- Explore the patient's perception of quality of life and treatment satisfaction.

**STATISTICAL ANALYSIS**

Key aspects of the planned analyses for OS and PFS.

- Kaplan-Meier method will be used to summarize the data;
- Two-sided p-value will be calculated using a stratified log-rank test and test for interaction with randomization strata and treatment group;
- HR and its 95% confidence interval will be obtained from a Cox proportional hazard model.
- A fixed-seed (hypergeometric) testing procedure will be used to control the overall type I error rate at 0.05;
- Sensitivity and subgroup analysis will be conducted to evaluate the robustness and consistency of the results from the primary analysis.