CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217564Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	NDA 217564
Priority or Standard	Priority
Submit Date(s)	March 30, 2023
Received Date(s)	March 30, 2023
PDUFA Goal Date	November 30, 2023
Division/Office	Division of Oncology 3/Office of Oncologic Diseases
Review Completion Date	See electronic stamp date
Established/Proper Name	Fruquintinib
(Proposed) Trade Name	FRUZAQLA
Pharmacologic Class	Kinase inhibitor
Applicant	Takeda Pharmaceuticals
Dosage form	1mg and 5mg capsules
Applicant proposed Dosing Regimen	5mg orally once daily, with or without food for the first 21 days of each 28 day cycle
Applicant Proposed Indication(s)/Population(s)	Treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti-VEGF therapy; and, if *RAS* wild-type, an anti-epidermal growth factor receptor (EGFR) therapy
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti-VEGF therapy; and, if *RAS* wild-type and medically appropriate, an anti-epidermal growth factor receptor (EGFR) therapy
Recommended Dosing Regimen	5 mg orally once daily for the first 21 days of each 28-day cycle

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OMPI=Office of Medical Policy Initiatives
DMPP=Division of Medical Policy Programs

Glossary

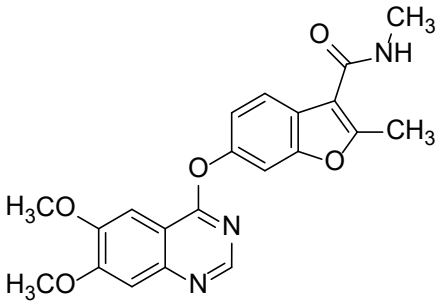
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome

REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1 Product Introduction

Fruquintinib is a small molecule kinase inhibitor of vascular endothelial growth factor receptors (VEGFR)-1, -2, and -3. The established pharmacologic class for fruquintinib is kinase inhibitor. The chemical name is 6-[(6,7-dimethoxyquinazolin-4-yl)oxy]-*N*,2-dimethyl-1-benzofuran-3-carboxamide. Its molecular formula is $C_{21}H_{19}N_3O_5$, which corresponds to a molecular weight of 393.39 g/mol. Fruquintinib has the following chemical structure:



Fruquintinib is supplied as 1 mg or 5 mg capsules for oral administration. The inactive ingredients are corn starch, microcrystalline cellulose, and talc. The 1 mg capsule shell contains FD&C Yellow No. 5 (tartrazine), FD&C Yellow No. 6 (sunset yellow FCF), gelatin, and titanium dioxide. The 5 mg capsule shell contains FD&C Blue No. 1 (brilliant blue FCF), FD&C Red No. 40 (allura red AC), gelatin, and titanium dioxide.

The proposed recommended dosage for fruquintinib is 5 mg orally once daily for the first 21 days of each 28-day cycle until disease progression or unacceptable toxicity.

FRUZAQLA (fruquintinib) is a new molecular entity and has not been previously marketed in the US. Fruquintinib has been approved in China since September 4, 2018, under the brand name Elunate. The indication approved in China is for the treatment of patients with metastatic colorectal cancer (mCRC) who had been previously treated with fluoropyrimidine, oxaliplatin-, and irinotecan-based chemotherapy, including those who have previously received an anti-VEGF biological therapy, or, if *RAS* wild-type, an anti-epidermal growth factor receptor (EGFR) therapy.

1.2 Conclusions on the Substantial Evidence of Effectiveness

The main trial providing substantial evidence of effectiveness for this NDA is Study

2019-013-GLOB1 (FRESCO-2) (NCT02314819). FRESCO-2 is an international, double-blind, placebo-controlled randomized trial in patients with metastatic colorectal cancer (mCRC) who had been previously treated with fluoropyrimidine, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and in the refractory setting, regorafenib and/or trifluridine/tipiracil. In addition, to be eligible, patients with *RAS* wild-type tumors must have received prior treatment with an anti-epidermal growth factor receptor (EGFR) antibody and patients with a microsatellite instability-high (MSI-H) status must have received prior therapy with an immune checkpoint inhibitor. Patients with uncontrolled hypertension (defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg), proteinuria ≥ 2+ or 24-hour urine protein ≥ 1.0 g/24 hours, conditions that could result in gastrointestinal hemorrhage (active gastric/duodenal ulcer or ulcerative colitis, active hemorrhage of an unresected gastrointestinal tumor, history of perforation or fistulas), a history of thromboembolic events or arterial embolic events, tumor invasion of a large vascular structure, or brain metastases were excluded from study participation.

Randomization was stratified by prior use of therapy in the refractory setting (trifluridine/tipiracil vs. regorafenib vs. trifluridine/tipiracil and regorafenib), *RAS* status (wild-type vs. mutated), and duration of metastatic disease (≤ 18 months vs. > 18 months).

Patients were randomized in a 2:1 ratio to receive either fruquintinib 5 mg PO daily (QD) on Days 1-21 of each-28 day cycle or matching placebo. Treatment was administered until disease progression or intolerable toxicity.

A total of 691 patients were randomly allocated, 461 patients into the fruquintinib arm and 230 patients into the placebo arm at 124 study sites in the US, Japan, Europe, and Australia. The primary endpoint of the trial was overall survival (OS), a direct measure of clinical benefit. The key secondary endpoint was progression-free survival (PFS) as assessed by investigator according to RECIST 1.1. Additional efficacy outcome measures were overall response rate (ORR), disease control rate (DCR), duration of response (DoR), and health-related quality of life (HRQoL) outcomes measured by the EORTC QLQ-C30 and EQ-5D-5L questionnaires.

In FRESCO-2, treatment with fruquintinib provided a statistically significant and clinically meaningful improvement in OS compared with placebo in a heavily pretreated population. The OS HR was 0.66 (95% CI: 0.55, 0.80; p<0.001) with a median OS of 7.4 months (95% CI: 6.7, 8.2) in the fruquintinib arm and 4.8 months (95% CI: 4.0, 5.8) for the placebo arm. The PFS HR was 0.32 (95% CI: 0.27, 0.39; p<0.001) with a median PFS was 3.7 months (95% CI: 3.5, 3.8) in the fruquintinib arm and 1.8 months (95% CI: 1.8, 1.9) in the placebo arm. PFS testing crossed the statistical significance boundary in these analyses too and although this benefit is clinically modest, these results confirmed the robustness of the survival benefit, a finding consistent in sensitivity analyses.

In addition, the Applicant submitted data from Study 2013-013-00CH1 (FRESCO), a

single country (China), double-blind, placebo-controlled randomized trial in patients with metastatic colorectal cancer (mCRC) who had been previously treated with fluoropyrimidine, oxaliplatin-, and irinotecan-based chemotherapy. This was a second trial that provided substantial evidence of a treatment effect; however, on its own, the results would not have been considered as applicable to the US patient population. The applicability to the US patient population could be considered however after submission of the results of FRESCO-2 as summarized above.

In FRESCO, prior treatment with therapy targeting VEGF and anti-EGFR drugs was allowed but not mandated. At the time of study conduct, regorafenib and trifluridine/tipiracil were not approved in China and this study preceded the use of immune checkpoint inhibitors in patients with MSI-H tumors. Patients older than 75 years of age or who had uncontrolled hypertension (defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg), proteinuria ≥ 2+ or 24-hour urine protein ≥ 1.0 g/24 hours, conditions that could result in gastrointestinal hemorrhage (active gastric/duodenal ulcer or ulcerative colitis, active hemorrhage of an unresected gastrointestinal tumor, history of perforation or fistulas), a history of thromboembolic events or arterial embolic events, body weight less than 40 kg, or brain metastases were excluded from study participation. Randomization was stratified by prior use of VEGF inhibitors (yes vs. no) and *KRAS* status (wild-type vs. mutated).

Patients were randomly allocated in a 2:1 ratio to receive either fruquintinib 5 mg PO daily (QD) on Days 1-21 of each-28 day cycle or matching placebo. Treatment was administered until disease progression or intolerable toxicity.

A total of 416 patients were randomized, 278 patients into the fruquintinib arm and 138 patients into the placebo arm. Seventy percent of patients received prior anti-VEGF therapy, and 14% received prior anti-EGFR therapy. The primary endpoint of the trial was overall survival (OS). Additional efficacy outcome measures were progression-free survival (PFS), overall response rate (ORR), disease control rate (DCR), duration of response (DoR), and stable disease duration.

In FRESCO, treatment with fruquintinib provided a statistically significant and clinically meaningful improvement in OS compared with placebo in a heavily pretreated population. The OS HR was 0.65 (95% CI: 0.51, 0.83; p<0.001) with a median OS of 9.3 months (95% CI: 8.2, 10.5) in the fruquintinib arm and 6.6 months (95% CI: 5.9, 8.1) for the placebo arm. The PFS HR was 0.26 (95% CI: 0.21, 0.34) with a median PFS was 3.7 months (95% CI: 3.7, 4.6) in the fruquintinib arm and 1.8 months (95% CI: 1.8, 1.8) in the placebo arm.

As stated above, given the differences in prior therapy and patient population, FDA did not consider FRESCO as an adequate stand-alone trial to support approval of fruquintinib. However, the results of the FRESCO study showed that in patients who were refractory to standard treatment with chemotherapy, treatment with fruquintinib provided clinically meaningful survival benefit. Although FRESCO-2 studied fruquintinib in a more refractory setting with disease progression after disease progression on

additional anticancer agents, in the context of the totality of the evidence, FDA considered that the requested indication for patients with mCRC with prior treatment with fluoropyrimidine, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if eligible, anti-EGFR therapy was supported.

The submitted evidence meets the statutory evidentiary standard for regular approval of fruquintinib for treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if *RAS* wild-type and medically appropriate, an anti-EGFR therapy. The observed improvement in survival the overall population with a HR of 0.66 in FRESCO-2 and 0.65 in FRESCO is statistically robust and clinically meaningful. This finding is supported by consistent results on secondary endpoints on both studies.

1.3 Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Fruquintinib is a small molecule kinase inhibitor of vascular endothelial growth factor receptors (VEGFR)-1, -2, and -3. Although fruquintinib is a new molecular entity, there is extensive clinical experience with other small molecules targeting this pathway, which has lead to the approval of multiple drugs in multiple indications, including colorectal cancer.

The safety and effectiveness of fruquintinib for the treatment of patients with metastatic colorectal cancer (mCRC) were established by the results of a two multicenter, double-blind, placebo-controlled, randomized trials, Studies 2019-013-GLOB1 (FRESCO-2) and 2013-013-00CH1 (FRESCO). FRESCO-2 was an international, multiregional study that enrolled patients with mCRC who had disease progression on/after treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan- combination chemotherapy, an anti VEGF/R biological therapy, and in the refractory setting, regorafenib and/or trifluridine/tipiracil. In addition, to be eligible, patients with *RAS* wild-type tumors must have received prior treatment with an anti- epidermal growth factor receptor (EGFR) antibody and patients with a microsatellite instability-high (MSI-H) status must have received prior therapy with an immune checkpoint inhibitor.

Randomization was stratified by prior use of therapy in the refractory setting (trifluridine/tipiracil vs. regorafenib vs. trifluridine/tipiracil and regorafenib), *RAS* status (wild-type vs. mutated), and duration of metastatic disease (≤ 18 months vs. > 18 months). Patients were randomized 2:1 ratio to receive either fruquintinib 5 mg PO daily (QD) on Days 1-21 of each-28-day cycle or matching placebo. Treatment was administered until disease progression or intolerable toxicity. The primary efficacy outcome was overall survival (OS). The main secondary efficacy outcome was progression-free survival (PFS) as determined by investigators.

A total of 691 patients were randomized (461 and 230 patients into fruquintinib and placebo arms respectively) at 124 study sites in the North America (18%), Europe (72%, and Asia Pacific (10%) regions. The demographics and baseline disease characteristics of the study population were balanced between the treatment arms. The median age was 64 years (range: 25 to 86), 47% age 65 or older; 56% male; 81% White, 9% Asian, and 3% Black; 88% of patients were non-Hispanic or Latino; 43% had an ECOG PS of 0 and 57% had an ECOG PS of 1. All patients had prior treatment with a fluoropyrimidine and 99.6% had treatment with oxaliplatin and irinotecan; 96% had treatment with a VEGF/R-targeting biological and 98% of patients with wild *RAS* tumors had treatment with an anti-EGFR biological; 92% of patients had received prior trifluridine/tipiracil, 48% received prior regorafenib, and 39% received both trifluridine/tipiracil and regorafenib.

In FRESCO-2, treatment with fruquintinib provided a statistically significant and modest although clinically meaningful improvement in OS compared with placebo in a heavily pretreated population. The OS HR was 0.66 (95% CI: 0.55, 0.80; p<0.001) with a median OS of 7.4 months (95% CI: 6.7, 8.2) in the fruquintinib arm and 4.8 months (95% CI: 4.0, 5.8) for the placebo arm. The PFS HR was 0.32 (95% CI: 0.27, 0.39; p<0.001) with a median PFS was 3.7 months (95% CI: 3.5, 3.8) in the fruquintinib arm and 1.8 months (95% CI: 1.8, 1.9) in the placebo arm. PFS testing crossed the statistical significance boundary in these analyses too and although this benefit is clinically modest, these results confirmed the robustness of the survival benefit, a finding consistent in sensitivity analyses.

The FRESCO study was a single country (China), double-blind, placebo-controlled randomized trial in patients with mCRC who had been previously treated with fluoropyrimidine, oxaliplatin-, and irinotecan-based chemotherapy. Prior treatment with therapy targeting VEGF and anti-EGFR drugs was allowed but not mandated. Randomization was stratified by prior use of VEGF inhibitors (yes vs. no) and KRAS status (wild-type vs. mutated). Patients were randomized in a 2:1 ratio to receive either fruquintinib 5 mg PO daily (QD) on Days 1-21 of each-28-day cycle or matching placebo. Treatment was administered until disease progression or intolerable toxicity. The primary efficacy outcome was overall survival (OS). The secondary efficacy outcome was progression-free survival (PFS) as determined by investigators.

A total of 416 patients were randomized, 278 and 138 patients into the fruquintinib and placebo arms respectively. The demographics and baseline disease characteristics of the study population were balanced between the treatment arms. The median age was 56 years (range: 23 to 75), 19% age 65 or older; 61% male; 100% Asian; 27% had an ECOG PS of 0 and 73% had an ECOG PS of 1. All patients had prior treatment with a fluoropyrimidine, oxaliplatin, and irinotecan; 70% had treatment with a VEGF/R-targeting biological and 25% of patients with wild *RAS* tumors had treatment with an anti-EGFR biological.

In FRESCO, treatment with fruquintinib provided a statistically significant and modest but clinically meaningful improvement in OS compared with placebo. The OS HR was 0.65 (95% CI: 0.51, 0.83; p<0.001) with a median OS of 9.3 months (95% CI: 8.2, 10.5) in the fruquintinib arm and 6.6 months (95% CI: 5.9, 8.1) for the placebo arm. The PFS HR was 0.26 (95% CI: 0.21, 0.34) with a median PFS was 3.7 months (95% CI: 3.7, 4.6) in the fruquintinib arm and 1.8 months (95% CI: 1.8, 1.8) in the placebo arm.

The adverse reaction profile observed in patients receiving fruquintinib in Studies FRESCO-2 and FRESCO is consistent with the known safety profile of multikinase inhibitors targeting VEGFR. The most common adverse reactions (incidence ≥ 20%) in FRESCO-2 in patients receiving fruquintinib with a difference of at least 5% compared with patients treated with placebo were fatigue (53%), hypertension (38%), stomatitis (31%), abdominal pain (25%), diarrhea (24%), hypothyroidism (21%), palmar-plantar erythrodysesthesia (19%), proteinuria (18%), dysphonia (18%), musculoskeletal pain (16%), and arthralgia (11%). The most

frequent (incidence ≥ 5%) Grade 3-4 adverse events in patients treated with fruquintinib in FRESCO-2 were hypertension (14%), fatigue (12%), and palmar-plantar erythrodysesthesia).

The most common adverse reactions (incidence ≥ 20%) in FRESCO in patients receiving fruquintinib with a difference of at least 5% compared with patients treated with placebo were hypertension (61%), proteinuria (55%), palmar-plantar erythrodysesthesia (49%), dysphonia (38%), stomatitis (33%), abdominal pain (29%), hemorrhage (28%), diarrhea (25%), fatigue (25%), musculoskeletal pain (22%), and anorexia (21%). The most frequent (incidence ≥ 5%) Grade 3-4 adverse events in patients treated with fruquintinib in FRESCO were fatigue (12%), hypertension (14%), hepatotoxicity (7%), and palmar-plantar erythrodysesthesia (6%).

Given the differences in prior therapy and patient population, FDA did not consider FRESCO as an adequate stand-alone trial to support approval of fruquintinib. However, the results of the FRESCO study showed that in patients who were refractory to standard treatment with chemotherapy, treatment with fruquintinib provided for a clinically meaningful survival benefit. Although FRESCO-2 studied fruquintinib in a more refractory setting after disease progression on additional anticancer agents, in the context of the totality of the evidence, FDA considered that the requested indication for patients with mCRC with prior treatment with fluoropyrimidine, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if eligible, anti-EGFR therapy, was supported.

The submitted evidence meets the statutory evidentiary standard for approval of fruquintinib for treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if *RAS* wild-type, an anti-EGFR therapy. The observed improvement in survival in the overall population with a HR of 0.66 in FRESCO-2 and 0.65 in FRESCO is statistically robust and clinically meaningful. This finding is supported by consistent results on secondary endpoints on both studies. The adverse reaction profile observed in patients receiving fruquintinib is consistent with the adverse reaction profile of other agents in the same pharmacological class and the disease setting. The risks of fruquintinib are acceptable considering the life-threatening nature of metastatic colorectal carcinoma.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Metastatic colorectal cancer (mCRC) is a serious disease with a poor prognosis. Colorectal cancer is the third most common cause of cancer mortality worldwide with more than 1.85 million cases and 850,000 deaths annually (Biller L, 2021). At diagnosis,	Refractory metastatic colorectal cancer is a serious, life-threatening disease with a poor prognosis. Estimated survival is less than 6 months.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	metastatic disease is present in 20% of patients and approximately another 25% who present with localized disease will later develop metastases. In patients diagnosed with metastatic disease, the estimated median survival is 36 months and the 5-year survival is 15% (SEER, 2023). The primary treatment for mCRC is systemic therapy combining cytotoxic chemotherapy and biologic therapy targeting the VEGF pathway; for some patients with certain biomarkers, there is available targeted therapy such as drugs against EGFR, HER2, BRAF V600, and immune checkpoint inhibitors for tumors that have microsatellite instability-high. However, irrespective of the molecular profile, in the refractory setting, the prognosis is poor and the estimated survival is less than 6 months.	
Current Treatment Options	Systemic chemotherapy combining fluoropyrimidines with oxaliplatin and irinotecan is the primary treatment for mCRC. First-line treatment combines a fluoropyrimidine with one of these agents (or both), and a combination of fluoropyrimidine and the agent not used before (oxaliplatin or irinotecan) is generally used upon disease progression. Bevacizumab, a monoclonal antibody that targets the VEGF pathway is generally used in combination with the fluoropyrimidine-based regimens. In addition, other biologics targeting the VEGF pathway are approved for the second line treatment of mCRC. For patients with tumors that are RAS wild type, antibodies targeting the EGFR pathway are available in combination with chemotherapy or as single agents in the refractory setting if the antibodies were not previously used. In addition, targeted therapies are available for patients with microsatellite instability-	Although standard of care chemotherapy improves survival in patients with advanced unresectable or metastatic colorectal carcinoma, treatment is palliative. Treatment options for the refractory setting are limited and with modest benefit. There is a need for more effective treatment.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	high tumors, BRAF V600 mutations, or HER2-positive tumors. After initial treatment with chemotherapy ± biologics and targeted therapies, only two drugs are approved for treatment in the refractory setting, regorafenib and trifluridine/tipiracil. Regorafenib was approved based on the CORRECT trial, a randomized controlled trial that compared regorafenib vs. placebo in 760 patients with previously treated mCRC. Treatment with regorafenib resulted in a statistically significant and clinically modest but meaningful survival improvement, with a median OS of 6.4 months (95% CI 5.8, 7.3) in the regorafenib arm and 5.0 months (95% 4.4, 5.8) in the control arm (HR 0.77, 95% CI 0.64, 0.94). trifluridine/tipiracil was approved based on the RECOURSE trial, a randomized controlled trial that compared trifluridine/tipiracil vs. placebo in 800 patients with previously treated mCRC. Treatment with trifluridine/tipiracil resulted in a statistically significant and clinically modest but meaningful survival improvement, with a median OS of 7.1 months (95% CI 6.5, 7.8) in the trifluridine/tipiracil arm and 5.3 months (95% 4.6, 6.0) in the control arm (HR 0.68, 95% CI 0.58, 0.81). While this NDA review was ongoing, the combination trifluridine/tipiracil and bevacizumab was approved based on the results of the SUNLIGHT trial, a randomized controlled trial comparing trifluridine/tipiracil with or without bevacizumab in 492 patients with previously treated mCRC. Treatment with trifluridine/tipiracil in combination with bevacizumab resulted in a statistically significant and clinically modest but meaningful survival improvement, with a median OS of 10.8 months (95% CI 9.4, 11.8) in the trifluridine/tipiracil and bevacizumab arm and 7.5 months (95% 6.3, 8.6) in the control arm (HR 0.61, 95% CI 0.49,	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	0.77). There are no drugs approved for the treatment of patients with disease progression after regorafenib or trifluridine/tipiracil ± bevacizumab. If patients are eligible to continue treatment, the treatment not received before (regorafenib or trifluridine/tipiracil) can be administered.	
Benefit	The approval is supported by two multicenter, double-blind, placebo-controlled, randomized trials, Studies 2019-013-GLOB1 (FRESCO-2) and 2013-013-00CH1 (FRESCO). FRESCO-2 was an international, multiregional study that enrolled patients with mCRC who had disease progression on/after treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-combination chemotherapy, an anti VEGF/R biological therapy, and in the refractory setting, regorafenib and/or trifluridine/tipiracil. In addition, to be eligible, patients with *RAS* wild-type tumors must have received prior treatment with an anti- EGFR antibody and patients with a MSI-H status must have received prior therapy with an immune checkpoint inhibitor. Patients were randomized 2:1 ratio to receive either fruquintinib or matching placebo. Treatment was administered until disease progression or intolerable toxicity. The major efficacy outcome was overall survival (OS). The main secondary endpoint was progression-free survival (PFS). A total of 691 patients were randomized, 461 and 230 patients into fruquintinib and placebo arms respectively, at sites in the North America (18%), Europe (72%), and Asia Pacific (10%) regions. The demographics and baseline disease characteristics	The submitted evidence meets the statutory evidentiary standard for approval. Results of a two well-controlled randomized study showed a statistically significant and clinically meaningful improvement in survival and a statistically significant effect on progression-free survival among patients who received fruquintinib compared to those who received placebo with chemotherapy in Study FRESCO-2 and FRESCO. These results were consistent across predefined subgroups and secondary endpoints. Although FRESCO-2 is a multiregional trial, characterization of the effect of fruquintinib across under represented minorities is insufficient. A post marketing study to adequately characterize the effect of fruquintinib in US underrepresented minorities was agreed with the Applicant.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	of the study population were balanced between the treatment arms. In FRESCO-2, treatment with fruquintinib provided a statistically significant and clinically meaningful improvement in OS compared with placebo in a heavily pretreated population. The OS HR was 0.66 (95% CI: 0.55, 0.80; p<0.001) with a median OS of 7.4 months (95% CI: 6.7, 8.2) in the fruquintinib arm and 4.8 months (95% CI: 4.0, 5.8) for the placebo arm. The PFS HR was 0.32 (95% CI: 0.27, 0.39; p<0.001) with a median PFS was 3.7 months (95% CI: 3.5, 3.8) in the fruquintinib arm and 1.8 months (95% CI: 1.8, 1.9) in the placebo arm. PFS testing crossed the statistical significance boundary in these analyses too and although this benefit is clinically modest, these results confirmed the robustness of the survival benefit, a finding consistent in sensitivity analyses. The FRESCO study was a single country (China), double-blind, placebo-controlled randomized trial in patients with mCRC who had been previously treated with fluoropyrimidine, oxaliplatin-, and irinotecan-based chemotherapy. Prior treatment with therapy targeting VEGF and anti-EGFR drugs was allowed but not mandated. Patients were randomized in a 2:1 ratio to receive either fruquintinib or matching placebo. Treatment was administered until disease progression or intolerable toxicity. The primary efficacy outcome was OS. The secondary efficacy outcome was progression-free survival (PFS). A total of 416 patients were randomized, 278 and 138 patients into the fruquintinib and placebo arms respectively. The demographics and baseline disease characteristics of the study population were balanced between the treatment arms. In	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	FRESCO, treatment with fruquintinib provided a statistically significant and clinically meaningful improvement in OS compared with placebo. The OS HR was 0.65 (95% CI: 0.51, 0.83; p<0.001) with a median OS of 9.3 months (95% CI: 8.2, 10.5) in the fruquintinib arm and 6.6 months (95% CI: 5.9, 8.1) for the placebo arm. The PFS HR was 0.26 (95% CI: 0.21, 0.34) with a median PFS was 3.7 months (95% CI: 3.7, 4.6) in the fruquintinib arm and 1.8 months (95% CI: 1.8, 1.8) in the placebo arm. Although the studies were conducted in different populations (patients in FRESCO were all enrolled in a single country, less patients received prior therapy with biologics, and no patient had prior treatment with regorafenib and/or trifluridine/tipiracil), treatment with fruquintinib resulted in a similar magnitude of benefit in overall survival. FDA's approval is mostly based on the results of FRESCO-2, while FRESCO provided supportive evidence to extend the indication to patients with no prior treatment with regorafenib and/or trifluridine/tipiracil. Although FRESCO-2 was a multiregional trial, it enrolled insufficient number of underrepresented minorities to fully characterize the effect of fruquintinib in these populations.	
Risk and Risk Management	The primary data supporting the safety of fruquintinib for the proposed indication was provided from data derived from 734 patients with previously treated mCRC who received at least one dose of fruquintinib in the FRESCO-2 and FRESCO studies. The most common adverse reactions in patients receiving fruquintinib (incidence ≥ 20%) in FRESCO-2 were fatigue,	The observed safety profile is acceptable when assessed in the context of the treatment of a life-threatening disease. Most of the adverse reactions to fruquintinib were manageable with supportive care and dose modification as needed. The significant and

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	hypertension, decreased appetite, palmar-plantar erythrodysesthesia, proteinuria, dysphonia, abdominal pain, diarrhea, hepatotoxicity, and hypothyroidism. In addition to the events listed above, patients in the FRESCO study also experienced hemorrhage, thrombocytopenia, weight decreased, and musculoskeletal pain. The adverse reaction profile observed in patients receiving fruquintinib in Studies FRESCO-2 and FRESCO is consistent with the known safety profile of multikinase inhibitors targeting VEGFR. Hypertension, hemorrhagic events, infections, gastrointestinal perforation, hepatotoxicity, proteinuria, and palmar-plantar erythrodysesthesia were expected and observed at similar incidences in FRESCO-2 and FRESCO.	potentially serious adverse reactions are adequately addressed in the Warnings and Precautions section and the dose modification recommendations included in product labeling.

1.4 Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	Section 8.1.1 (endpoint discussion and secondary or exploratory COA (PRO) endpoints subsection
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
□	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
□	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1 Analysis of Condition

Colorectal cancer (CRC) is the fourth most common cancer and the second most common cause of cancer mortality in the United States. In 2023, approximately 153,020 people in the U.S. will be diagnosed with CRC (35.9 per 100,000) and 52,550 (13.1 per 100,000) will die from the disease (SEER, 2023). There is a higher incidence of CRC in American Indian/Alaskan American (AI/AN) and Non-Hispanic Black (NHB) populations (48.6 and 41.7 per 100,000 respectively), who also have higher mortality rates (18.6 and 17.6 per 100,000 in AI/AN and NHB populations, respectively). Although the median age at diagnosis in the US is 66 years old (67% of patients have between 55 and 84 years of age), the incidence of early-onset CRC is rising (Siegel R, 2020 and Biller, L, 2021).

Incidence of CRC varies geographically, with decreasing rates in highly developed countries primarily attributed to screening programs and increased uptake of colonoscopy, although lifestyle and dietary changes might also contribute. The 5-year survival for patients diagnosed with metastatic disease is 15% (SEER, 2023). Overall survival from diagnosis of metastatic disease is approximately 30 months (Biller L, 2021; Venook A, 2014) but is dependent upon clinicopathologic and genomic features. Upon disease progression, prognosis is poor, with median overall survival following treatment with standard of care fluoropyrimidine, oxaliplatin, and irinotecan of approximately 6 or 7 months (Stivarga USPI; Lonsurf USPI).

2.2 Analysis of Current Treatment Options

The standard of care first-line treatment of metastatic CRC includes a fluoropyrimidine and either oxaliplatin or irinotecan (or both). Upon progression, second-line treatment includes a fluoropyrimidine and either oxaliplatin or irinotecan, whichever was not used in the first-line. Bevacizumab, a monoclonal antibody that targets the VEGF pathway is generally administered in combination with the fluoropyrimidine-based regimens. In addition, other biologics targeting the VEGF pathway are approved for the second-line treatment of mCRC. For patients with tumors that are *RAS* wild type, antibodies targeting the EGFR pathway are available in combination with chemotherapy or as single agents in the refractory setting if the antibodies were not previously used. In addition, targeted therapies are available for patients with microsatellite instability-high tumors, *BRAF* V600E mutations, or HER2-positive tumors.

After progression on the aforementioned treatments, approved therapies in the US include regorafenib or trifluridine/tipiracil. Both regorafenib and trifluridine/tipiracil were approved based on improvement on overall survival (OS). In the RECOURSE trial, the

median OS of patients receiving trifluridine/tipiracil was 7.1 months (95% confidence interval [CI]: 6.5, 7.8) compared to 5.3 months (95% CI: 4.6, 6) in patients receiving placebo (hazard ratio [HR] 0.68, 95% CI 0.58, 0.81) (Lonsurf USPI). In the CORRECT trial, the mOS of patients receiving regorafenib was 6.4 months (95% CI: 5.8, 7.3) compared to 5 months (95% CI: 4.4, 5.8) in patients receiving placebo (HR 0.77, 95% CI: 0.64, 0.94) (Stivarga USPI). The overall response rate (ORR) was 1.5% and 1% with trifluridine/tipiracil and regorafenib, respectively. While this application was under review, on August 2, 2023, FDA approved the combination of trifluridine/tipiracil with bevacizumab based on the results of the SUNLIGHT trial, which randomized patients with refractory disease to standard of care treatment with trifluridine/tipiracil with or without bevacizumab. The addition of bevacizumab to trifluridine/tipiracil resulted in an improved survival (HR 0.61, 95% CI 0.49, 0.77) with a median of 10.8 months (95% CI 9.4, 11.8) in the combination arm vs. 7.5 months (95% CI 6.3, 8.6) in the trifluridine/tipiracil alone arm.

Additional treatment options exist for select biomarker-positive subsets of mCRC as there are available therapies for patients with tumors that are *RAS*-wild type, HER2-positive, *BRAF V600E*-mutated, or are microsatellite instability high or mismatch repair deficient (MSI-High/dMMR). In addition, if harboring *NTRK* or *RET* gene alterations, there are available treatments approved for tissue-agnostic indications.

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

Fruquintinib is a new molecular entity and has not been previously marketed in the US. Fruquintinib has been approved in China since September 4, 2018, under the brand name Elunate. The indication approved in China is for the treatment of patients with metastatic colorectal cancer (mCRC) who had been previously treated with fluoropyrimidine, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, or, if *RAS* wild-type, an anti-epidermal growth factor receptor (EGFR) therapy.

3.2 Summary of Presubmission/Submission Regulatory Activity

The following summarizes the key regulatory history for fruquintinib:

- *August 25, 2016*: Hutchison MediPharma Ltd. (HutchMed) submitted an original Investigational New Drug Application (IND) containing Protocol 2015-013-00US1, entitled "A Multi-Center, Open-Label, Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics of Fruquintinib in Advanced Solid Tumors in USA," for fruquintinib (HMPL-013) in advanced solid tumors. A Study May Proceed letter was issued on September 23, 2019.

- *February 12, 2020*: Type B Meeting, End of Phase 2 to discuss the development of fruquintinib for the treatment of patients with mCRC who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and, if *RAS* wild-type, an anti-EGFR therapy.
    - FDA advised HutchMed that it was unlikely that the results of Studies 2012-013-00CH1 and 2013-013-00CH1 (FRESCO) alone would be adequate to support a marketing application for fruquintinib as the results of these studies have limited applicability to the U.S. population as the studies were conducted in a single region and the standard of care was different to the standard of care in the U.S., particularly regarding use of monoclonal antibodies and treatment with regorafenib and/or trifluridine/tipiracil. FDA clarified that the dose-finding and activity-estimating ongoing U.S. trial, Study, 2015-013-00US1 would only provide limited safety and PK data.
    - For the planned Study 2019-013-GLOB1 (FRESCO-2), FDA recommended revising the study population (prior treatment with immune checkpoint inhibitors and molecularly targeted therapy for patients with MSI-H/dMMR or *RAS* wild-type tumors), revisions for clarification, and revisions of the statistical plan.
    - HutchMed stated that separate clinical trials to evaluate fruquintinib PK in subjects with moderate or severe renal impairment and in subjects

with mild or moderate hepatic impairment were planned to inform labeling and dosing in these patient populations.

- *June 15, 2020*: FDA granted Fast Track Designation to fruquintinib for the treatment of patients with mCRC who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-vascular endothelial growth factor (VEGF) biological therapy, and, if *RAS* wild-type, an anti-epidermal growth factor receptor (EGFR) therapy.

- *August 2, 2021*: Type B meeting, CMC - Written Response. FDA agreed with HutchMed's proposals for starting materials, proposed control strategies for potential genotoxic impurities and particle size distribution, and stability protocols. FDA deferred judgement on the adequacy of the dissolution test conditions until the proposed test conditions were revised and resubmitted for discussion or at the time of the NDA review.

- *March 29, 2022*: Type C meeting – Written Response. FDA generally agreed with the proposed format of an NDA submission.

- *October 25, 2022*: Type B meeting – Written Response. FDA did not agree with the revised proposal for the dissolution testing strategy and provided additional recommendations.

- *November 1, 2022*: FDA granted the Applicant rolling review for the application.

- *December 15, 2022*: A teleconference was held to discuss clinical site inspection readiness in sites in China and gain alignment with FDA in advance of submission.

    - After the October 20, 2022, pre-NDA meeting, HutchMed became aware of three military hospital sites in China enrolling patients in the FRESCO study that will not be amenable to inspection. These three military hospital sites account for 28 (6.7%) of 416 patients enrolled in the FRESCO study. HutchMed anticipated that the remaining 25 FRESCO clinical sites will be inspection-ready at the time of submission.

    - FDA clarified that based on prior interactions, the FRESCO 2 study will be the pivotal trial for the upcoming NDA and that the FRESCO study will be supportive. FDA stated that inclusion of the data from the FRESCO study in the label, specifically Section 14, will be a review issue.

- July 24, 2023: HutchMed submitted correspondence notifying FDA of the

change of ownership of the NDA to Takeda Pharmaceuticals US, Inc. (Takeda). FDA acknowledged the change of ownership on July 28, 2023.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1 Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) was consulted to conduct inspections of the study Contract Research Organization (CRO), (b) (4) and 3 clinical sites. Site #17090 (Dr. Sara Lonardi) was selected because it had the highest patient enrollment in Study FRESCO-2. Site #41020 was selected as it had the highest patient enrollment in the US and based on results of prior inspections and site # 41060 was selected based on previous inspection history. The OSI team concluded that inspections of the clinical investigators in these sites (Drs. Lonardi, Hochster, and Dasari, as well as the CRO (b) (4) revealed no discrepancies or regulatory violations and that FRESCO-2 appears to have been conducted adequately, with acceptable data in support of the proposed indication.

4.2 Product Quality

The Office of Pharmaceutical Quality (OPQ) recommends approval of NDA 217564 for the commercialization of FRUZAQLA (fruquintinib) capsules, 1 and 5 mg. Based on OPQ's evaluation of the submission, the Applicant provided adequate information on the proposed drug product to ensure the identity, strength, purity, and quality of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling and labels include adequate information to meet the regulatory requirements. Refer to the OPQ's review of this application for additional information.

4.3 Clinical Microbiology

This NDA was reviewed by OPQ's Division of Microbiology Assessment. The microbiology reviewers did not identify issues that would preclude approval of fruquintinib capsules. Fruquintinib should be stored at room temperature 20°C - 25°C (68°F - 77°F); excursions permitted to 15°C - 30°C (59°F - 86°F).

4.4 Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1 Executive Summary

Fruquintinib is a small molecule kinase inhibitor of vascular endothelial growth factor receptors (VEGFR)-1, -2, and -3. VEGFR signaling is implicated in tumor angiogenesis, growth, and progression in a variety of solid tumors. The established pharmacologic class for fruquintinib is kinase inhibitor.

Fruquintinib (HMPL-013) inhibited VEGFR2 activity with an IC50 of 15 nM. Additionally, fruquintinib was able to inhibit the phosphorylation of VEGFR2 with an IC50 of 0.6 nM. The inhibitory activity of fruquintinib on 264 kinases was evaluated using a [32P-ATP] incorporation assay and showed fruquintinib inhibited VEGFR-1, -2, and -3 with IC50s of 33, 35, and 0.5 nM, respectively. This assay also showed that fruquintinib moderately inhibited RET and FGFR1 with IC50s of 128 and 181 nM, respectively.

In in vitro activity assays, fruquintinib inhibited VEGF-induced proliferation of human umbilical vein endothelial cells (HUVECs) with an IC50 of 1.6 nM. Fruquintinib inhibited HUVEC tube formation with an IC50 < 30 nM. Cytotoxicity assays showed that fruquintinib had minimal cytotoxic activity against HUVECs with an IC50 of 18.7 μM and no cytotoxic activity against any of the human tumor cell lines tested.

In in vivo activity assays, fruquintinib inhibited VEGF-induced VEGFR2 phosphorylation for up to 8 hours post-dose in the lung tissue of mice treated with a single dose of 2.5 mg/kg fruquintinib. Additionally, anti-tumor efficacy of fruquintinib was evaluated in a colon cancer xenograft model using HT-29 tumor cells implanted in nude BALB/c mice. Fruquintinib was able to inhibit tumor growth in a dose-dependent manner with anti-tumor activity starting at 0.77 mg/kg.

Safety pharmacology studies assessed the effects of fruquintinib on the cardiovascular system, central nervous system (CNS), and respiratory function. Fruquintinib did not have a toxicologically significant effect on cardiovascular or respiratory function in dogs or neurobehavioral function in rats.

Fruquintinib binds to plasma protein of various species in a concentration-independent manner. In human plasma, 95.3% of fruquintinib was bound to plasma protein. Following a single oral dose of radiolabeled fruquintinib, wide distribution of fruquintinib was observed with the highest radioactivity observed in the esophagus, large intestine, small intestine, stomach, bladder, uveal tract, and pigmented skin. No major metabolites were observed. Elimination studies showed that fruquintinib was mainly excreted via the fecal route in rats (~71%) with some elimination via the urine (~22%).

In a 13-week repeat-dose toxicology study in rats, animals were orally administered fruquintinib at 0, 0.3, 0.6, or 1.2 mg/kg daily with a 4-week recovery period. On Day 44, the dose in the 1.2 mg/kg group was increased to 2.4 mg/kg due to a lack of observed

toxicities. A single early mortality was observed in a male animal receiving 2.4 mg/kg on Day 78. Clinical observations in the early mortality animal included broken teeth and decreased body weight. Hematology findings in this animal included decreases in platelets and reticulocytes. Histopathology findings in this animal included hemorrhage and necrosis of the adrenal gland, decreased bone marrow cellularity, degeneration and necrosis of the Brunner's gland of the duodenum associated with severe neutrophilic inflammation, and increased thickness of the physis in the femur. In surviving animals, broken teeth were observed starting at 0.6 mg/kg (approximately 1.2 times the recommended clinical dose based on BSA) that increased in frequency and severity with dose. Additionally, decreases in body weight and food consumption were observed in surviving animals, which may have been due to the broken teeth. In animals receiving 1.2/2.4 mg/kg and/or with broken teeth, powdered feed was provided. In surviving animals receiving 2.4 mg/kg (approximately 4.8 times the recommended clinical dose based on BSA), hematology and clinical chemistry findings included decreases in reticulocytes and increases in triglycerides, respectively. Histopathology findings in these animals included decreases in cellularity in bone marrow in the femur and increases in physis thickness in the femur in males and females. Spleen mineralization was observed in female animals.

In a 13-week repeat-dose toxicology study in dogs, animals were orally administered fruquintinib at 0, 0.03, 0.06, or 0.12 mg/kg daily with a 4-week recovery period. No early mortalities were observed. Clinical findings included red discolored feces and discolored oral mucosa starting at 0.06 mg/kg (approximately 0.4 times the recommended clinical dose based on BSA) and excessive salivation, red discharge, abnormally brown teeth, and oral mucosa ulceration starting at 0.12 mg/kg (approximately 0.8 times the recommended clinical dose based on BSA). Animals receiving 0.12 mg/kg fruquintinib also exhibited a decrease in body weight that was associated with a decrease in food consumption. Hematology findings included an increase in fibrinogen starting at 0.03 mg/kg and a decrease in neutrophils starting at 0.06 mg/kg. Clinical chemistry findings included a decrease in albumin/globulin ratio driven by an increase in globulin levels starting at 0.03 mg/kg. Histopathology findings included increased physis thickness in the femur and vacuolation in the cortex of the adrenal gland starting at 0.03 mg/kg (approximately 0.2 times the recommended clinical dose based on BSA) and decreased cellularity in the bone marrow of the femur starting at 0.12 mg/kg (approximately 0.8 times the recommended clinical dose based on BSA).

In an embryo-fetal development study in female rats, once daily oral administration of fruquintinib at doses of 0, 0.025, 0.1, or 0.25 mg/kg on gestation day (GD) 6 through 17 resulted in fetal toxicity. These findings included external, vascular, and skeletal abnormalities in offspring starting at 0.1 mg/kg (approximately 0.5 times the recommended clinical dose based on BSA), a trending increase in early resorption and post implantation loss, and a reduction in live fetuses at 0.25 mg/kg (approximately 0.2 times the recommended clinical dose based on BSA).

Based on the toxicity profile of fruquintinib and the elimination half-life of 42 hours, labeling advises that females of reproductive potential use effective contraception

during treatment with fruquintinib and for 2 weeks following the final dose. Additionally, labeling advices to avoid breastfeeding during treatment with fruquintinib and for 2 weeks following the final dose.

Fruquintinib was not mutagenic in the in vitro bacterial reverse mutation assay or clastogenic in the in vitro chromosomal aberration assay in Chinese hamster ovary (CHO) cells. The in vivo bone marrow micronucleus assay in rats was negative. Carcinogenicity studies were not warranted to support marketing of fruquintinib for the current indication.

The nonclinical pharmacology and toxicology data submitted to this NDA are adequate to support the approval of fruquintinib for the proposed indication.

5.2 Referenced NDAs, BLAs, DMFs

None.

5.3 Pharmacology

Primary Pharmacology

Summary of IC50s for VEGFR2 Kinase

Compounds	Assay No.	VEGFR2 IC_{50} (μM)
Fruquintinib	1	0.013
	2	0.018
	3	0.013
	Mean±SD	0.015 ± 0.003
M11 (HM5025423)	1	0.028
	2	0.031
	3	0.026
	Mean±SD	0.028 ± 0.002

IC_{50}=the concentration of a compound that is required for 50% inhibition of a specific biological or biochemical function in vitro; SD=standard deviation; VEGFR2=vascular endothelial growth factor receptor 2

(Excerpted from Applicant's Submission)

VEGFR2 kinase activity was assessed in vitro using a recombinant VEGFR2 catalytic domain and changes in activity were measured via a FRET-based z-lyte assay kit. Recombinant VEGFR2 was incubated with substrate peptide, ATP, and various concentrations of fruquintinib or metabolite 11 (HM5025423, M11). Following incubation, a development agent was added and VEGFR2 activity was measured via absorbance at 460 nm and 535 nm. Fruquintinib and M11 inhibited VEGFR2 activity to a similar degree with IC50s of 15 and 28 nM, respectively.

Inhibitory Activity of Fruquintinib on Other Kinases

Kinase	fruquintinib IC50 or IH%@ 1μM
VEGFR1(Flt1)	33*
VEGFR2 (KDR)	35*
VEGFR3 (Flt4)	0.5*
Ret(h)	128*
FGFR1(h)	181*
cKit(h)	458*
FGFR2(h)	553*
PDGFRα(h)	601*
Fms(h)	698*
FGFR3(h)	738*
PDGFRβ(h)	>10000(22%*)
Flt3 (h)	>10000 (-13%*)
EphB4	>3000
c-Met	>10000
EGFR	>30000
Tie2	>10000
CHK1	>10000
CDK1	>10000
CDK2	>10000
CDK5	>10000
Abl(h)	14%*

Notes: IC_{50} was determined by HMP and Millipore.
* The kinases activity was detected by Millipore using ^{32}p-ATP incorporation method.

(Excerpted from Applicant's Submission)

The inhibitory activity of fruquintinib on 264 kinases was evaluated using a [32P-ATP] incorporation assay performed by (b) (4) in addition to in-house testing using RET-based Z-lyte, EGFR kinase Z-lyte, TRANSCREENER fluorescence polarization ADP, and CHK1 kinase KLISA assays. A single concentration of 1 μM fruquintinib was used. Fruquintinib inhibited VEGFR 1, 2, and 3 with IC50s of 33, 35, and 0.5 nM, respectively. Additionally, moderate inhibition of RET and FGFR were observed with IC50s of 128 and 181 nM, respectively.

Inhibition of VEGFR2 Phosphorylation in HEK293-KDR cells

compounds	Assay No.	IC_{50} (μM)
		(DELFIA)
fruquintinib	1	0.0007
	2	0.0004
	3	0.0008
	Mean±SD	0.0006±0.0002

(Excerpted from Applicant's Submission)

The inhibition of VEGF-induced VEGFR2 phosphorylation by fruquintinib was evaluated using VEGFR2 (KDR) overexpressing HEK293-KDR cells. HEK293-KDR cells were starved and subsequently treated with various concentrations of fruquintinib and

stimulated with recombinant human VEGF. Cells were lysed, and lysates were incubated with plate-bound anti-VEGFR2 capture antibody. Phosphorylation status of captured VEGFR2 was detected using a DELFIA Eu-N1-labeled anti-phosphotyrosine antibody, where fluorescence was measured at 340 nm excitation and 620 nm emission. Fruquintinib inhibited VEGFR2 phosphorylation with an IC50 of 0.6 nM.

IC50 of Fruquintinib on VEGF-induced HUVEC Proliferation

compounds	Repeat No.	IC_{50} (μM)
	n	
fruquintinib	1	0.0021
	2	0.0012
	Mean	0.0016

(Excerpted from Applicant's Submission)

Inhibition of VEGF-induced proliferation was evaluated using primary HUVECs incubated with recombinant human VEGF and various concentrations of fruquintinib. Proliferation was determined as a measure of optical density. Fruquintinib inhibited VEGF-induced proliferation of primary HUVECs with an IC50 of 1.6 nM.

Inhibition of Fruquintinib on Tube Formation

	compounds (μM)	Tube total length	Inhibition (%)
cell	0.00	720	0
fruquintinib	0.03	185	74
	0.3	40	94

(Excerpted from Applicant's Submission)

To evaluate the ability of fruquintinib to inhibit HUVEC tube formation, primary HUVECs were seeded in wells pre-coated with basement membrane matrix. Cells were incubated with various concentrations of fruquintinib and endothelial cell tube lengths were measured under 40x magnification. Fruquintinib inhibited tube formation with an IC50 < 30 nM.

Cytotoxicity of Fruquintinib in Cell Lines

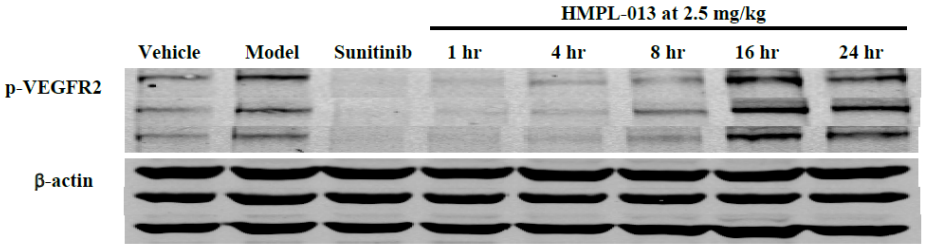
Tissue Source	Cell name	Medium + 10%FBS	Cell numbers/well	Fruquintinib	Sunitinib
Human Breast Carcinoma	Bcap-37	DMEM	8000	> 30	4.7
Human Ovary Adenocarcinoma	SKOV-3	IMDM	8000	> 30	> 30
Human Non-Small Cell Lung Carcinoma	A549	DMEM	8000	> 30	3.9
Human Large Cell Lung Carcinoma	NCI-H460	RPMI 1640	8000	> 30	6.5
Human Hepatocellular Carcinoma	HEPG2	DMEM	8000	> 30	5.4
Human Stomach Gastric Adenocarcinoma	AGS	IMDM	8000	> 30	15.5
Human Colon Cancer	SW620	L-15	8000	> 30	6.9
Human Colon Cancer	HT-29	M-5A	8000	> 30	5.2
Human Skin Epidermoid Carcinoma	A431	DMEM	8000	> 30	9.8
Human Skin Malignant Melanoma	A375	DMEM	30000	> 30	9.4
Human Hepatocellular Carcinoma	QSG-7701	DMEM	8000	> 30	10.4
Human Umbilical Vein Endothelial Cell	HUVEC (prepared in house)	RPMI 1640	5000	18.7	3.5

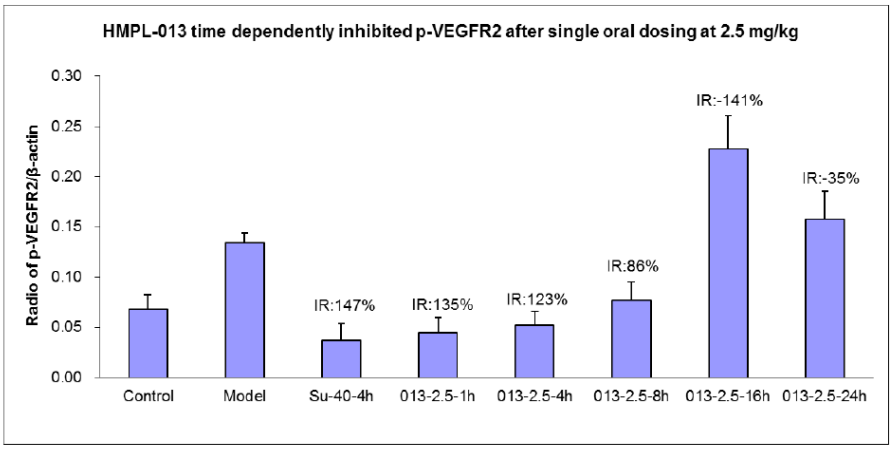
Abbreviations: DMEM = Dulbecco's Modified Eagle Medium; FBS = fetal bovine serum; IC_{50} = half maximal inhibitory concentration; IMDM = Iscove's Modified Dulbecco's Medium; L-15 = Leibovitz's L-15 medium; M-5A = McCoy's 5A medium; RPMI = Roswell Park Memorial Institute.

(Excerpted from Applicant's Submission)

Cytotoxicity of fruquintinib was evaluated in various cell lines in vitro, where cells were incubated with various concentrations of fruquintinib for 48 hours and cell viability was subsequently measured via optical density at 492 nm. Fruquintinib did not induce cytotoxicity in any of the tumor lines tested and induced slight cytotoxicity in human umbilical vein endothelial cells (HUVEC) with an IC50 of 18.7 μM.

Effect of Fruquintinib on VEGF-induced VEGFR2 Phosphorylation in Mouse Lung



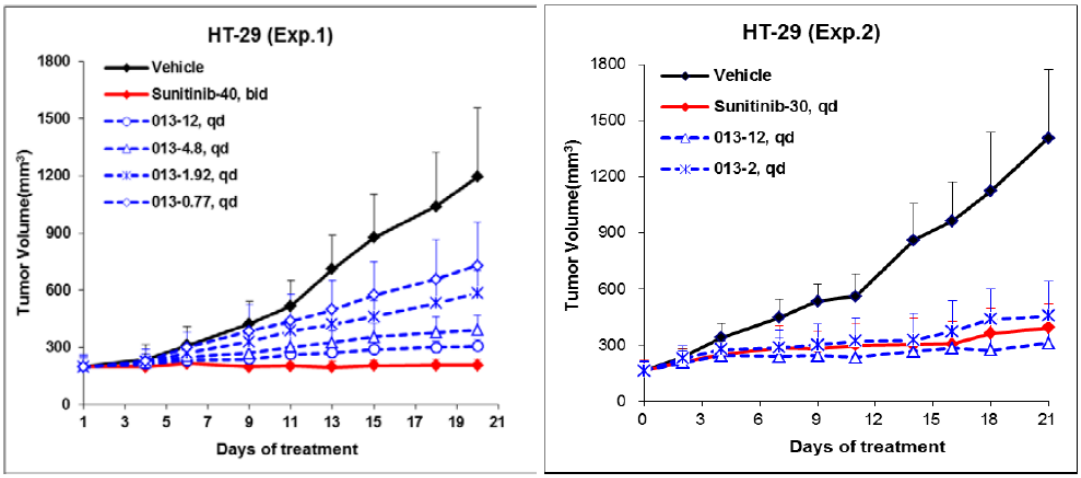


IR: inhibitory rate

(Excerpted from Applicant's Submission)

The effect of fruquintinib (HMPL-013) on in vivo VEGF-induced VEGFR2 phosphorylation was evaluated in the lung tissue of nude mice that received intravenous VEGF followed by 2.5 mg/kg fruquintinib. Animals were euthanized and lungs were harvested at various time points. The lung tissue was processed and phosphorylation status of VEGFR2 was evaluated via western blot. Fruquintinib inhibited VEGFR2 phosphorylation in mouse lung tissue up to 8 hours post-dosing.

Fruquintinib Anti-tumor Activity in an HT-29 Xenograft Tumor Model



(Excerpted from Applicant's Submission)

In vivo anti-tumor activity was evaluated in xenograft models using HT-29 colon cancer cells. Nude BALB/c mice were implanted with HT-29 tumor cells and tumors were allowed to grow for 10 to 11 days. Animals received vehicle control, sunitinib control, or 0.77, 1.92, 4.8, or 12 mg/kg fruquintinib orally once daily. Fruquintinib inhibited tumor growth in a dose-dependent manner with activity being observed starting at 0.77 mg/kg.

Secondary Pharmacology

Fruquintinib was evaluated in radioligand binding assays using ~80 different receptors, ion channels, and transporters. In these assays, fruquintinib did not induce stimulation or inhibition higher than 20% in any of the tested targets.

Safety Pharmacology

Cardiovascular
The potential for fruquintinib and metabolite M11 to inhibit the human ether-a-go-go related gene (hERG) potassium channel was evaluated in vitro in CHO cells. The IC50s of fruquintinib and metabolite M11 for inhibition of hERG current were found to be >13.08 μM and >6.05 μM, respectively.

The cardiovascular effects of fruquintinib were evaluated in vivo in a single dose study in Beagle dogs, where animals were administered 0, 0.085, 0.17, or 0.34 mg/kg fruquintinib orally (3/sex/group). Cardiovascular parameters were evaluated pre-dose and 0.5, 1, 2, 3, 4, 5, and 6 hours post-dose. Fruquintinib did not have any toxicologically significant effects on cardiovascular function following a single oral dose up to 0.34 mg/kg.

Respiratory
The respiratory effects of fruquintinib were evaluated in vivo in a single dose study in Beagle dogs, where animals were administered 0, 0.085, 0.17, or 0.34 mg/kg fruquintinib orally (3/sex/group). Respiratory parameters were evaluated pre-dose and 0.5, 1, 2, 3, 4, 5, and 6 hours post-dose. Fruquintinib did not have any toxicologically significant effects on respiratory function following a single oral dose up to 0.34 mg/kg.

Central Nervous System (CNS)
The effects of fruquintinib on the CNS were evaluated in ICR mice treated with a single dose of 0, 0.5, 5, or 10 mg/kg fruquintinib orally or 2.5 mg/kg of positive control diazepam orally (10/sex/group). Behavioral parameters were evaluated pre-dose and 0.5, 1, 2, 3, 4, 5, 6, and 24 hours post-dose. Fruquintinib did not have any toxicologically significant effects on central nervous system function following a single dose up to 10 mg/kg.

5.4 ADME/PK

Type of Study | **Major Findings**

Absorption

Pharmacokinetic Study of HMPL-013 and Its Metabolites HM5024093 (M9) and HM5025423 (M11) Following a Single PO Administration of HMPL-013 in Sprague-Dawley Rats (Study DMPKR20150008-E-01)

Single oral administration @ 20 mg/kg in SD Rats (n=3, mean ± SD)

Parameters	Unit	HMPL-013		M5024093 (M9)		HM5025423 (M11)	
		Male	Female	Male	Female	Male	Female
MRT	h	5.50±0.292	6.24±0.297	-	-	-	-
$t_{1/2}$	h	2.42±0.793	7.72±0.284	-	-	-	-
AUC_{last}	ng·h/mL	37548±11909	32059±9364	40.5±33.9	42.4±7.96	445±122	469±162
$AUC_{0-\infty}$	ng·h/mL	37620±11837	32084±9368	-	-	-	522±206
C_{max}	ng/mL	4003±784	3543±1200	8.02±7.31	7.32±1.83	32.7±11.7	29.7±10.9
T_{max}	h	3.33±1.15	2.67±1.15	5.33±2.31	5.33±2.31	8.00±0.00	8.00±0.00
AUC_M/P ratio*	-	-	-	0.0963%± 0.0576%	0.138%± 0.0400%	1.20%± 0.137%	1.45%± 0.0985%

*: AUC_M/P ratio = AUC_{last} of metabolite /AUC_{last} of parent drug in each animal ×100%.
-: No data.

(Excerpted from Applicant's Submission)

Pharmacokinetic study of HMPL-013 and its metabolites HM5024093 (M9), HM5025423 (M11) following a single oral administration of HMPL-013 in Beagle dogs (Study DMPKR20150004-E-01)

Single oral administration @ 1 mg/kg in Beagle Dogs (n=3, mean ± SD)

Parameters	Unit	HMPL-013		M5024093(M9)		HM5025423(M11)	
		Male	Female	Male	Female	Male	Female
MRT	h	42.9±9.19	28.5±5.82	-	-	-	-
$t_{1/2}$	h	26.1±5.76	17.7±3.35	-	-	-	-
AUC_{0-t}	h·ng/mL	4927±3213	7311±4000	200±173	282±233	224±215	344±392
$AUC_{0-\infty}$	h·ng/mL	5990±3842	7904±4464	-	-	-	-
C_{max}	ng/mL	148±144	337±304	4.61±4.15	9.25±9.66	5.14±4.69	7.50±7.38
T_{max}	h	10.7±11.5	10.7±11.5	17.3±26.6	10.7±11.5	32.0±27.7	40.0±13.9
AUC_ M/P ratio*	%	-	-	3.06±2.72	3.52±1.02	3.30±2.92	3.65±2.94

*: Average AUC_M/P ratio = ∑ (individual AUC0-t of metabolite / AUC0-t of parent drug with the same gender×100%)/n

(Excerpted from Applicant's Submission)

Distribution

Type of Study	Major Findings

Evaluation of the protein binding of HMPL-013 in nude mouse, rat, dog, and human plasma with rapid equilibrium dialysis method (Study DMPKR20150039-E-02)

Fruquintinib

Compounds	species	Concentration (μM)	Protein binding (%)		Recovery (%)	Equilibrium(%)
			Mean	SD		
HMPL-013	Buffer	1	-	-	-	96.9%
		3	-	-	-	100%
		10	-	-	-	93.7%
	Nude mouse	1	91.2%	0.46%	100%	-
		3	92.7%	0.22%	105%	-
		10	92.8%	0.24%	111%	-
	Rat	1	96.2%	0.07%	108%	-
		3	95.6%	0.22%	100%	-
		10	96.5%	0.12%	95.4%	-
	Dog	1	87.3%	0.83%	106%	-
		3	88.7%	0.36%	103%	-
		10	88.2%	0.76%	92.9%	-
	Human	1	95.4%	0.19%	101%	-
		3	95.3%	0.02%	108%	-
		10	95.3%	0.02%	94.9%	-
Hydrocortisone	Buffer	5	-	-	-	101%
	Human		48.8%	4.93%	115%	-
Ketoconazole	Buffer	5	-	-	-	98.0%
	Human		98.0%	0.18%	96.0%	-

"-": No data.

(Excerpted from Applicant's Submission)

Evaluation of the Protein Binding of HMPL-013-M11 in Mouse, Rat, Dog, Monkey and Human Plasma with Rapid Equilibrium Dialysis Method (Study DMPKR20210018-E-01)

Metabolite HM5025423 (M11)

Compound	Species	Conc.(μM)	Protein Binding	Recovery	Stability (6 h/0h)	Equilibrium
HMPL-013-M11	Buffer	1	-	-	104%	94.3%
	Mouse		96.8%	98.6%	96.0%	-
	Rat		96.6%	91.1%	95.4%	-
	Dog		94.8%	91.9%	95.8%	-
	Monkey		95.6%	99.3%	93.1%	-
	Human		97.7%	99.1%	96.4%	-

(Excerpted from Applicant's Submission)

Tissue Distribution of [^{14}C]HMPL-013-Derived Radioactivity Following a Single Oral Dose of [^{14}C]HMPL-013 in Rats Using Quantitative Whole Body Autoradiography (Study RPT03316)

Concentrations of Radioactivity in Tissues (>5000 ng equivalents/g) and Pigmentation Differences

Tissue	Cmax (ng equivalents [^{14}C]fruquintinib/g)
Esophagus wall	12902
Large intestine wall	11616
Small intestine wall	9417
Stomach wall (glandular)	7421
Urinary bladder wall	6592
Uveal tract	5058
Pigmented skin	888
Non-pigmented skin	491

Type of Study	Major Findings

Metabolism

Metabolism of HMPL-013 in liver microsomes: Metabolite Identification and Inter-Species Comparison (Study DMPKR20160009-E-01)

Areas of Metabolites Under the Curve in Liver Microsomes after 60 min Incubation

Metabolites	M1 (*m/z*: 380)	M2 (*m/z*: 410)	M1+M7 (*m/z*: 380)	M9 (*m/z*: 381)	M10 (*m/z*: 410)	M11 (*m/z*: 380)
DLM-60min	5.25E+06	4.09E+06	6.80E+06	NF	1.31E+07	2.93E+05
HLM-60min	4.66E+06*	2.64E+06	4.84E+06	5.38E+04	9.57E+06	1.77E+05
MKLM-60min	2.92E+07*	1.48E+07	2.96E+07	NF	4.51E+07	2.25E+06
RLM-60min	1.21E+07	1.55E+07	2.42E+07	7.27E+04	2.02E+07	6.40E+05

* May including the peak of M7, because the molecular weight of M7 was the same as M1 and not separated with M1.

NF: not found.

DLM=dog liver microsome; HLM=human liver microsome; MKLM=monkey liver microsome; RLM=rat liver microsome

(Excerpted from Applicant's Submission)

Excretion

Absorption, Metabolism and Excretion of [14C]HMPL-013 in Male and Female Sprague-Dawley Rats after a Single Oral Administration of 2 mg/100 µCi/kg of [^{14}C]HMPL-013 (Study RTC00537)

Sample	% of Radioactive Dose (Mean)	
	Males	Females
Urine	24.47	20.23
Feces	69.65	73.11
Cage Rinse/Wash	1.52	2.45
Total	95.63	95.79

TK data from general toxicology studies

13-Week Oral Gavage Toxicity and Toxicokinetic Study with HMPL-013 in Sprague Dawley Rats with a 4-Week Recovery (Study 8426159)

Fruquintinib

Analyte	Interval (Day)	Group	Dose Level (mg/kg/day)	Sex	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (h*ng/mL)
HMPL-013	1	2	0.3	Male	2.00	140	905
				Female	1.00	168	647
				MF	1.00	148	829
HMPL-013	1	3	0.6	Male	2.00	300	1170
				Female	2.00	351	2180
				MF	2.00	325	1670
HMPL-013	1	4	1.2	Male	4.00	502	2790
				Female	1.00	652	3090
				MF	1.00	526	2940
HMPL-013	44	4	2.4	Male	4.00	1840	16100
				Female	2.00	2290	16700
				MF	2.00	1830	16400
HMPL-013	91	2	0.3	Male	2.00	268	1530
				Female	1.00	401	1630
				MF	2.00	305	1640
HMPL-013	91	3	0.6	Male	2.00	497	2150
				Female	2.00	760	4360
				MF	2.00	628	3260
HMPL-013	91	4	2.4	Male	4.00	2230	18200
				Female	2.00	2050	13600
				MF	2.00	1880	15900

AUC_{0-t} = Area under the concentration-time curve from 0 to the time of the last measurable concentration; C_{max} = Maximum observed concentration; MF = Males and females combined; $t_{1/2}$ = Half-life; T_{max} = Time of maximum observed concentration.

Note: Combined male and female (MF) parameters were calculated by combining concentration data for all animals (male and female) at each dose level on each interval and using these data as a separate composite profile for toxicokinetic (TK) analysis. These parameters are not an average of the values calculated for males and females separately.

Metabolite HM5025423 (M11)

Analyte	Interval (Day)	Group	Dose Level (mg/kg/day)	Sex	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (h*ng/mL)
HM5025423	1	2	0.3	Male	8.00	0.830	a
				Female	12.0	0.703	a
				MF	12.0	0.598	a
HM5025423	1	3	0.6	Male	8.00	2.25	12.6
				Female	8.00	2.86	20.5
				MF	8.00	2.56	16.5
HM5025423	1	4	1.2	Male	12.0	3.31	28.4
				Female	8.00	4.23	40.7
				MF	12.0	3.57	34.6
HM5025423	44	4	2.4	Male	12.0	27.9	388
				Female	8.00	17.6	277
				MF	12.0	21.0	333
HM5025423	91	2	0.3	Male	8.00	2.61	35.0
				Female	8.00	2.39	18.6
				MF	8.00	2.50	30.3
HM5025423	91	3	0.6	Male	8.00	3.91	61.3
				Female	8.00	5.21	72.3
				MF	8.00	4.56	66.8
HM5025423	91	4	2.4	Male	12.0	31.6	496
				Female	8.00	15.2	247
				MF	12.0	22.3	371

AUC_{0-t} = Area under the concentration-time curve from 0 to the time of the last measurable concentration; C_{max} = Maximum observed concentration; MF = Males and females combined; $t_{1/2}$ = Half-life; T_{max} = Time of maximum observed concentration.

Note: Combined male and female (MF) parameters were calculated by combining concentration data for all animals (male and female) at each dose level on each interval and using these data as a separate composite profile for toxicokinetic (TK) analysis. These parameters are not an average of the values calculated for males and females separately.

a For Analyte HM5025423 in Group 2, the values for AUC are not reported for profiles with fewer than three quantifiable concentrations.

(Excerpted from Applicant's Submission)

13-Week Oral Capsules Toxicity and Toxicokinetic Study with HMPL-013 in Beagles Dogs with a 4-Week Recovery (Study 8449374)

Type of Study	Major Findings

Fruquintinib

Analyte	Interval (Day)	Group	Dose Level (mg/kg/day)	Sex	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (h*ng/mL)
HMPL-013	1	2	0.03	Male	8.00	13.0	209
				Female	2.00	17.4	199
				MF	2.00	15.2	204
HMPL-013	1	3	0.06	Male	8.00	23.6	390
				Female	2.00	28.9	417
				MF	2.00	26.3	403
HMPL-013	1	4	0.12	Male	1.00	69.1	992
				Female	2.00	73.2	872
				MF	1.00	71.2	932
HMPL-013	91	2	0.03	Male	4.00	18.0	312
				Female	2.00	17.1	284
				MF	3.00	17.6	298
HMPL-013	91	3	0.06	Male	4.00	35.5	594
				Female	2.00	41.5	802
				MF	3.00	38.5	698
HMPL-013	91	4	0.12	Male	2.00	129	1820
				Female	2.00	80.4	1140
				MF	2.00	105	1480

Note: MF means combined sexes.
Median values are presented for T_{max}.

Metabolite HM5025423 (M11)

Analyte	Interval (Day)	Group	Dose Level (mg/kg/day)	Sex	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (h*ng/mL)
HM5025423	1	2	0.03	Male	12.0	0.348	5.61
				Female	24.0	0.470	6.04
				MF	24.0	0.409	5.85
HM5025423	1	3	0.06	Male	12.0	0.587	9.63
				Female	24.0	1.06	13.2
				MF	24.0	0.821	11.4
HM5025423	1	4	0.12	Male	24.0	1.32	21.1
				Female	24.0	1.88	24.8
				MF	24.0	1.60	23.0
HM5025423	91	2	0.03	Male	24.0	1.16	19.1
				Female	12.0	1.06	17.5
				MF	18.0	1.11	18.3
HM5025423	91	3	0.06	Male	0.00	2.04	33.2
				Female	24.0	2.31	44.4
				MF	6.00	2.17	38.8
HM5025423	91	4	0.12	Male	4.00	5.20	98.3
				Female	12.0	4.71	77.3
				MF	4.00	4.96	87.8

Note: MF means combined sexes.
2Median values are presented for T_{max}.

(Excerpted from Applicant's Submission)

TK data from reproductive toxicology studies

Type of Study	Major Findings
Oral Gavage Embryo-Fetal Development Study, Including Toxicokinetics, with HMPL-013 in Rats (Study 8449387)	

Fruquintinib

Analyte	Interval	Group	Dose Level (mg/kg/day)	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (h*ng/mL)
HMPL-013	GD6	2	0.025	2.00	15.8	107
		3	0.100	1.00	48.0	234
		4	0.250	2.00	145	1070
HMPL-013	GD17	2	0.025	2.00	18.7	114
		3	0.100	1.00	78.4	310
		4	0.250	2.00	187	1260

Metabolite HM5025423 (M11)

Analyte	Interval	Group	Dose Level (mg/kg/day)	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (h*ng/mL)
HM5025423	GD 6	4	0.250	8.00	0.940	*
HM5025423	GD 17	4	0.250	8.00	0.883	*

* = For group 4, the values for AUC are not reported for profiles with fewer than three quantifiable concentrations.
For group 2 and group 3, no TK analysis was performed as all concentration values were BLQ.

(Excerpted from Applicant's Submission)

5.5 Toxicology

5.5.1 General Toxicology

Study title/ number: 13-Week Oral Gavage Toxicity and Toxicokinetic Study with HMPL-013 in Sprague Dawley Rats with a 4-Week Recovery (8426159)

Key Findings:

- **Mortality:** One male animal receiving 1.2/2.4 mg/kg was prematurely euthanized on Day 78 due to moribund condition
- **Hematology/Clinical Chemistry:** ↓ platelets and reticulocytes; ↑ phosphate, ALT, and triglycerides
- **Clinical signs/Histopathology:** Broken teeth associated with decreased body weight and food consumption; dose-dependent increase in physis thickness of the femur, mast cell infiltration in the mesenteric lymph node, and mineralization in the spleen.

GLP compliance: Yes; 21 CFR Part 58

Methods

Dose and frequency of dosing: 0, 0.3, 0.6, or 1.2 mg/kg daily; 1.2 mg/kg dose increased to 2.4 mg/kg on Day 44 due to lack of toxicities

Route of administration: Oral

Formulation/Vehicle: (b) (4) in DI water

Species/Strain:	SD rats
Number/Sex/Group:	15/sex/group
Age:	7.4 to 8.4 weeks old
Satellite groups/ unique design:	Control TK: 3/sex/group Low, Mid, High TK: 6/sex/group
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Mortality	Additional information on the one animal receiving 1.2/2.4 mg/kg that was prematurely euthanized on Day 78: • Clinical findings in this animal included hunched posture, thinness, red nasal discharge, broken teeth, and discolored skin. A significant decrease in body weight was also observed between Days 57 and 78, which may be due to the broken teeth. • Hematology findings included a decrease in platelet and reticulocyte levels. • Histopathology findings included hemorrhage and necrosis of the adrenal gland, decreased bone marrow cellularity, degeneration and necrosis of the Brunner's gland of duodenum associated with severe neutrophilic inflammation, and increased thickness of the physis in the femur.
Clinical Signs	Clinical signs in the surviving animals included broken teeth in male and female animals starting at 0.6 mg/kg that increased in frequency and severity with dose, which potentially contributed to a decrease in food consumption and weight loss.
Body Weights	Significant decreases in body weights (males: -15%; females: -8%) associated with decreased food consumption (males: -20%; females: -20%) were observed in 1.2/2.4 mg/kg dosed male animals starting at Day 43 and in 1.2/2.4 mg/kg dosed female animals starting at Day 78.
Ophthalmoscopy	Unremarkable
Hematology	

Terminal Sacrifice (% change compared to controls on Day 92):

Test	Male			Female		
	Low	Mid	High	Low	Mid	High
Platelets	-	-	-19%	-	-	-
Reticulocytes	-	-	-23%	-	-	-23%

Recovery:
All hematology findings were reversible following the recovery period.

Clinical Chemistry	

Terminal Sacrifice (% change compared to controls on Day 92):

Test	Male			Female		
	0.3 mg/kg	0.6 mg/kg	1.2/2.4 mg/kg	0.3 mg/kg	0.6 mg/kg	1.2/2.4 mg/kg
Alanine Aminotransferase	-	-	62%	-	-	75%
Phosphate	14%	12%	18%	-	-	-
Triglycerides	-	-	18%	-	-	23%

Recovery:
All findings excluding the increase in phosphate in male animals and the increase in ALT in female animals receiving 1.2/2.4 mg/kg were reversible following the recovery period.

Urinalysis	Unremarkable
Gross Pathology	Unremarkable
Organ Weights	Unremarkable

Histopathology
Adequate battery: Yes

Terminal Sacrifice (excluding findings in 1.2/2.4 mg/kg early mortality):

Finding	Finding Modifier	Severity	Male				Female			
			Control	0.3 mg/kg	0.6 mg/kg	1.2/2.4 mg/kg	Control	0.3 mg/kg	0.6 mg/kg	1.2/2.4 mg/kg
TOOTH		**# Animals Examined**	**10**	**10**	**10**	**9**	**10**	**10**	**9**	**10**
CELLULARITY, INCREASED	osteoblast/ osteoclast; alveolar bone	1 OF 5			1				1	
		2 OF 5				9				1
		3 OF 5								8
		4 OF 5								1
		Total			1	9			1	10
DEGENERATION/ NECROSIS	incisor layers	1 OF 5		1	1				3	
		2 OF 5		2	2					
		3 OF 5			3				2	1
		4 OF 5				9				4
		5 OF 5								5
		Total		3	6	9			5	10
FRACTURE					3	9			1	8
		Total			3	9			1	8
INFLAMMATION	mixed cell; periodontium	1 OF 5			1	1			1	2
		2 OF 5				3				3
		3 OF 5				4				4
		4 OF 5								1
		Total			1	8			1	10
NECROSIS/ INFLAMMATION	pulp	1 OF 5		1	1				1	
		2 OF 5				1				2
		3 OF 5			3	2				5
		4 OF 5				6				1
		5 OF 5								2
		Total		1	4	9			1	10
BONE, FEMUR		**# Animals Examined**	**10**	**10**	**10**	**9**	**10**	**10**	**10**	**10**
PHYSIS THICKNESS, INCREASED		1 OF 5				2				4
		2 OF 5				2				1
		3 OF 5				3				1
		4 OF 5				1				
		Total				8				6
LIVER		**# Animals Examined**	**10**	**10**	**10**	**9**	**10**	**10**	**10**	**10**
HYPERPLASIA	bile duct	1 OF 5	1	1	2	2				
		2 OF 5	1			2				
		Total	2	1	2	4				
LYMPH NODE, MESENTERIC		**# Animals Examined**	**10**	**10**	**10**	**9**	**10**	**10**	**10**	**10**
INFILTRATE	sinuses; mast cells	1 OF 5		2		3	1	1	2	
		2 OF 5	3		1	2			2	1
		3 OF 5				3				5
		Total	3	2	1	8	1	1	4	6
SPLEEN		**# Animals Examined**	**10**	**0**	**0**	**9**	**10**	**10**	**10**	**10**
MINERALIZATION		1 OF 5							1	4
		2 OF 5							1	3
		3 OF 5								2
		Total							2	9
BONE MARROW, FEMUR		**# Animals Examined**	**10**	**10**	**10**	**9**	**10**	**10**	**10**	**10**
CELLULARITY, DECREASED		1 OF 5				5				4
		2 OF 5				1				2
		Total				6				6

Severity ratings: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked; 5 = severe

Recovery:
All histopathology findings excluding tooth findings were reversible or trending towards recovery following the recovery period.

-: indicates reduction in parameters compared to control.

Study title/ number: 13-Week Oral Capsules Toxicity and Toxicokinetic Study with HMPL-013 in Beagles Dogs with a 4-Week Recovery (8449374)

Key Findings:

- No mortality at any dose
- **Hematology/Clinical Chemistry:** ↑ platelets and fibrinogen, ↓ neutrophils; ↑ globulin and triglycerides, ↓ albumin/globulin ratio driven by increase in globulin
- **Clinical signs/Histopathology:** Excessive salivation with occasional red discharge, abnormally brown teeth, discoloration and ulceration of oral mucosa, red discolored feces; dose-dependent increase in physis thickness and decrease in bone marrow cellularity of the femur, dose-dependent vacuolation of the cortex of the adrenal gland

GLP compliance: Yes; 21 CFR Part 58

Methods

Dose and frequency of dosing:	0, 0.03, 0.06, or 0.12 mg/kg daily
Route of administration:	Oral
Formulation/Vehicle:	(b) (4) (w/w) corn starch, (b) (4) (w/w) microcrystalline cellulose, (b) (4) talc (w/w), 1.92% (w/w) control article
Species/Strain:	Beagle dogs
Number/Sex/Group:	5/sex/group
Age:	7.5 to 8.7 months old
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Mortality	No mortalities were observed.
Clinical Signs	0.12 mg/kg: Excessive salivation and red discharge; abnormally brown teeth; oral mucosa ulceration 0.06 and 0.12 mg/kg: Red discolored feces; discolored oral mucosa
Body Weights	Decreases in body weights (males: -11%; females: -8%) associated with decreased food consumption (males: -61%; females: -40%) were observed in 0.12 mg/kg males and females starting at Day 18.
Ophthalmoscopy	Unremarkable
ECG	Unremarkable

Hematology

Terminal Sacrifice (% change compared to controls on Day 88):

Test	Male			Female		
	0.03 mg/kg	0.06 mg/kg	0.12 mg/kg	0.03 mg/kg	0.06 mg/kg	0.12 mg/kg
Fibrinogen	35%	47%	213%	-	63%	91%
Platelets	-	15%	48%	-	-	-
Neutrophils	-	-	-21%	-	-	-28%

Recovery:
All hematology findings were reversible or trending towards recovery following the recovery period.

Clinical Chemistry

Terminal Sacrifice (% change compared to controls on Day 88):

Test	Male			Female		
	0.03 mg/kg	0.06 mg/kg	0.12 mg/kg	0.03 mg/kg	0.06 mg/kg	0.12 mg/kg
Albumin/Globulin	-17%	-13%	-39%	-	-10%	-24%
Globulin	15%	14%	39%	-	11%	22%
Triglycerides	-	-	148%	-	-	-

Recovery:
All clinical chemistry findings were reversible or trending towards recovery following the recovery period.

Urinalysis — Unremarkable

Gross Pathology — Unremarkable

Organ Weights — Unremarkable

Histopathology
Adequate battery: Yes

Terminal Sacrifice (Day 88):

Finding	Finding Modifier	Severity	Male				Female			
			Control	0.03 mg/kg	0.06 mg/kg	0.12 mg/kg	Control	0.03 mg/kg	0.06 mg/kg	0.12 mg/kg
BONE, FEMUR		**# Animals Examined**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
PHYSIS THICKNESS, INCREASED		1 OF 5		1	1					1
		2 OF 5		1						1
		3 OF 5				3				
		Total		2	1	3				2
BONE MARROW, FEMUR		**# Animals Examined**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
CELLULARITY, DECREASED		1 OF 5				1				
		3 OF 5								1
		4 OF 5				1				
		Total				2				1
EPIDIDYMIS		**# Animals Examined**	**3**	**3**	**3**	**3**	**0**	**0**	**0**	**0**
ASPERMIA		4 OF 5				1				
		Total				1				
ADRENAL GLAND (Cortex)		**# Animals Examined**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
VACUOLATION	increased; zona glomerulosa	1 OF 5		2	2		1	1		
		2 OF 5			1	2		2	2	
	increased; zona fasciculata; increased; zona glomerulosa	3 OF 5		1	1	1			1	3
		Total		3	3	3	1	3	3	3
THYMUS		**# Animals Examined**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
CELLULARITY, DECREASED	lymphocytes	1 OF 5	1							
		3 OF 5				2				
		Total	1			2				

Severity ratings: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked; 5 = severe

Recovery:
All histopathology findings were reversible or trending toward recovery following the recovery period.

-: indicates reduction in parameters compared to control.

5.5.2 Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)
Study title/ number: HMPL-013: Bacterial Reverse Mutation Assay (8456880)
Key Study Findings:

- Fruquintinib did not increase the number of revertant colonies in all tester strains with or without S9 metabolic activation; therefore, fruquintinib was negative for mutagenicity in the reverse mutation assay.

GLP compliance: Yes; OECD
Test system: *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA102; tested at concentrations up to 5000 µg/plate; +/- S9 activation
Study is valid: Yes

In Vitro Assays in Mammalian Cells
Study title/ number: HMPL-013: In Vitro Chinese Hamster Ovary Chromosome Aberration Assay (8456884)
Key Study Findings:

- Fruquintinib was negative for clastogenicity in the in vitro chromosomal aberration assay

GLP compliance: Yes; OECD
Test system: Chinese hamster ovary (CHO) cells; +/- S9 activation; incubated with up to 50 µg/mL fruquintinib for 3 hours with or without S9 activation and up to 25 µg/mL fruquintinib for 20 hours without S9 activation;
Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)
Study title/ number: HMPL-013: Rat Micronucleus and Alkaline Comet Assay (8456891)
Key Study Findings:

- Fruquintinib did not induce an increase in micronucleated polychromatic erythrocytes in the bone marrow and did not induce DNA strand breaks in the liver; therefore, fruquintinib was negative for in micronucleus induction and in vivo clastogenecity.

GLP compliance: Yes; OECD
Test system: Sprague-Dawley rats; dose range finding study performed in male and females, definitive assay performed solely in males; animals administered 0, 500, 1000, or 2000 mg/kg/day for 3 days (3 total administrations); bone marrow and liver samples taken after 48 hours.
Study is valid: Yes

5.5.3 Carcinogenicity

Not conducted per ICH S9.

5.5.4 Reproductive and Developmental Toxicology

Embryo-Fetal Development
Study title/ number: Oral Gavage Embryo-Fetal Development Study, Including Toxicokinetics, with HMPL-013 in Rats (8449387)
Key Study Findings

- At 0.25 mg/kg (0.2 times the recommended clinical dose of 5 mg based on BSA), a trending increase in early resorption was observed as well as an increase in post implantation loss and a reduction in live fetuses
- At doses ≥ 0.1 mg/kg (0.5 times the recommended clinical dose of 5 mg based on BSA), external, vascular, and skeletal abnormalities were observed in offspring
- Fruquintinib was positive for embryo lethality and teratogenicity

GLP compliance:	Yes; 21 CFR Part 58

Methods

Dose and frequency of dosing:	0, 0.025, 0.1, or 0.25 mg/kg daily starting on Day 6 post-mating (GD 6) through Day 17 post-mating (GD 17)
Route of administration:	Oral
Formulation/Vehicle:	(b) (4) (w/v) in DI water
Species/Strain:	Sprague-Dawley rats
Number/Sex/Group:	22/females/group
Satellite groups:	Control TK: 3/females/group; Treated TK: 6/females/group
Study design:	Time-mated females were shipped prior to GD 4 and treated starting GD 6 through GD 17 with necropsy/cesarean section performed on GD 21
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	No early mortalities were observed.
Clinical Signs	Dose-dependent decreased activity, head bobbing, ataxia, and irregular respiration was observed immediately after dosing starting at 0.1 mg/kg.
Body Weights	Unremarkable
Necropsy findings Cesarean Section Data	**LD:** Unremarkable **MD:** Unremarkable **HD:** A trending increase in early resorption was observed as well as an increase in post implantation loss and a statistically significant reduction in live fetuses.
Necropsy findings Offspring [malformations, variations, etc.]	**LD:** Unremarkable **MD:** Edema (65 fetuses), protruding tongue (4 fetuses); vascular abnormalities (absent aortic arch and innominate artery, malpositioned/retroesophageal subclavian artery, variation of left side umbilical cord); skeletal abnormalities (unilateral/bipartite ossification of lumbar centrum and thoracic centrum) **HD:** Edema (108 fetuses), cranial meningocele (28 fetuses), bent tail (4 fetuses), short tail (17 fetuses); vascular abnormalities (absent/malpositioned aortic arch, absent ductus arteriosus, malpositioned/retroesophageal subclavian artery, absent innominate artery, fluid-filled thoracic cavity); skeletal abnormalities (malformation of lumbar hemi-vertebrae, unossified forelimb metacarpals and phalanx; misaligned/unossified caudal vertebrae, supernumerary lumbar vertebra, unilateral/bipartite ossification of lumbar centrum, unilateral/bipartite/non-ossification of thoracic centrum)

LD: low dose; MD: mid dose; HD: high dose

5.5.5 Other Toxicology Studies

Study title/ number: A Phototoxicity Study of HMPL-013 via Oral Gavage in Guinea Pigs (19186PT02)

Key Study Findings:

- When treated with fruquintinib, skin reactions did not occur in non-irradiated or irradiated guinea pigs.
- Fruquintinib was not considered phototoxic.

GLP compliance: Yes; 21 CFR Part 58
Test system: Hartley guinea pigs; animals administered 0, 5, 25, or 100 mg/kg fruquintinib orally as a single dose; observations were made at 1, 24, 48, and 72 hours after UV exposure
Study is valid: Yes

X _____ X _____
Primary Reviewer Team Leader

6 Clinical Pharmacology

6.1 Executive Summary

Fruquintinib is a kinase inhibitor of vascular endothelial growth factor receptors (VEGFR)-1, -2, and -3. Fruquintinib is indicated for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if *RAS* wild-type, an anti-EGFR therapy. The Applicant proposed a fruquintinib dosage of 5 mg taken orally with or without food once daily for the first 21 days for each 28-day cycle. This dosing schedule is referred as 3/1 (3 weeks on/1 week off) in this review.

The clinical pharmacology key review questions focused on dosage recommendations for the general population, dosage recommendations for patients with hepatic or renal impairment, and dosage recommendations for patients receiving strong and moderate CYP3A4 inhibitors or inducers with fruquintinib (a substrate of CYP3A4).

The dosage for fruquintinib was selected based on PK and safety information obtained from a dose escalation trial and a randomized dose-ranging trial. In the dose escalation trial, the maximum tolerated dose was determined to be 4 mg for QD continuous dosing schedule or 6 mg for QD 3/1. The 4 mg QD continuous and 5 mg QD 3/1 dosing regimens were evaluated in a trial in patients with mCRC. The 5 mg QD 3/1 showed a more favorable safety profile, was selected as the RP2D, and used in the randomized Studies FRESCO (conducted in China) and FRESCO-2.

No dosage modifications are recommended for patients with renal impairment as renal excretion is not a major excretion pathway of fruquintinib. No clinically significant differences in the pharmacokinetics of fruquintinib were observed in patients with mild hepatic impairment compared to patients with normal hepatic function; thus, no dosage modifications are recommended for these patients. Fruquintinib has not been sufficiently studied in patients with moderate or severe hepatic impairment. There are no adequate pharmacokinetics and safety data to provide dosage recommendation for patients with moderate hepatic impairment. Fruquintinib is not recommended for use in patients with severe hepatic impairment due to hepatotoxicity.

Clinical drug-drug interaction studies were conducted to support instructions for concomitant use. Concomitant use of fruquintinib with strong or moderate inducers of CYP3A4 should be avoided as concomitant use decreases AUC and Cmax of fruquintinib. No dose adjustment is required for fruquintinib when used concomitantly with CYP3A inhibitors as no clinically significant differences in AUC and Cmax of fruquintinib were observed when used concomitantly with a strong CYP3A inhibitor.

6.1.1 Recommendations

The Clinical Pharmacology review team has reviewed the information contained in NDA 217564 and recommends approval. The key review issues with specific recommendations and/or comments are summarized in Table 1 below.

Table 1. Summary of key review issues and recommendations for NDA 217564

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The primary evidence of efficacy and safety is supported by the randomized Phase 3 Study 2019-013-GLOB1 (FRESCO-2) and Study 2013-013-00CH1 (FRESCO) trials.
General dosing instructions	The proposed fruquintinib dosage is 5 mg taken orally with or without food once daily for the first 21 days followed by 7 days off treatment for each 28-day cycle.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• Not recommended for use in patients with severe hepatic impairment. • No dosage adjustment is recommended for patients with mild hepatic impairment. • No dose adjustment is recommended for patients with renal impairment. • No dose adjustment is required based on age (18 to 82 years), sex, race (Asian, Black, and White), ethnicity (Hispanic/Latino vs. non-Hispanic/Latino), body weight (48 to 108 kg).
Drug Interactions	• Concomitant use of strong or moderate CYP3A inducers should be avoided. • No dose adjustment is required for fruquintinib when used concomitantly with CYP3A inhibitors. • No dose adjustment is required for P-glycoprotein (P-gp) substrate when used concomitantly with fruquintinib. • No dose adjustment is required for breast cancer resistance protein (BCRP) substrate when used concomitantly with fruquintinib.
Labeling	Generally acceptable. The review team has specific content and formatting changes to the proposed labeling. Labeling language was reviewed, corrected, and updated according to the guidance of clinical pharmacology section of labeling for human prescription drug and biological products - content and format (published December 2016).

Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed tablets formulation was used in Study 2019-013-GLOB1 (FRESCO-2).

6.1.2 Post Marketing Requirements and Commitments

No clinical pharmacology post-marketing requirements or commitments will be issued.

6.2 Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

Fruquintinib PK properties following a single dose and multiple doses were assessed in clinical studies. The results from in vitro studies, in vivo clinical pharmacology studies in healthy participants (mass balance, food effect and acid reducing agents drug-drug interaction (DDI), renal impairment, hepatic impairment, DDI studies with CYP3A4 modulators, P-gp substrates, or BCRP substrates), dose-finding and randomized controlled studies in patients with mCRC as well as population PK analysis conducted on pooled data were integrated to describe the ADME properties of fruquintinib in humans and assess intrinsic and extrinsic factors that may affect the PK of fruquintinib.

The outcomes of the exposure-response analyses for safety and efficacy were conducted using data from studies in healthy subjects (Studies 2020-013-00US1 and 2020-013-00US2), dose-finding studies in patients with advanced solid tumors including CRC (Studies 2009-013-00CH1 and 2015-013-00US1), and randomized controlled studies in patients with mCRC (Studies 2012-013-00CH3 and 2019-013-GLOB). The potential relationship between fruquintinib concentration and heart rate-corrected QT interval (QTc) was evaluated using a concentration-QTc analysis. In addition, a physiologically based PK (PBPK) model was developed to aid in the assessment of potential DDIs.

Summary of Clinical Pharmacokinetics:

The fruquintinib steady-state geometric mean (% coefficient of variation [CV]) maximum concentration (Cmax) is 300 ng/mL (28%) and area under the concentration-time curve for the dosing interval ($AUC_{0\text{-}24h}$) is 5880 ng·h/mL (29%) at the recommended dosage. The fruquintinib Cmax and $AUC_{0\text{-}24h}$ are dose-proportional across the dosage range of 1 to 6 mg (0.2 to 1.2 times the recommended dosage). Fruquintinib steady state is achieved after 14 days with a mean $AUC_{0\text{-}24h}$ accumulation of 4-fold.

An overview of the ADME properties, clinical PK, and DDI potential of fruquintinib is provided below.

Absorption
Median time to achieve peak plasma fruquintinib concentration (tmax) was approximately 2 hours.

Effect of Food

Administration of fruquintinib 5 mg with a high-fat meal (800 to 1000 calories, 50% fat) had no clinically significant differences in fruquintinib PK compared with administration at fasted administration. The geometric mean ratios (GMRs) of high-fat meal/fasted and 90% CIs of GMRs for Cmax and AUC are within the 80.00% to 125.00% interval. Please refer to Study 2020-013-00US1 results in Section 7.3.1.

Distribution

The mean (SD) apparent volume of distribution of fruquintinib is approximately 46 (13) L. In vitro, plasma protein binding of fruquintinib was approximately 95% and blood-to-plasma concentration ratio in human blood was 0.46 to 0.60.

Elimination

The fruquintinib arithmetic mean (SD) elimination half-life is approximately 42 (11) hours and the apparent clearance is 14.8 (4.4) mL/min.

Metabolism

Metabolism is the main route of elimination of fruquintinib. Fruquintinib is primarily eliminated by CYP450 and non-CYP450 (i.e., sulfation and glucuronidation) metabolism. CYP3A and to a lesser extent CYP2C8, CYP2C9, and CYP2C19 are the CYP450 enzymes involved in fruquintinib metabolism. Following single oral administration of radiolabeled fruquintinib 5 mg, approximately 72.5% of the plasma radioactivity was fruquintinib, and 17.3% was attributed to the major circulating metabolite M11 (N-demethylation). At steady-state after multiple QD dose, the mean M11-to-fruquintinib ratio was approximately 30% for C_{max} and $AUC_{0\text{-}24h}$. M11 is 10-fold less potent against VEGFR-2 compared to fruquintinib. M11 is not considered as an active metabolite.

Excretion

Following oral administration of a 5 mg radiolabeled fruquintinib dose, approximately 60% of the dose was recovered in urine (0.5% unchanged) and 30% of the dose was recovered in feces (5% unchanged).

Specific Populations

No clinically significant differences in the pharmacokinetics of fruquintinib were observed based on age (18 to 82 years), sex, race (Asian [N = 140], Black [N = 29], and

White [N = 359]), ethnicity (Hispanic/Latino [N = 28] vs. non-Hispanic/Latino [N = 505]), body weight (48 to 108 kg), mild [N = 177) to moderate (N = 42) renal impairment (CrCL 30 to 89 mL/min), or mild (N = 133) hepatic impairment (total bilirubin less than or equal to ULN with AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN with any AST).

The effect of moderate to severe hepatic impairment (total bilirubin greater than 1.5 times ULN and any AST) on fruquintinib pharmacokinetics is unknown.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Strong CYP3A inducers: Fruquintinib Cmax decreased by 12% and AUC_{inf} by 65% following concomitant use with rifampin (strong CYP3A inducer).

Moderate CYP3A inducers: Fruquintinib Cmax is predicted to decrease by 4% and AUC_{inf} by 32% following concomitant use with efavirenz (moderate CYP3A inducer).

Other Drugs: No clinically significant differences in fruquintinib AUC_{inf} (increased by 10%) and Cmax (decreased by 6%) were observed when used concomitantly with itraconazole (strong CYP3A inhibitor). The GMRs (90% CI) of fruquintinib without/with concomitantly with rabeprazole (proton pump inhibitor; gastric acid reducing agent) were 1.08 (1.01, 1.15) and 1.03 (0.94, 1.14) for AUC_{inf} and Cmax, respectively.

No clinically significant differences in the pharmacokinetics of the following drugs were observed or predicted when used concomitantly with fruquintinib: dabigatran etexilate (P-gp substrate) or rosuvastatin (BCRP substrate). See Section 7.3.2 for details.

In Vitro Studies

Cytochrome P450 Enzymes: Fruquintinib is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A, or an inducer of CYP1A2, CYP2B6, CYP3A.

Transporter Systems: Fruquintinib is not a substrate of P-glycoprotein (P-gp), organic anion transporting polypeptide(OATP)1B1 or OATP1B3. Fruquintinib is not an inhibitor of OATP1B1, OATP1B3, organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, multidrug and toxin extrusion protein (MATE)1, or MATE2-K.

Summary of Exposure-Response (E-R) Analyses

Because of the different regimens tested for fruquintinib (QD continuous and QD 3/1), the average daily AUC over the 28-day cycle (AUC_{ave}) was used for both the safety and efficacy E-R analyses. In addition, the minimum plasma concentration at steady state (Cmin,SS) was investigated in the efficacy E-R analyses, and Cmax at steady state

(Cmax,SS) was investigated for the safety E-R analysis. A regimen covariate (QD continuous and QD 3/1) was investigated along with Cmin,SS and Cmax,SS to account for the different regimens tested.

Exposure-efficacy relationship:
The exposure-efficacy analyses included data from mCRC patients in Studies 2019-013-GLOB1 (FRESCO-2), 2012-013-00CH3, and 2015-013-00US1. Exposure-efficacy analyses for OS and PFS are not clinically meaningful.

Exposure-safety relationship:

The efficacy-safety analyses included data from patients in Studies 2009-013-00CH1, 2012-013-00CH3, 2015-013-00US1, and FRESCO-2. Higher model-predicted fruquintinib CmaxSS was associated with a higher probability of Grade ≥3 dermatological toxicity. Compared to the QD 3/1 regimen, the QD continuous regimen was associated with a higher probability of Grade ≥ 3 dermatological toxicity, any-grade hemorrhage, and Grade ≥3 proteinuria.

A mean increase in QTc interval > 20 milliseconds (ms) was not observed at the approved recommended dosage.

6.2.2 General Dosing and Therapeutic Individualization

General Dosing

The Applicant-proposed dosage of fruquintinib is 5 mg QD 3/1 taken orally with or without food. The primary evidence of efficacy and safety was obtained from two randomized studies, FRESCO-2 and FRESCO, at the proposed dosage with or without food. The proposed dosage was tolerable in both studies and achieved a clinically meaningful and statistically significant improvement in OS. Higher steady-state Cmax of fruquintinib was associated with a higher probability of Grade 3 and above dermatological toxicity in an exposure-safety analysis. There was no obvious relationship between exposure and OS in an exposure-safety analysis with the limitation that all the patients in the analysis were treated with fruquintinib 5 mg QD 3/1 as starting dosage. Additional details of exposure-response analyses are discussed in Section 20.4

The proposed dosage appears to be an appropriate dosage based on the overall benefit risk profile in the proposed indication, but there are limited data to characterize efficacy and safety profiles at doses below 5 mg QD 3/1.

Therapeutic Individualization

No clinically significant differences in the pharmacokinetics of fruquintinib were observed based on age (18 to 82 years), sex, race (Asian [N = 140], Black [N = 29], and White [N = 359]), ethnicity (Hispanic/Latino [N = 28] vs. non-Hispanic/Latino [N = 505]),

body weight (48 to 108 kg), or mild (N = 133) hepatic impairment (total bilirubin less than or equal to ULN with AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN with any AST). The effect of moderate to severe hepatic impairment (total bilirubin greater than 1.5 times ULN and any AST) on fruquintinib pharmacokinetics is unknown. Refer to Section 20.4 for more details.

The renal excretion of fruquintinib is minimal with 0.5% unchanged fruquintinib recovered in urine in the mass balance Study 2015-013-00CH2. The negligible role of renal function on fruquintinib elimination is also supported by the interim PK data from the dedicate renal impairment Study 2021-013-00US2 and population PK analysis.

Outstanding Issues

There are no outstanding clinical pharmacology issues.

6.3 Comprehensive Clinical Pharmacology Review

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

Table 2. General Pharmacology and Pharmacokinetic Highlights

Pharmacology	
Mechanism of Action	Fruquintinib is a kinase inhibitor of vascular endothelial growth factor receptors (VEGFR)-1, -2, and -3.
Active Moieties	Fruquintinib
QT Prolongation	A concentration-QT analysis (N = 205; N = 137 in the fruquintinib arm and 68 in the placebo arm) suggested that fruquintinib does not cause a mean increase in QTc interval > 20 milliseconds at the proposed dosage.
General Information	
Bioanalysis	See Section 20.4.
Healthy Volunteers vs. Patients	Fruquintinib and M11 exposures were similar between healthy and patient populations. A comparison of fruquintinib PK between healthy participants and participants with cancer was conducted for fruquintinib Cmax and AUC following a single dose of fruquintinib 5 mg. PK data from Studies 2020-013-00US1 and 2020-013-00US2 were used to characterize fruquintinib PK in the healthy population. PK data from Study 2015-013-00US1 (5-mg dose level only) were used to characterize fruquintinib PK in participants with cancer. Fruquintinib and M11 AUC were similar between healthy participants and participants with cancer. In a PopPK analysis, the effects of health status (ie, healthy versus patients) on the exposures of fruquintinib and M11 were negligible.

Drug exposure at steady state following the therapeutic dosing regimen	The geometric mean (%CV) C_{max} was 300 ng/mL (28%) and AUC_{0-24h} was 5880 ng·h/mL (29%) following fruquintinib 5 mg once daily for 21 days with 7 days off, of each 28-day cycle in patients with advanced solid tumors.		
Minimal effective dose or exposure	The minimal effective dose or exposure has not been identified. For the 3/1 QD schedule, 5 mg is the lowest starting dose studied in patients with mCRC. For the continuous QD schedule, 4 mg is the lowest starting dose studied in patients with mCRC.		
Maximal tolerated dose or exposure	The maximal tolerated dose (MTD) was 4 mg QD on a continuous schedule or 6 mg QD on 3/1 schedule.		
Dose Proportionality	Fruquintinib exposure (AUC and Cmax) increased with increasing oral dose in a dose-proportional manner after a single dose and after repeated dosing (1 to 6 mg QD). Additional details are provided in section 19.4.2.		
Accumulation	The mean accumulation ratio at steady state is approximately 4.		
Variability	%CV for Cmax steady state = 28% %CV AUCtau steady state = 29%		
Absorption			
Oral absolute bioavailability	Absolute oral bioavailability has not been determined		
Formulation development	Only one formulation was developed and used throughout the clinical development program of fruquintinib. The formulation and manufacturing process of the 1-mg and 5-mg capsules used in the pivotal clinical efficacy studies FRESCO-2 and FRESCO are the same as that of the proposed commercial 1-mg and 5-mg capsules.		
Bioequivalent (BE) or relative Bioavailability (BA) GMR (90% CI)	Study 2013-013-00CH2: No clinically relevant difference between 5 mg fruquintinib capsules from two manufacturing sites (N=22)		
	Cmax	AUC_{last}	AUC_{inf}
	106.54 (100.15, 113.33)	101.14 (97.91, 104.47)	100.84 (97.58, 104.22)
Bioequivalent (BE) or relative Bioavailability (BA) GMR (90% CI)	Study 2014-013-00CH5: No clinically relevant difference between 5 mg fruquintinib capsules from two manufacturing sites (N=24)		
	Cmax	AUC_{last}	AUC_{inf}
	93.06 (86.23, 100.43)	96.68 (93.12, 100.37)	96.81 (93.24, 100.52)
Oral T_{max}	Median t_{max} was approximately 2 hours.		
Food effect Fed/ Fasted GMR (90% CI)	Study 2020-013-00US1: No clinically relevant difference between administration with a high-fat meal (800 to 1000 calories, 50% fat) and administration under overnight fasted conditions.		

	Cmax (N =14 Fed; N = 13 fasted)	AUC_{last} (N=13)	AUC_{inf} (N=14 fed, N = 13 fasted)
	0.97 (0.86, 1.10)	1.06 (0.99, 1.13)	1.04 (0.97, 1.11)
Acid reducing agents (ARAs) (with/without) GMR (90% CI)	Study 2020-013-00US1: Fruquintinib absorption was not affected by the concomitant administration of rabeprazole (N=12)		
	Cmax	AUC_{last}	AUC_{inf}
	1.03 (0.94, 1.14)	1.07 (1.01, 1.14)	1.08 (1.01, 1.15)
Substrate transporter systems [in vitro]	Not a substrate of P-gp, OATP1B1 or OATP1B3.		
Distribution			
Volume of Distribution	The mean (SD) apparent volume of distribution is 46 (13) L.		
Plasma Protein Binding	Plasma protein binding of fruquintinib is approximately 95%.		
Blood to Plasma Ratio	Blood-to-plasma concentration ratio in human blood was 0.46 to 0.60.		
Elimination			
Half-life	The half-life of fruquintinib is approximately 42 hours		
Clearance	The mean (SD) apparent clearance of fruquintinib is 14.8 (4.4) mL/min.		
Metabolism			
Primary metabolic pathway(s)	In vitro, fruquintinib is primarily metabolized by CYP3A4 with contributions by CYP2C8, CYP2C9, CYP2C19; and non-CYP enzyme systems. In vivo, fruquintinib PK was impacted by the coadministration of a strong CYP3A4 inducer (rifampin) but not by a strong CYP3A inhibitor (itraconazole) The major circulating metabolite was M11 (N-demethylation product). At steady-state, the mean M11-to-fruquintinib ratio was approximately 30% for Cmax and AUC_{0-24h}. In vitro, M11 was 10-fold less potent against VEGFR-2 compared to fruquintinib. Therefore, M11 is not considered as an active metabolite.		
Inhibitor/Inducer	Fruquintinib is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A, or an inducer of CYP1A2, CYP2B6, CYP3A at therapeutically relevant concentrations. In vivo, fruquintinib is not an inhibitor of P-gp and BCRP after a single dose. In vivo single dose data, with the support from PBPK modeling approaches, suggested that fruquintinib is not an inhibitor of P-gp and BCRP at the proposed recommended dosage. Fruquintinib is not an inhibitor of OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, or MATE2-K at therapeutically relevant concentrations.		
Excretion			

Primary excretion pathways	In Study 2015-013-00CH2, following a single oral administration of a radiolabeled dose of fruquintinib 5 mg, approximately 60% of the dose was recovered in urine and 30% in feces. Unchanged [^{14}C]fruquintinib accounting for 0.50% of the administered dose in urine and 5.34% of the administered dose in feces.

6.3.2 Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The primary evidence of efficacy was obtained from two randomized Phase 3 Study FRESCO-2 and FRESCO. See Section 7 for more details.

FRESCO-2 was a global study in patients with mCRC who had been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if *RAS* wild-type, an anti-EGFR therapy. Patients were randomized (2:1) to receive fruquintinib at the proposed dosage in the treatment arm (n=461) or placebo in the control arm (n=230). The primary endpoint was OS. The fruquintinib arm achieved a clinically meaningful and statistically significant improvement in OS compared to the control arm; the median OS was 7.4 months (95% CI: 6.7, 8.2) in the fruquintinib arm compared to 4.8 months (95% CI: 4.0, 5.8) in placebo arm and the hazard ratio for OS was 0.66 (95% CI: 0.55, 0.80). Details regarding FRESCO-2 are provided in Section 8.

Evidence of efficacy was also observed in the FRESCO study, conducted in China. Patients with mCRC with disease progression after/on therapy with fluoropyrimidine, oxaliplatin, and irinotecan (with or without anti-VEGF and/or EGFR-targeting biologicals) and no prior treatment with TAS-102 or regorafenib were randomized 2:1 to receive fruquintinib at the proposed dosage in the treatment arm (n=278) or placebo (N=138) in the control arm. The FRESCO study demonstrated a median OS of 9.3 months (95% CI: 8.2, 10.5) for the fruquintinib arm versus 6.6 months (95% CI: 5.9, 8.1) for the placebo arm and a hazard ratio of 0.65 (95% CI: 0.51, 0.83).

Fruquintinib 5 mg QD 3/1 was also studied in Study 2015-013-00US1, which enrolled patients with mCRC, breast cancer, and other solid tumors. The study was conducted in the US to support dosage selection for FRESCO-2. In addition, similar PK were observed in the US patients and China patients.

In an exposure-safety analysis, higher steady-state Cmax of fruquintinib was associated with a higher probability of Grade ≥ 3 dermatological toxicity. No significant relationship has been identified between exposure and OS in an exposure-efficacy analysis. The exposure-efficacy analysis is limited given all the patients in the analysis were treated with the proposed dosage as starting dosage.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed dose of 5 mg QD 3/1 is effective and generally well tolerated in the proposed indication. This dosage regimen provides a favorable benefit-risk profile compared to placebo arm in Study FRESCO-2 and FRESCO.

In an exposure-safety analysis, higher steady-state Cmax of fruquintinib was associated with a higher probability of Grade 3 and above dermatological toxicity. There was no significant relationship between exposure and OS in an exposure-efficacy analysis. The exposure-efficacy relationship is limited by all the patients in the analysis were administered with the proposed dosage as starting dosage. Due to the limitation of data, efficacy and safety profiles at doses below 5 mg QD 3/1 has not been well characterized to determine if the proposed dosage is the optimal dosage. Additional details of exposure-response analyses are discussed in Section 20.4.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No clinically significant differences in the PK of fruquintinib were observed based on age (18 to 82 years), sex, race (Asian, Black, or White), or body weight (48 to 108 kg).

Renal impairment:

Renal excretion of fruquintinib is minimal (0.5% unchanged fruquintinib recovered in urine) in the mass balance Study 2015-013-00CH2. The negligible role of renal function on fruquintinib elimination is also supported by the interim PK data from the dedicated renal impairment Study 2021-013-00US2. No clinically relevant differences in fruquintinib exposures were observed in participants with moderate renal impairment (CrCL 30-59 mL/min, N = 8), or severe renal impairment (CrCL 15-29 mL/min, N=3) compared to historical data in healthy subjects (Table 3). In addition, mild to moderate renal impairment (30 to 89 mL/min) had no effect on fruquintinib clearance in PopPK analysis. Therefore, no dose adjustments are required in subjects with renal impairment.

Table 3. Summary of Statistical Comparison for Fruquintinib Exposure Parameters (Study 2021-013-00US2)

Test	Analyte	Dependent	Reference GeoLSM (N)	Test GeoLSM (N)	Ratio %	90% CI Lower	90% CI Upper	Total CV%
Moderate	Fruquintinib	AUC_{0-inf}	5548.75 (40)	6007.99 (8)	108.28	92.70	126.48	24.20
		AUC_{0-t}	5331.06 (40)	5781.06 (8)	108.44	93.47	125.81	23.20
		C_{max}	121.96 (41)	105.37 (8)	86.40	73.95	100.95	24.30
Severe	Fruquintinib	AUC_{0-inf}	5548.75 (40)	4567.10 (3)	82.31	64.99	104.24	23.80
		AUC_{0-t}	5331.06 (40)	4365.23 (3)	81.88	65.35	102.59	22.70
		C_{max}	121.96 (41)	92.05 (3)	75.48	59.79	95.28	23.50

GeoLSM=geometric least-squares mean
Source: Table 5 in Topline Pharmacokinetic Report Study 2021-013-00US2

Hepatic impairment:

In the popPK analysis, mild hepatic impairment (total bilirubin ≤ ULN with AST > ULN or total bilirubin > 1 to 1.5 x ULN with any AST) did not have a clinically meaningful effect on fruquintinib exposure. No dose adjustment is required for patients with mild hepatic impairment.

The effect of moderate or severe hepatic impairment (total bilirubin > 1.5 x ULN and any AST) on the pharmacokinetics and safety of fruquintinib has not been adequately studied. Fruquintinib is not recommended for use in patients with severe hepatic impairment due to hepatotoxicity. See Section 20 for details. To provide recommendations for dose adjustments based on hepatic impairment, FDA applied the NCI-ODWG criteria instead of Child-Pugh Score as NCI-ODWG criteria are considered more relevant and applicable to patients with mCRC. Of note, in the hepatic impairment Study 2021-013-00US1, no clinically relevant differences in fruquintinib exposures were observed in 8 participants with moderate hepatic impairment (Child-Pugh B); however, fruquintinib has not been studied in mCRC patients with liver cirrhosis/fibrosis and other characteristics that define the Child-Pugh Score and even if exposure remains similar, the potential exists for increasing the risk of complications or decompensation in mCRC patients with more severe cirrhosis (Child-Pugh B or C). In Study 2021-013-00US1, there were only one participant with moderate hepatic impairment and seven participants with mild hepatic impairment or normal hepatic function per NCI-ODWG criteria. As a result, there are not adequate pharmacokinetics and safety data to provide dose recommendation for patients with moderate hepatic impairment per NCI-ODWG criteria.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Effect of Food

In Study 2020-013-00US1, there were no clinically relevant differences in fruquintinib Cmax and AUC when fruquintinib was administered with a high-fat meal (800 to 1000 calories, 50% fat) or when administered under overnight fasted conditions (as described in Section 7.3.1). Fruquintinib can be taken without regard to food.

Coadministration with CYP3A4 Inhibitors

In Study 2020-013-00US2, coadministration of fruquintinib with itraconazole (a strong CYP3A4 inhibitor) did not result in clinically relevant differences in fruquintinib Cmax and AUC (Table 4). No dose modifications are required for CYP3A4 inhibitors.

Table 4. Comparison of Fruquintinib Exposure Following Administration of Fruquintinib Alone and With Itraconazole (Study 2020-013-00US2)

Parameter	GeoLSM				Fruquintinib + Itraconazole/ Fruquintinib LS GMR [90% CI]
	n	Fruquintinib (5 mg) + Itraconazole (200 mg)	n	Fruquintinib (5 mg)	
Fruquintinib					
AUC_{0-t} (h•ng/mL)	14	5950.20	14	5563.54	1.07 (1.01, 1.13)
AUC_{inf} (h•ng/mL)	14	6352.09	14	5780.99	1.10 (1.04, 1.16)
C_{max} (ng/mL)	14	120.12	14	128.10	0.94 (0.86, 1.03)

GeoLSM=geometric least-squares mean
Source: Table 9 in 2.7.2 Summary of Clinical Pharmacology Studies

Coadministration with CYP3A4 Inducers

Coadministration of fruquintinib with rifampin (a strong CYP3A4 inducer) decreased the fruquintinib C_{max} by 12% and AUC by 65% (Study 2020-013-00US2). The PBPK model predicted a decrease in fruquintinib AUC by approximately 32% when fruquintinib is coadministered with a moderate CYP3A4 inducer (i.e., efavirenz). Coadministration of fruquintinib with a strong or moderate CYP3A4 inducers may decrease fruquintinib activity and should be avoided. Given the decrease in fruquintinib is approximately 32% with efavirenz and the decrease is close to the bioequivalence cutoff of 20%, no dose adjustment is recommended if it is not possible to avoid concomitant use of a moderate CYP3A inducer and fruquintinib. No dose modifications are required for mild CYP3A4 inducers.

Coadministration with Acid-Reducing Agents

Coadministration of the proton pump inhibitor rabeprazole (40 mg QD) had no clinically relevant effect on the single oral dose PK profile of fruquintinib (2020-013-00US1). Therefore, no dose modifications are needed with coadministration with acid-reducing agents.

Coadministration with P-gp Substrates

Coadministration of a single 5 mg dose of fruquintinib with dabigatran etexilate (a P-gp substrate) slightly decreased dabigatran etexilate exposure by 10% for C_{max} and 9% for AUC. PBPK analysis results were consistent with the clinical findings (see PBPK review in Appendix 20.4)

Coadministration with BCRP Substrates

Coadministration of a single 5 mg dose of fruquintinib with rosuvastatin (a BCRP substrate) slightly decreased rosuvastatin exposure by 16% for C_{max} and 19% for AUC. PBPK analysis results were consistent with the clinical findings (see PBPK review in Appendix 20.4)

Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?

Yes, the to-be-marketed formulation the same as the clinical trial formulation.

X	X
Primary Reviewer	Team Leader
Wentao Fu Hezhen Wang Miyoung Yoon Javier Blanco	Jason Moore Youwei Bi Yuching Yang Jeffrey Kraft

7 Sources of Clinical Data and Review Strategy

7.1 Table of Clinical Studies

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Table 5. Listing of Clinical Trials Relevant to this NDA

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	No. of patients enrolled	Study Population
2019-013-GLOB1 (FRESCO-2)	Randomized, double-blind, placebo-controlled, multicenter study conducted globally	Fruquintinib/placebo 5 mg QD 3/1 oral	Primary: OS Secondary: PFS (Key), ORR, DCR, and DoR.	Fruquintinib: 461 Placebo: 230	Refractory mCRC
2013-013-00CH1 (FRESCO)	Randomized, double-blind, placebo-controlled, multicenter study conducted in China	Fruquintinib/placebo 5 mg QD 3/1 oral	Primary: OS Secondary: PFS, ORR, ORR, DCR, DoR, and duration of SD	Fruquintinib: 278 Placebo: 138	Patients with mCRC who have received at least 2 prior lines of chemotherapy
2012-013-00CH1	Randomized, double-blind, placebo-controlled, multicenter conducted in China	Fruquintinib/placebo 5 mg QD 3/1; oral	Primary: PFS Secondary: ORR, DCR, OS	Fruquintinib: 47 Placebo: 24	Patients with advanced CRC who had progressed with 2 or more lines of standard chemotherapy
2012-013-00CH3	Randomized, open-label, 2-center in China	Fruquintinib:4 mg QD continuous dosing group or 5 mg QD 3/1; oral	Safety, PK, and preliminary antitumor activity	Fruquintinib: 62	Patients with advanced CRC who had progressed with 2 or more lines of standard chemotherapy
2015-013-00US1	Open-label, multicenter conducted in U.S.	Fruquintinib; 3 or 5 mg QD 3 weeks on/1 week off; oral	Safety, PK, and preliminary antitumor activity	Dose Escalation (3 mg QD) cohort: 7; Dose Escalation (5 mg QD) + Cohort A: 13; Cohort B: 41; Cohort C: 40; Cohort D: 14; Cohort E: 12	Dose Escalation: patients with advanced solid tumors Expansion: patients with advanced solid tumors (Cohort A), with refractory mCRC (Cohorts B and C), and with metastatic breast cancer (Cohorts D and E).

7.2 Review Strategy

The review of efficacy and safety was primarily based on evaluation of the pivotal trial, Study 2019-013-GLOB1 (FRESCO-2), which was a muti-regional, randomized, double blind, placebo-controlled study of fruquintinib plus best supportive care (BSC) versus placebo plus BSC in patients with mCRC who had disease progression on or were intolerant to prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGFR biological therapy, if *RAS*-wild-type, an anti-EGFR therapy, and regorafenib or trifluridine/tipiracil (or both) in the refractory setting ("4th line setting").

In addition, the review of efficacy and safety was supported by Study 2013-013-00CH1 (FRESCO), which was a single-country, double-blind, placebo-controlled randomized study of fruquintinib plus best supportive care (BSC) versus placebo plus BSC in patients with mCRC who had prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; patients may have received other agents like anti-VEGF or anti-EGFR monoclonal antibodies, but use of these drugs was not mandated. In this trial, patients did not receive prior regorafenib or trifluridine/tipiracil ("3rd line setting").

The clinical review of efficacy included primary analyses using the clinical datasets to supplement and/or confirm studies results as reported in the Clinical Study Reports (CSR) for Studies FRESCO-2 and FRESCO and the Summary of Clinical Efficacy (SCE).

The safety analyses included data from a larger group of patients in the integrated safety analysis set for the metastatic colorectal cancer population (ISAS-mCRC) and the integrated safety analysis set for the expanded metastatic colorectal cancer population (ISAS-Expanded mCRC). The ISAS-mCRC population (n=1172; 781 in fruquintinib the arm and 391 in the placebo arm) included all patients from 3 randomized, placebo-controlled, double-blinded mCRC studies (FRESCO-2 excluding patients from the open-label Japanese safety lead-in; FRESCO, and 2012-013-00CH1) who received at least 1 dose of study drug (fruquintinib or placebo). The ISAS-Expanded mCRC population (n=911) included all patients with mCRC who received at least 1 dose of fruquintinib monotherapy at the dosing schedule used in FRESCO-2 and FRESCO (fruquintinib 5 mg 3/1).

The review of safety included review of the clinical study reports (CSR), SDTM and analysis datasets, line-listings, case report forms (CRFs), and patient narratives from FRESCO-2 and FRESCO. The clinical reviewers confirmed the Applicant's safety analyses, conducting analyses of primary data using the JMP software and supplementary analyses performed by the OCE safety team. Data from the 4-month Safety Update included safety data using a data cut-off date of March 31, 2023. Studies which contributed patient safety data for the 120-day safety updated were 2015-013-00US1 (Dose Escalation Cohorts + Cohorts A to C), 2015-013-00US1 (Cohorts D and

E), 2019-013-GLOB1 (FRESCO-2), and 2018-013-00CH3 Monotherapy EC Cohort. At the time of the original data submission, only 49 (5.4%) patients were still receiving treatment in the Expanded mCRC group (all patients with mCRC who had received fruquintinib). At the time of data cut-off for the 120-day update, only 7 patients (0.8%) remained on treatment. Safety data for the remaining 5.4% of patients in the Expanded mCRC group was included in the update. There was no substantial change in the incidence of any of the AEs reported previously and review of patient narratives did not identify any new safety signals.

8 Statistical and Clinical and Evaluation

8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1 Study 2019-013 - GLOB1 (FRESCO-2)

Trial Design

FRESCO-2 was a muti-regional, randomized, double-blind, placebo-controlled study of fruquintinib plus BSC versus placebo plus BSC in patients with mCRC with disease progression on or were intolerant to prior treatment with:

- fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy,
- an anti-VEGFR biological therapy,
- trifluridine/tipiracil (TAS-102) and/or regorafenib.

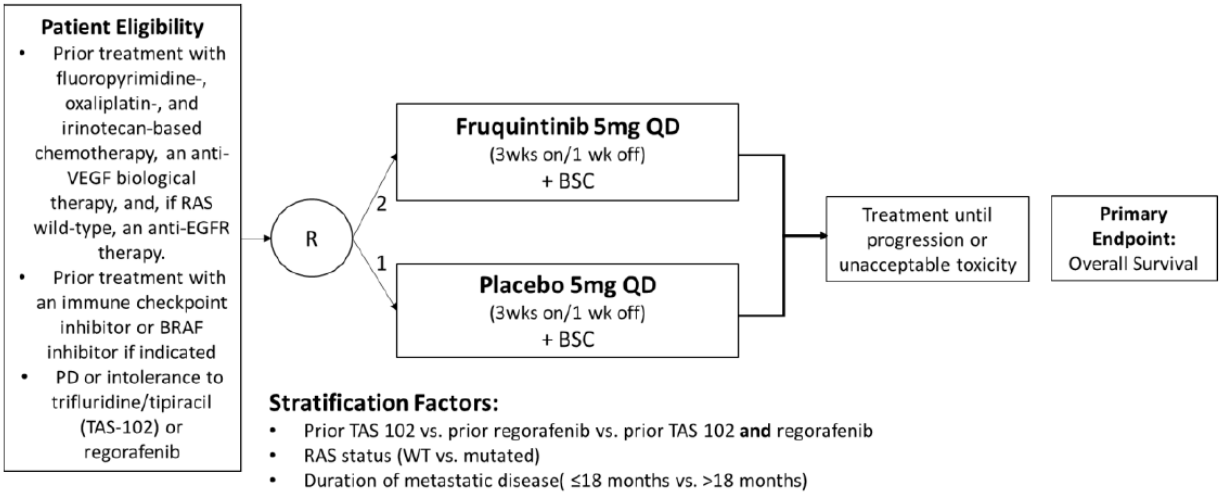
In addition, patients with

- *RAS*-wild-type tumors must have received an anti-EGFR therapy
- tumors that are microsatellite instability-high/mismatch repair deficient (MSI-H/dMMR) must have received an immune checkpoint inhibitor
- tumors that harbor *BRAF V600* mutations must have received treatment with a *BRAF* inhibitor.

Eligible patients were randomized in a 2:1 ratio to receive either fruquintinib in combination with BSC or matching placebo in combination with BSC. Randomization was stratified by:

- Prior therapy with TAS-102 vs. regorafenib vs. both TAS-102 and regorafenib
- *RAS* status (wild-type vs mutant)
- Duration of metastatic disease (≤ 18 months vs > 18 months)

Figure 1. FRESCO-2: Study Schema



Additional key eligibility criteria included age ≥ 18 years old (Japan only: ≥ 20 years), ECOG PS 0 or 1, measurable disease per RECIST 1.1, LVEF ≥ 50% by echocardiogram, body, weight ≥40kg, and normal organ function as follows: absolute neutrophil count (ANC) ≥ 1.5×10^9/L, platelet count ≥100 × 10^9/L, and hemoglobin ≥ 9.0 g/dL, serum total bilirubin ≤1.5 × the upper limit of normal (ULN), ALT or AST ≤2.5 × ULN in subjects without hepatic metastases or ≤ 5 × ULN in subjects with hepatic metastases, serum creatinine ≤1.5 × ULN or creatinine clearance ≥60 mL/min, urine dipstick or urinalysis with protein ≤2+ or 24-hour urine protein ≤1.0 g/24-h. Participants with 1+ proteinuria must have had a 24-hour urine collection to assess urine protein level.

Patients with uncontrolled hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mm Hg); history of or active gastric/duodenal ulcer or ulcerative colitis, active gastrointestinal hemorrhage, history of perforation or fistulas; history or presence of hemorrhage within 2 months prior to screening, history of a thromboembolic event within 6 months prior to screening; stroke and/or transient ischemic attack within 12 months prior to screening; clinically significant cardiovascular disease (LVEF) <50% by echocardiogram; corrected QT interval using the Fridericia method (QTcF) >480 msec; surgery or invasive procedure within 60 days prior to the first dose of study drug or unhealed surgical incision; tumor invasion of a large vascular structure or untreated brain metastases were excluded from trial participation. In addition, the study did not enroll patients with known HIV infection; patients with chronic hepatitis B virus (HBV) infection or HCV infection should have had undetectable viral load.

Fruquintinib, at a dose of 5 mg, was administered orally, once daily, 3 weeks on/1 week off of each 4 week cycle). Study drug could be administered either in the fasting state or after meals, around the same time each day. The protocol allowed for dose interruptions or dose reductions. Three dose levels for dose-modification were predefined (5 mg QD, 4 mg QD, or 3 mg QD, all in a 3 week on/1 week off schedule). The protocol included general guidelines for dose-modification as well as guidelines for dose-modification based on specific toxicities including palmar-plantar erythrodysesthesia, proteinuria, hypertension, decreased platelet count, hemorrhage, and abnormal liver function.

Patients were treated until disease progression, unacceptable toxicity, or withdrawal of consent. If patients experienced a clinical benefit, in the opinion of the investigator, then the patient may have been allowed to continue treatment pending consultation with the sponsor.

Tumor evaluation was performed every 8 weeks until there was progression of disease (PD), death, new anti-cancer treatment, or study completion, whichever came first. Figure 1 presents the schematics of the FRESCO-2 study design.

Statistical Analysis Plan

Efficacy Endpoints Definition and Analysis Methods:

Overall survival (OS): The primary endpoint of OS is defined as the time from date of randomization to death from any cause. Patients without report of death at the time of analysis were censored at the date last known alive. Patients with no post-randomization data were censored at the date of randomization.

The difference between the treatment arms with respect to OS in all-randomized population was tested using the stratified log-rank test. The total number of deaths in each arm, Kaplan-Meier estimate of median OS along with its 95% CIs is presented below. The hazard ratio (HR) between the 2 treatment groups (fruquintinib vs placebo) and the corresponding 95% CIs, was calculated from a stratified Cox proportional hazard model (i.e. accounting for stratification factors used for randomization).

Progression-free survival (PFS): The key secondary efficacy endpoint was PFS, which was defined as the time (months) from randomization until the first radiographic documentation of objective progression, as assessed by the investigator using RECIST v1.1, or death from any cause. The censoring rules, as described the table below, were considered for PFS analysis. PFS was analyzed similar to OS and will be formally tested only if OS is statistically significant.

Table 6. Censoring Rules for PFS

Situation	Date of Progression or Censoring	Outcome
PD documented from radiological assessment visits	Date of first documented disease progression	Event
Death without PD or death before first documented PD or death after one missing radiological assessment visit	Date of death	Event
No baseline nor post-baseline radiological assessments available	Date of randomization	Censored
No death nor PD by the time of data cut-off for final analysis	Date of last adequate radiological assessment	Censored
Early discontinuation (lost to follow-up or withdrawal of consent) of study without death or PD	Date of last adequate radiological assessment	Censored
New anti-tumor therapy started prior to PD	Date of last adequate radiological assessment prior to or on date of initiation of new therapy visit	Censored
Death or PD occurred after two or more consecutive missed radiological assessment visits	Date of last adequate radiological assessment prior to missed visits	Censored

ORR: ORR is defined as the proportion of subjects experiencing a best overall response

of confirmed complete response (CR) or partial response (PR), per RECIST v1.1, as determined by the investigator. ORR estimate along with its 95% CI, calculated using Clopper-Pearson exact binomial method for each treatment group. The ORR between the treatment groups were compared using the stratified Cochran-Mantel Hanzel (CMH) test. There was no alpha control pre-specified for testing ORR hypothesis and therefore the p-value from stratified CMH test for testing ORR will be considered nominal.
Comment: Investigator assessments of PFS and ORR were acceptable because the primary endpoint was overall survival (a direct measure of clinical benefit).

DoR: DoR is defined as the time from the first occurrence of PR or CR by RECIST 1.1, until the first document disease progression by investigator per RECIST 1.1, or death, whichever comes first. The censoring rules for DoR analysis were similar to PFS censoring rules. DoR is analyzed descriptively using KM methodology similar to OS.

Patient reported outcomes (PRO): Quality of life was assessed by using European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30: cancer-specific; and EQ-5D-5L questionnaires. The compliance rate at each visit and change from baseline in the scores of overall global health status and a few selected subscales was summarized by visit and each treatment group.

Sample Size Calculation:
Sample size for this study was calculated to assess for a statistically significant difference in OS. Assuming that the median OS of 5 months in the placebo arm and 6.8 months in the fruquintinib arm, a total of 480 events were needed to detect a hazard ratio of 0.73 with 90% power to detect superiority of the fruquintinib arm over placebo arm at a 1-sided significance level of 0.025. Assuming a yearly drop-out rate of 10%, approximately 687 subjects were planned to be randomized to this study over approximately 15 months.

Interim Analysis:
There were no planned interim analysis for efficacy. However, the study included one interim futility (non-binding) analysis to be performed based on 160 OS events (1/3 of total planned OS events).

Protocol Amendments

The following is a summary of major protocol amendments. The original protocol is dated February 25, 2020. Minor changes for clarification and addition of provisions for the treatment of patients upon disease progression were implemented in Amendment 1, dated April 8, 2020, before any patient was enrolled into the trial.

October 30, 2020 – Global Amendment 2 (when 11 patients had enrolled)

- Increased the number of patients from 522 to up to 687 to account for the increase in statistical power of the study from 80% to 90% and expanded the planned number of sites from 100 to 140 sites. Increased the planned duration of the study to enroll the additional patients.

- Added inclusion criterion requiring prior treatment with BRAF inhibitor for BRAF V600E mutated patients

March 16, 2021 – Global Amendment 3

- Prohibited live vaccines during the study and for 3 months after the last dose of study drugs

June 24, 2021 – Global Amendment 4

- Removed the protocol instruction to avoid proton pump inhibitor drugs and H2 blockers to align with recent data indicating that concomitant use with fruquintinib had no effect on PK parameters
- Increased the number of planned sites from 140 to 160

8.1.2 Study 2019-013- GLOB1 (FRESCO-2): Study Results

Compliance with Good Clinical Practices

The submission (Module 2, Section 2.5) contains a statement that all studies included in the clinical development of fruquintinib were undertaken in accordance with the standard operating procedures of the Applicant and/or delegated contract research organization, which comply with the principles of Good Clinical Practice for the design, conduct, and analysis of clinical studies. The protocol, amendments, administrative letters, and subject informed consent form received Institutional Review Board/Independent Ethics Committee approval prior to implementation. Compliance audits were performed as part of implementing quality assurance, and audit certificates are provided as applicable in the individual study reports.

Significant protocol violations are summarized below in the “Protocol Violations / Deviations” section. After review of the reported protocol deviations, the FDA review team determined that there was no impact on the interpretability of study results. In addition, as stated in Section 4.1, FDA inspections of the CRO and selected study sites revealed no discrepancies or regulatory violations in the conduct of FRESCO-2 and the OSI team concluded that the trial appears to have been conducted adequately.

Financial Disclosure

The submission included a Form 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) completed by the Applicant. All financial disclosure materials in Section 1.3.4 (Financial Disclosure) were reviewed refer to Section 19.2 for additional details).

One investigator from the FRESCO-2 study, (b) (6) received from HutchMed a total of (b) (6) conversion). These payments represented remuneration for consulting services provided by (b) (6) to Hutchmed. Services included participation in advisory boards and review of a variety of clinical documents for surufatinib and

fruquintinib (b) (6) site enrolled (b) (6) in the fruquintinib and placebo arms respectively), which represent (b) (6) % of the overall study population. The review team considers that any potential bias is likely mitigated by the design of the study as a double-blind study and the use of overall survival as the major efficacy outcome.

Data Quality and Integrity

The submission was of adequate quality for the clinical and statistical review. The review did not uncover any data integrity issues.

Patient Disposition

FRESCO-2 was initiated on 14 August 2020. A total of 691 patients were randomized (2:1 ratio) receive either fruquintinib + BSC (N=461) or placebo + BSC (N=230). Six hundred and eighty-six patients received fruquintinib or placebo, 458 with fruquintinib and 228 with placebo; the 5 patients who did not receive treatment had medical complications that precluded treatment.

As of the data cutoff date of 24 June 2022, there were 671 (97%) patients who discontinued study treatment; 441 (96%) in the fruquintinib arm and 230 (100%) in the placebo arm. The main reason (60.5% of patients) for treatment discontinuation was disease progression.

Patient disposition for the FRESCO-2 study is presented in Table 7.

Table 7. FRESCO-2: Patient Disposition

	Fruquintinib N=461; n (%)	**Placebo N=230; n (%)**
Randomized (ITT)	461 (100)	230 (100)
Treated	458 (99.3)	228 (99.1)
Discontinued treatment	441 (95.7)	230 (100)
Reason for treatment discontinuation		
Disease progression	271 (58.8)	147 (63.9)
Adverse event	92 (20.0)	40 (17.4)
Investigator Decision	33 (7.2)	19 (8.3)
Death	4 (0.9)	4 (1.7)
Withdrawal of consent	6 (1.3)	2 (0.9)
Patient decision with follow-up	16 (3.5)	3 (1.3)
Lost to follow-up	1 (0.2)	1 (0.4)
Other	18 (3.9)	14 (6.1)
Reason for study discontinuation		
Death	317 (68.8)	173 (75.2)
Withdrawal of consent	14 (3.0)	8 (3.5)

Lost to follow-up	3 (0.7)	0
Adverse event	1 (0.2)	0
Other	2 (0.4)	3 (1.3)

Protocol Violations/Deviations

There were 17 major protocol violations (14 in the fruquintinib arm and 3 in the placebo arm) that could potentially impact the primary objectives of the study. This included 12 inclusion/exclusion violations on the fruquintinib arm which were due to the patient not having received prior anti-VEGF biological therapy (inclusion criterion #4). Five of these 12 patients were reported to have contraindications to treatment with anti-VEGF biological therapy. In the placebo arm, failure to meet inclusion criterion #4 was reported in two patients and one patient had another malignancy diagnosed within 5 years prior to randomization (exclusion criterion 28). Two patients randomized to the fruquintinib arm received an incorrect investigational product or kit. Overall, these protocol violations do not impact the interpretability of study results. The reported protocol violations and deviations are unlikely to be a major source of bias.

Table 8. FRESCO-2: Major Protocol Violations

	Fruquintinib + BSC N=461; n (%)	**Placebo + BSC N=230; n (%)**
Major Protocol Violations	14 (3.0)	3 (1.3)
Inclusion or exclusion criteria	12 (2.6)	3 (1.3)*
Incorrect investigational product or kit	2 (0.4)	0

*According to the CSR there was one additional patient who was found to have a protocol violation after database lock. This was a patient in the placebo arm who never received prior treatment with TAS-102 or regorafenib

Other major protocol deviations occurred that would not be expected to impact the primary objective of the study, but could potentially increase the risk of the intervention. These included violations of inclusion/exclusion criteria in 168 (36%) patients on the fruquintinib arm and 80 (35%) patients on the placebo arm; and also use of a prohibited concomitant medication in 45 (10%) patients on the fruquintinib arm and 25 patients (11%) on the placebo arm. These protocol violations were relatively balanced across treatment arms and are unlikely to be a source of bias.

Demographic Characteristics

Six hundred and ninety-one patients from 124 study sites in 14 countries (Australia, Austria, Belgium, Czech Republic, Estonia, France, Germany, Great Britain, Hungary, Italy, Japan, Poland, Spain, and the U.S.) were randomized. Spain had the highest enrollment with 180 (26%) patients randomized followed by the U.S with 124 (18%), and Italy with 111 (16%). Patients were randomized in a 2:1 fashion with 461 (67%) patients randomized to fruquintinib plus BSC and 230 (33%) patients randomized to placebo plus BSC.

Patient demographics were generally balanced between the two treatment arms with the exception of the proportion of men (53% vs 61% in the fruquintinib and placebo arms, respectively) (Table 9). Median age at randomization was 64 years in both arms (range: 25 to 82 years). Black or African American and Latino/Hispanic patients were underrepresented in the trial (3% and 4.9% respectively) as compared with the proportion of Black or African American patients with mCRC in the U.S. This was a multi-regional trial with 10% of patients enrolled in the Asia Pacific region (including Japan and Australia), 72% in Europe, and 18% in North America. Table 9 summarizes the demographic characteristics of FRESCO-2.

Table 9. FRESCO-2: Demographic Characteristics

	Fruquintinib + BSC N=461; n (%)	Placebo + BSC N=230; n (%)	Total N=691; n (%)
Sex			
Female	216 (46.9)	90 (39.1)	306 (44.3)
Male	245 (53.1)	140 (60.9)	385 (55.7)
Age, years			
Median (range)	64 (25, 82)	64 (30, 86)	64 (25, 86)
Age Group			
< 65 years old	247 (53.6)	119 (51.7)	366 (53.0)
≥ 65 years old	214 (46.4)	111 (48.3)	325 (47.0)
ECOG PS			
0	196 (42.5)	102 (44.3)	298 (43.1)
1	265 (57.5)	128 (55.7)	393 (56.9)
Race			
American Indian or Alaska Native	0	1 (0.4)	1 (0.1)
Asian	43 (9.3)	18 (7.8)	61 (8.8)
Black or African American	13 (2.8)	7 (3.0)	20 (2.9)
Native Hawaiian or Other Pacific Islander	3 (0.7)	2 (0.9)	5 (0.7)
White	367 (79.6)	192 (83.5)	559 (80.9)
Multiple Races	2 (0.4)	0	2 (0.3)
Other/Not Reported/ Unknown	33 (7.2)	10 (4.3)	43 (6.2)
Ethnicity			
Hispanic or Latino	20 (4.3)	14 (6.1)	34 (4.9)
Not Hispanic or Latino	405 (87.9)	202 (87.8)	607 (87.8)
Not Reported/	36 (7.8)	14 (6.1)	50 (7.2)

Unknown			
Region and Country			
Asia Pacific	50 (10.8)	22 (9.6)	72 (10.4)
Europe	329 (71.4)	166 (72.2)	495 (71.6)
North America	82 (17.8)	42 (18.3)	124 (17.9)

Most patients (85%) in the FRESCO-2 study enrolled with multiple sites of metastatic disease and the majority of patients (72%) had metastases to the liver at baseline. In total, 170 (37%) patients on the fruquintinib arm and 85 (37%) patients on the placebo arm had *RAS* wild-type tumors. Relatively few patients had *BRAF* V600E-mutated (3%) or MSI-H/dMMR (1%) tumors (MSI status was ascertained in >90% of patients). Table 10 summarizes the disease characteristics of patients enrolled in FRESCO-2.

Table 10. FRESCO-2: Disease Characteristics

	Fruquintinib + BSC N=461; n (%)	**Placebo + BSC N=230; n (%)**	**Total N=691; n (%)**
Primary Tumor Site at Diagnosis			
Colon Left	192 (41.6)	92 (40.0)	284 (41.1)
Colon Right	97 (21.0)	53 (23.0)	150 (21.7)
Colon Right and Left	4 (0.9)	2 (0.9)	6 (0.9)
Colon Unknown	25 (5.4)	13 (5.7)	38 (5.5)
Rectum Only	143 (31.0)	70 (30.4)	213 (30.8)
Duration of Metastatic Disease			
Median (min, max)	37.9 (6.0, 192.8)	41.0 (7.1, 147.1)	39.0 (6.0, 192.8)
≤ 18 months	37 (8.0)	13 (5.7)	50 (7.2)
> 18 months	424 (92.0)	217 (94.3)	641 (92.8)
Metastatic Sites			
Multiple	400 (86.8)	189 (82.2)	589 (85.2)
Single	61 (13.2)	41 (17.8)	102 (14.8)
Liver Metastases Present			
No	122 (26.5)	74 (32.2)	196 (28.3)
Yes	339 (73.5)	156 (67.8)	495 (71.6)
***RAS* Status**			
Mutant	291 (63.1)	145 (63.0)	436 (63.1)
Wild-type	170 (36.9)	85 (37.0)	255 (36.9)
***BRAF* Mutation Status**			
V600E mutation	7 (1.5)	10 (4.3)	17 (2.5)
Other	53 (11.5)	22 (9.6)	75 (10.9)
Wild-type	401 (87.0)	198 (86.1)	599 (86.7)
Microsatellite/Mismatch Repair Status			
MSI-H and/or dMMR	5 (1.1)	4 (1.7)	9 (1.3)

MSS and/or pMMR	427 (92.6)	215 (93.5)	644 (93.2)
Unknown	29 (6.3)	11 (4.8)	40 (5.8)

Per inclusion criteria, nearly all patients (>99%) on the FRESCO-2 study had received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. Ninety-six percent of patients in either arm had previously received an anti-VEGF biologic and 98% of *RAS* wild-type patients had previously received anti-EGFR therapy. Thirty-seven percent of patients had previously received both an anti-VEGF biologic and an anti-EGFR therapy. Nearly all (99%) of those who received only anti-VEGF biologic and not anti-EGFR antibodies were *RAS*-mutated. A total of 32 patients, 21 on the fruquintinib arm and 11 on placebo had previously received an immune checkpoint inhibitor. This included 4 and 2 patients with MSI-H/dMMR tumors on the fruquintinib and placebo arms, respectively. Among 17 patients with *BRAF* V600E-mutated tumors, 4 and 5 patients on the fruquintinib and placebo arms, respectively, previously received a BRAF inhibitor. More patients had previously received treatment with TAS-102 (92%) than regorafenib (48%). Thirty-nine percent of patients had previously received both TAS-102 and regorafenib. Prior therapies are summarized in Table 11.

Table 11. FRESCO-2: Prior Therapies

	Fruquintinib + BSC N=461; n (%)	**Placebo + BSC N=230; n (%)**	**Total N=691; n (%)**
Prior Fluoropyrimidine, Oxaliplatin, and Irinotecan			
Fluoropyrimidine	460 (99.8)	230 (100)	690 (99.9)
Oxaliplatin	460 (99.8)	228 (99.1)	688 (99.6)
Irinotecan	459 (99.6)	229 (99.6)	688 (99.6)
Prior EGFR Inhibitor			
No	281 (61.0)	142 (61.7)	423 (61.2)
Yes	180 (39.0)	88 (38.3)	268 (38.8)
***RAS* Wild-Type with Prior EGFR Inhibitor (*RAS* Wild-Type: n=170, n=85)**			
No	3 (1.8)	2 (2.4)	5 (2.0)
Yes	167 (98.2)	83 (97.6)	250 (98.0)
Prior VEGF Inhibitor			
No	16 (3.5)	9 (3.9)	25 (3.6)
Yes	445 (96.5)	221 (96.1)	666 (96.4)
Prior Therapy with TAS-102 and/or Regorafenib			
Prior regorafenib	221 (47.9)	109 (47.4)	330 (47.8)
Prior TAS-102	421 (91.3)	212 (92.2)	633 (91.6)
Both TAS-102 and regorafenib	181 (39.3)	91 (39.6)	272 (39.4)

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

In FRESCO-2, the median relative dose intensity for fruquintinib and placebo were 92% and 98%, respectively, suggesting that patients were relatively compliant with the treatment schedule. No patients were discontinued from treatment due to noncompliance.

Efficacy Results – Primary Endpoint

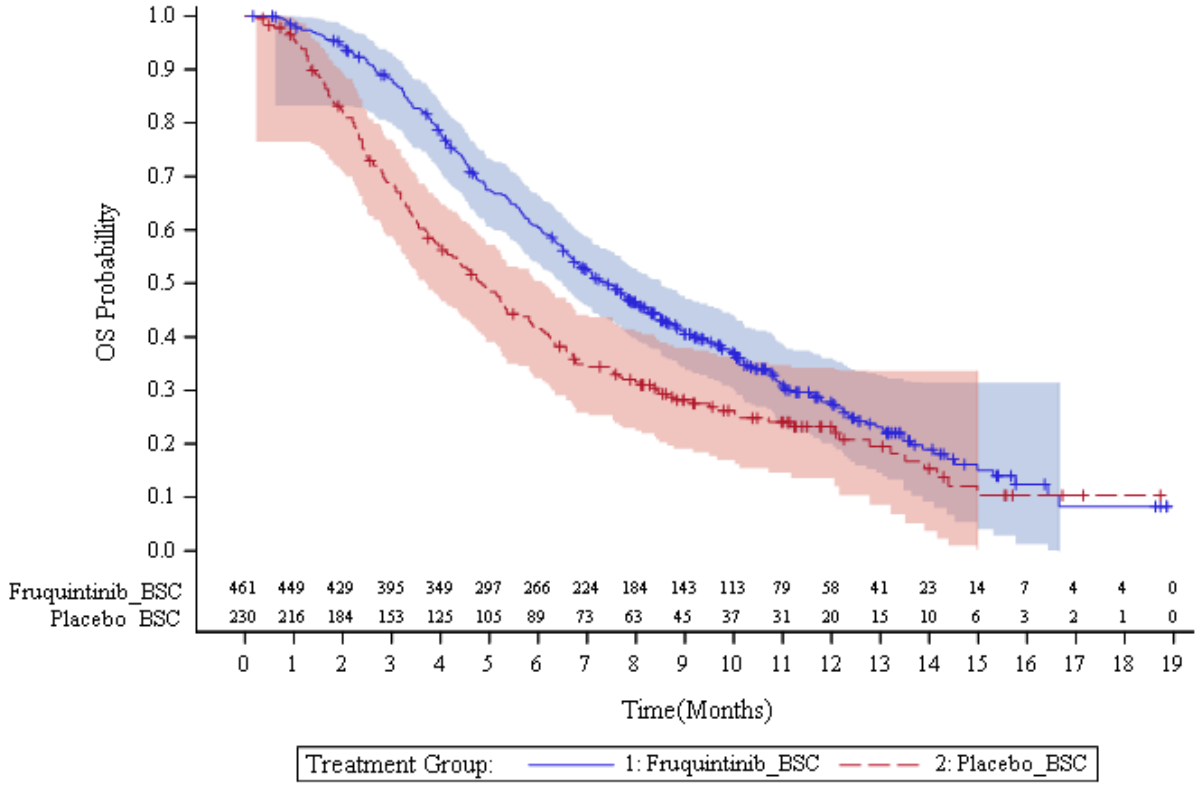
A statistically significant and clinically meaningful improvement in OS was observed in patients treated with fruquintinib + BSC compared with those treated with placebo + BSC (HR of 0.66 [95% CI: 0.55, 0.80; p-value< 0.001]). Median OS in the fruquintinib + BSC arm was 7.4 months (95% CI:6.7, 8.2) and in the placebo+BSC arm was 4.8 months (95% CI: 4.0, 5.8). Results of the OS analysis are summarized below in Table 12 and Figure 3.

Table 12. FRESCO-2: OS Analysis Results

	Fruquintinib + BSC N=461	**Placebo + BSC N=230**
Number of patients with event (%)	317 (69%)	173 (75%)
Median in months (95% CI)	7.4 (6.7, 8.2)	4.8 (4.0, 5.8)
Adjusted Hazard Ratio[a] (95% CI)	0.66 (0.55, 0.80)	
P-Value[b]	<0.001	

[a]: Adjusted for stratification factors.
[b]: 2-sided p-value computed from stratified log-rank test.

Figure 2. FRESCO-2: OS Survival Curves

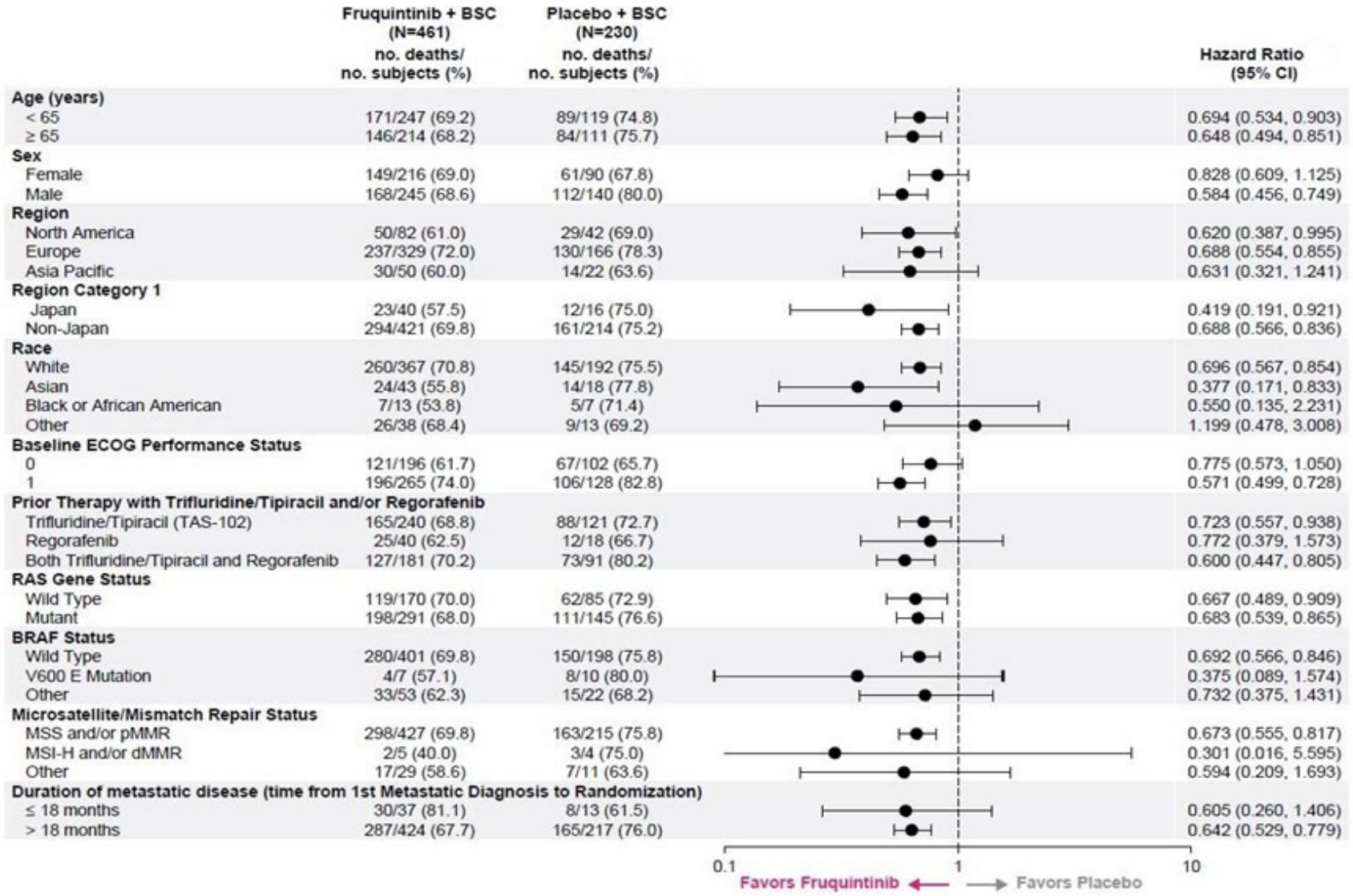


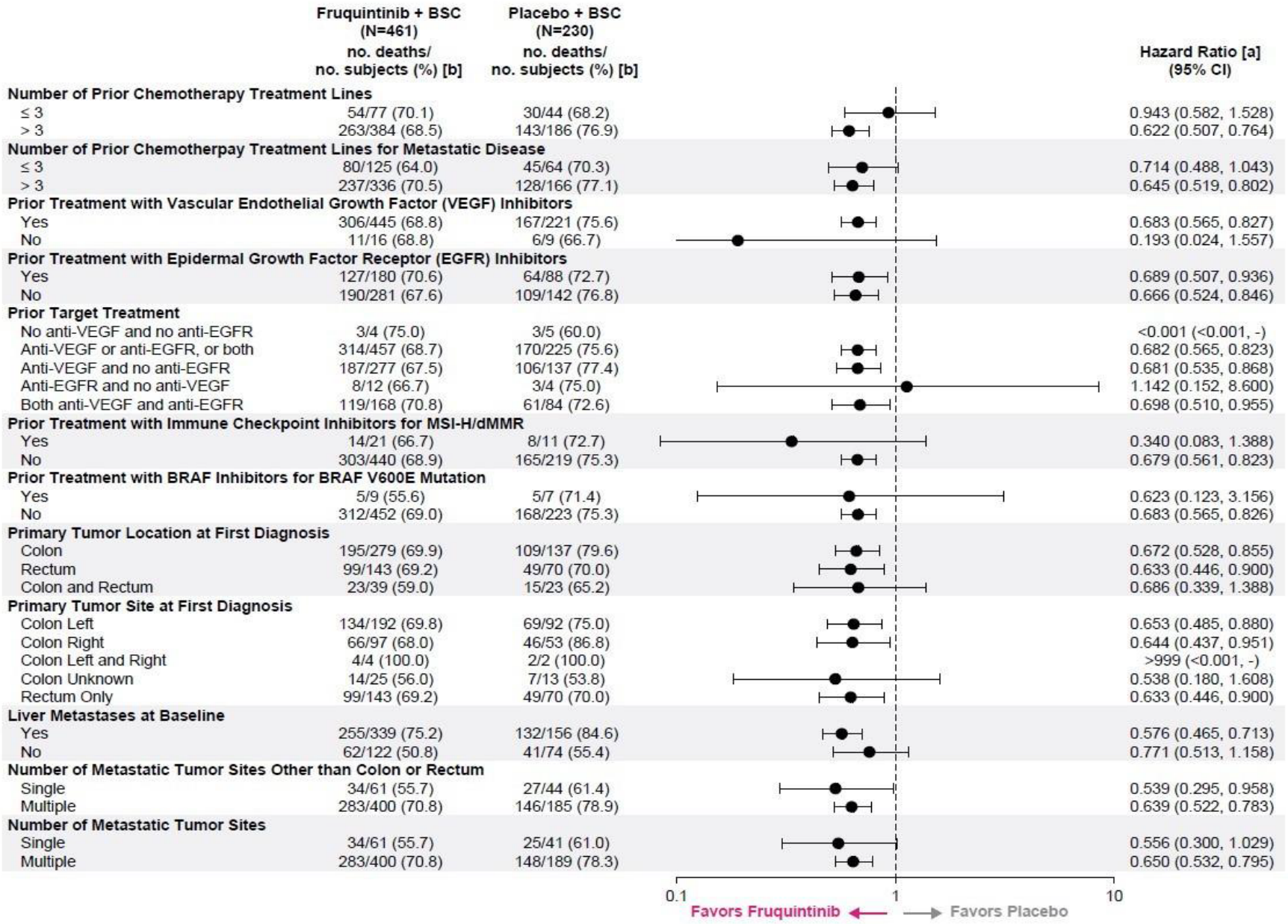
OS Exploratory Subgroup Analysis:

Exploratory subgroup analysis in a set of prespecified demographic and disease characteristics at baseline were performed. Note that the subgroup analysis results are considered exploratory because the study was not designed to formally test for OS improvement in the reported subgroups. In subgroups with adequate sample size, the OS results were consistent with the overall results.

A forest plot of the OS HR (unstratified) along with number of events in a set of preselected subgroups is presented in Figure 3.

Figure 3. FRESCO-2: OS Exploratory Subgroup Analysis




Fruquintinib + BSC (N=461)
no. deaths/ no. subjects (%) [b]
Placebo + BSC (N=230)
no. deaths/ no. subjects (%) [b]
Hazard Ratio [a] (95% CI)
Number of Prior Chemotherapy Treatment Lines
≤ 3 54/77 (70.1) 30/44 (68.2) 0.943 (0.582, 1.528)
> 3 263/384 (68.5) 143/186 (76.9) 0.622 (0.507, 0.764)
Number of Prior Chemotherpay Treatment Lines for Metastatic Disease
≤ 3 80/125 (64.0) 45/64 (70.3) 0.714 (0.488, 1.043)
> 3 237/336 (70.5) 128/166 (77.1) 0.645 (0.519, 0.802)
Prior Treatment with Vascular Endothelial Growth Factor (VEGF) Inhibitors
Yes 306/445 (68.8) 167/221 (75.6) 0.683 (0.565, 0.827)
No 11/16 (68.8) 6/9 (66.7) 0.193 (0.024, 1.557)
Prior Treatment with Epidermal Growth Factor Receptor (EGFR) Inhibitors
Yes 127/180 (70.6) 64/88 (72.7) 0.689 (0.507, 0.936)
No 190/281 (67.6) 109/142 (76.8) 0.666 (0.524, 0.846)
Prior Target Treatment
No anti-VEGF and no anti-EGFR 3/4 (75.0) 3/5 (60.0) <0.001 (<0.001, -)
Anti-VEGF or anti-EGFR, or both 314/457 (68.7) 170/225 (75.6) 0.682 (0.565, 0.823)
Anti-VEGF and no anti-EGFR 187/277 (67.5) 106/137 (77.4) 0.681 (0.535, 0.868)
Anti-EGFR and no anti-VEGF 8/12 (66.7) 3/4 (75.0) 1.142 (0.152, 8.600)
Both anti-VEGF and anti-EGFR 119/168 (70.8) 61/84 (72.6) 0.698 (0.510, 0.955)
Prior Treatment with Immune Checkpoint Inhibitors for MSI-H/dMMR
Yes 14/21 (66.7) 8/11 (72.7) 0.340 (0.083, 1.388)
No 303/440 (68.9) 165/219 (75.3) 0.679 (0.561, 0.823)
Prior Treatment with BRAF Inhibitors for BRAF V600E Mutation
Yes 5/9 (55.6) 5/7 (71.4) 0.623 (0.123, 3.156)
No 312/452 (69.0) 168/223 (75.3) 0.683 (0.565, 0.826)
Primary Tumor Location at First Diagnosis
Colon 195/279 (69.9) 109/137 (79.6) 0.672 (0.528, 0.855)
Rectum 99/143 (69.2) 49/70 (70.0) 0.633 (0.446, 0.900)
Colon and Rectum 23/39 (59.0) 15/23 (65.2) 0.686 (0.339, 1.388)
Primary Tumor Site at First Diagnosis
Colon Left 134/192 (69.8) 69/92 (75.0) 0.653 (0.485, 0.880)
Colon Right 66/97 (68.0) 46/53 (86.8) 0.644 (0.437, 0.951)
Colon Left and Right 4/4 (100.0) 2/2 (100.0) >999 (<0.001, -)
Colon Unknown 14/25 (56.0) 7/13 (53.8) 0.538 (0.180, 1.608)
Rectum Only 99/143 (69.2) 49/70 (70.0) 0.633 (0.446, 0.900)
Liver Metastases at Baseline
Yes 255/339 (75.2) 132/156 (84.6) 0.576 (0.465, 0.713)
No 62/122 (50.8) 41/74 (55.4) 0.771 (0.513, 1.158)
Number of Metastatic Tumor Sites Other than Colon or Rectum
Single 34/61 (55.7) 27/44 (61.4) 0.539 (0.295, 0.958)
Multiple 283/400 (70.8) 146/185 (78.9) 0.639 (0.522, 0.783)
Number of Metastatic Tumor Sites
Single 34/61 (55.7) 25/41 (61.0) 0.556 (0.300, 1.029)
Multiple 283/400 (70.8) 148/189 (78.3) 0.650 (0.532, 0.795)
0.1
1
10
Favors Fruquintinib
Favors Placebo

Efficacy Results – Secondary and other relevant endpoints

A statistically significant difference between patients treated with fruquintinib + BSC compared with those treated with placebo + BSC was demonstrated in the key secondary endpoint of PFS (HR of 0.32 [95% CI: 0.27, 0.39; p-value< 0.001]). Approximately 85% of the patients treated with fruquintinib + BSC either progressed or died compared to 93% in the placebo + BSC arm and the median PFS was 3.7 months (95% CI: 3.5, 3.8) and 1.8 months (95% CI:1.8, 1.9), respectively. Results of the PFS analysis are summarized below in Table 13 and Figure 4.

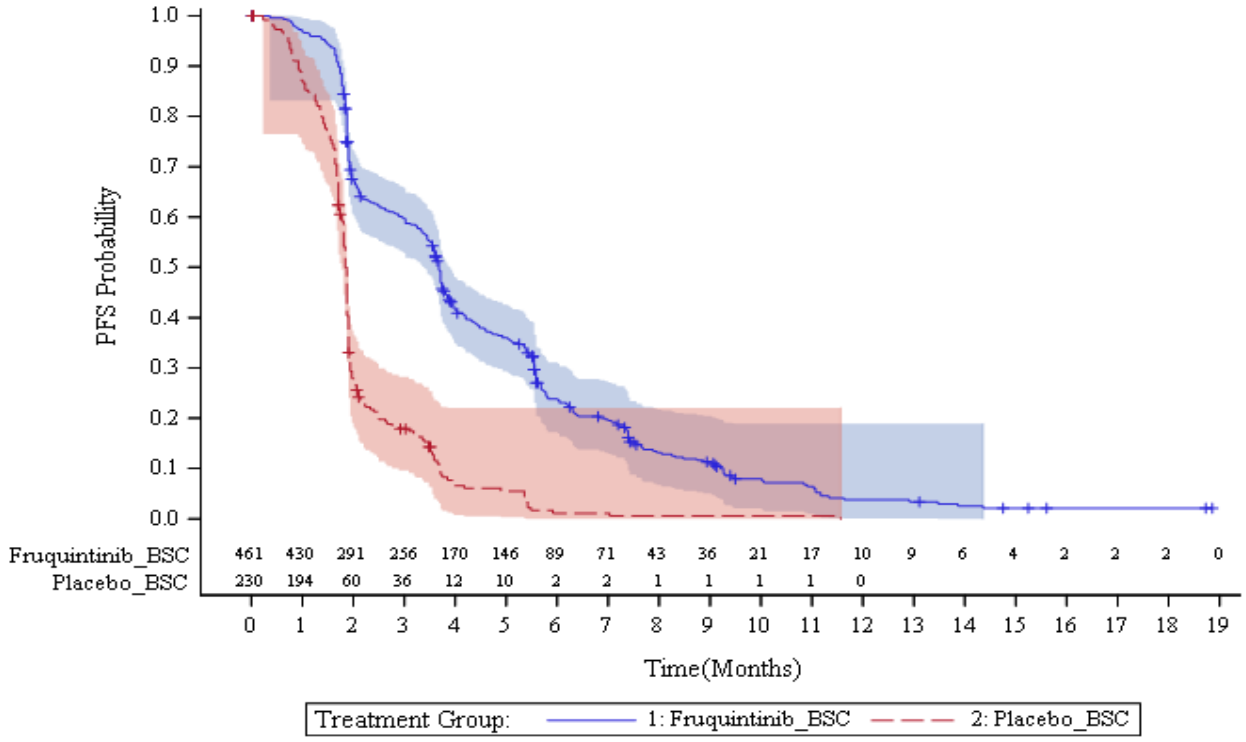
Among the 691 patients, investigator assessed confirmed ORR was 1.5% (n=7) in the fruquintinib + BSC arm and 0% in the placebo + BSC arm. All the responders had a partial response and no complete responses were observed. Of the 7 patients who had a response, 1 died, 1 had PD, and 5 had not progressed nor died as of the data cutoff date. Median DoR was 10.7 months (95% CI: 3.9, not estimable) in the fruquintinib + BSC arm and not estimable for the placebo arm.

Table 13. FRESCO-2: PFS, ORR and DoR Analysis Results

	Fruquintinib + BSC N=461	**Placebo + BSC N=230**
PFS		
Number of patients with event (%) # Patients with PD # Deaths	392 (85%) 301 (65%) 91 (20%)	213 (93%) 167 (73%) 46 (20%)
Median in months (95% CI)	3.7 (3.5, 3.8)	1.8 (1.8, 1.9)
Hazard Ratio[a] (95% CI)	0.32 (0.27, 0.39)	
P-Value[b]	<0.001	
ORR		
# Patients with response, n (%) 95% exact CI	7 (1.5%) (0.6, 3.1)	0 (0, 1.6)
DOR		
Median DoR in months (95% CI)	10.7 (3.9, Not Estimable)	Not estimable
Range	2.1+, 16.9+	-

[a]: Adjusted for stratification factors.
[b]: 2-sided p-value computed from stratified log-rank test.

Figure 4. FRESCO-2: PFS curves



Dose/Dose Response

Only one dose was investigated in the randomized, placebo controlled, clinical trials designed to assess the safety and efficacy of fruquintinib (FRESCO and FRESCO-2); therefore conclusions regarding the effectiveness of lower (or higher) doses cannot be made. Refer to the clinical pharmacology review for population-PK analyses and exposure-response analyses.

Durability of Response

Durability of response could not be adequately evaluated as only 7 (1.5%) patients on the fruquintinib arm had an objective response. No patients on the placebo arm had an objective response. The effect of fruquintinib appears to be cytostatic and therefore duration of response is not an adequate outcome to assess the benefit of fruquintinib.

Persistence of Effect

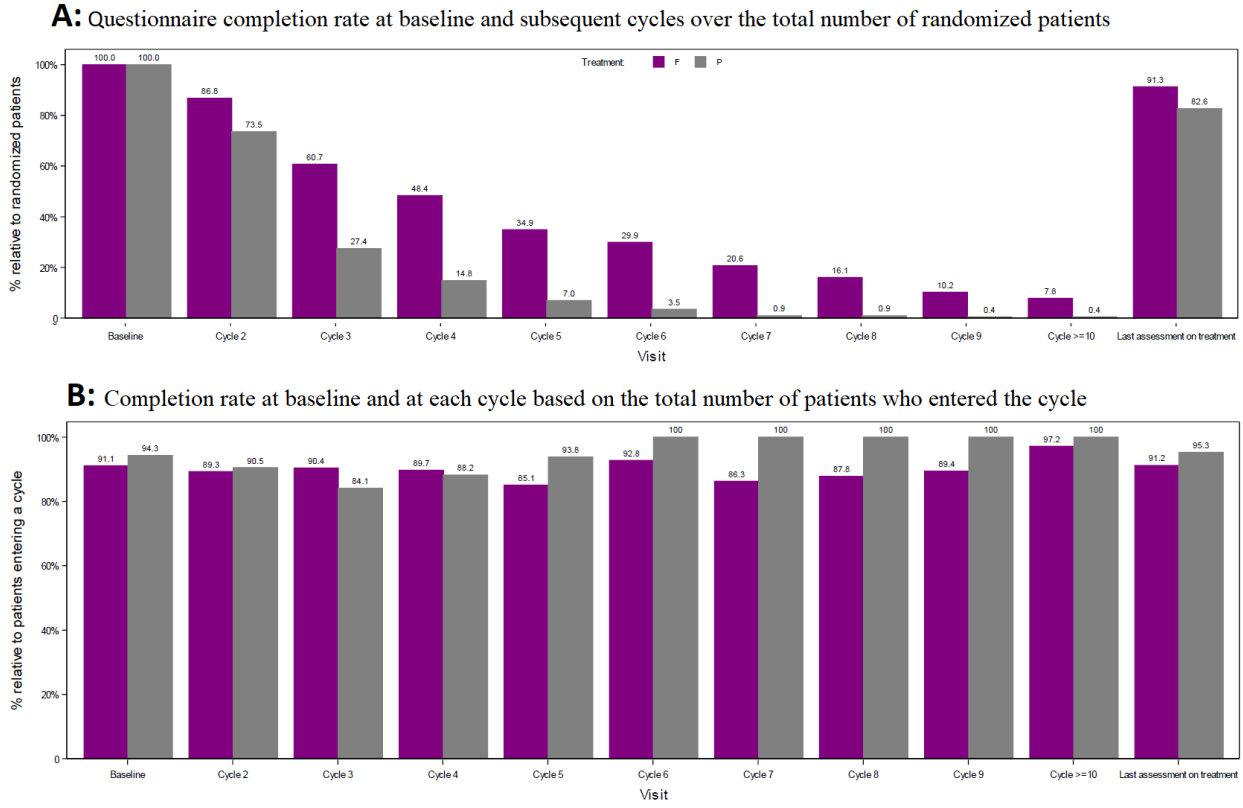
Persistence of effect is a term better suited for continuous variables (e.g., hypertension, biomarker assessments, etc.) and is not intended to characterize or compare treatment effects on selected endpoints. Treatment effect and study outcomes are described elsewhere in this section.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Quality of life (QoL) was assessed in this study using cancer-specific EORTC-QLQ-C30 and EQ-5D-5L patient reported outcomes (PRO) questionnaires. These questionnaires were completed by the patients at Screening and Day 1 of each cycle until treatment is discontinued.

Figure 5 below includes the summary of the EORTC-QLQ-C30 questionnaire completion rates both with respect to total number of randomized patients (Panel A) and total number of patients who entered the cycle and who were expected to complete the questionnaire (Panel B).

Figure 5: Summary of Completion rates for EORTC-QLQ-C30 Questionnaire



Number of Subjects who were on-treatment and were eligible to complete the PRO Questionnaire at each cycle											
F	461	400	280	223	161	138	95	74	47	≤36	
P	230	169	63	34	16	8	2	2	1	≤1	

Source: Figure-8 FRESCO-2 Clinical Study Report
F = Fruquintinib; P = Placebo.

Although the compliance rate was maintained at greater than 80% in the 2 treatment groups over time (Panel B), the number of patients who received the treatment and were eligible to complete the PRO Questionnaire at each subsequent cycle decreased due to attrition. Due to a very small proportion of patients who completed PROs after Cycle 3 in the placebo arm and lack of multiplicity adjustment for any PRO endpoints,

no PRO results are included in this review. While the results of the PRO analyses were claimed by the Applicant to be generally supportive of a favorable risk:benefit assessment, FDA considered these analyses exploratory and no comparative effect can be made.

Additional Analyses Conducted on the Individual Trial

Crossover was not allowed for patients in the placebo arm. Subsequent anticancer medication was received by 134 (29%) patients in the fruquintinib arm and 79 (34%) of patients in the placebo arm. The most common subsequent therapies in the fruquintinib arm included fluorouracil (10%), oxaliplatin (8%), regorafenib (8%), irinotecan (6%), capecitabine (6%), and bevacizumab (5%). The most common subsequent therapies in the placebo arm included fluorouracil (14%), oxaliplatin (11%), bevacizumab (8%), folinic acid (8%), regorafenib (8%), irinotecan (6%), and capecitabine (5%). There were no imbalances in subsequent therapy received that would be expected to impact the primary endpoint of overall survival.

8.1.3 Study 2013-013-00CH1 (FRESCO)

Trial Design

FRESCO was a single-country, double-blind, placebo-controlled study of fruquintinib plus BSC versus placebo plus BSC in patients with mCRC with disease progression on/after at least 2 prior lines of therapy, including a fluoropyrimidine, oxaliplatin, and irinotecan; prior treatment with VEGF and EGFR targeted biologics was allowed but not mandated. Eligible patients were randomized in a 2:1 ratio to either of the treatment arms. Randomization was stratified by:

- Prior use of VEGF inhibitors (Yes vs. No)
- *KRAS* gene status (Wild-type vs. Mutant)

Fruquintinib or placebo 5 mg daily were administered for the first 21 days of each 28-day cycle (3 weeks on/1 week off). Patients received fruquintinib or placebo until disease progression, intolerable toxicity, withdrawal of consent, or upon determination of the investigator that continued treatment was not in the patient's best interest.

Additional key eligibility criteria included age ≥ 18 years old, ECOG PS 0 or 1, LVEF ≥ 50% by echocardiogram, body, weight ≥ 40kg and normal organ function as follows: absolute neutrophil count (ANC) ≥ 1.5×10^9/L, platelet count ≥100×10^9/L, and hemoglobin ≥ 9.0 g/dL, ALT or AST ≤2.5 × ULN in subjects without hepatic metastases or ≤ 5 × ULN in subjects with hepatic metastases, serum creatinine ≤1.5 × ULN or creatinine clearance ≥50 mL/min, urine dipstick or urinalysis with protein ≤2+ or 24-hour urine protein ≤1.0 g/24-h. Participants with 1+ proteinuria must undergo a 24-hour urine collection to assess urine protein level.

Patients with uncontrolled hypertension (systolic blood pressure ≥140 mmHg and/or

diastolic blood pressure ≥90 mm Hg); history of or active gastric/duodenal ulcer or ulcerative colitis, active gastrointestinal hemorrhage, history of perforation or fistulas; history or presence of hemorrhage within 2 months prior to screening, history of a thromboembolic event within 6 months prior to screening; stroke and/or transient ischemic attack within 12 months prior to screening; clinically significant cardiovascular disease (LVEF) <50% by echocardiogram; unhealed surgical incision; and/or untreated brain metastases were excluded from trial participation.

The primary efficacy endpoint was OS. Secondary efficacy endpoints were PFS, ORR, DCR (with duration of stable disease ≥ 8 weeks), and duration of response (DoR) as assessed by investigator using RECIST 1.1. Tumor assessments were performed every 8 weeks until PD.

Statistical Analysis Plan

Refer to the FRESCO-2 Statistical Analysis Plan sub-section for definitions of all the efficacy endpoints and the corresponding analysis methods. Unlike in FRESCO-2 trials, the multiplicity adjustment for testing all the secondary endpoints was not clearly specified in this study.

Sample Size Calculation:
Sample size for this study was calculated to assess for a significant difference in OS. Assuming that the median OS of 6.3 months in the placebo arm and 9 months in the fruquintinib arm, a total of 280 events were needed to detect a hazard ratio of 0.7 with 80% power to detect superiority of the fruquintinib arm over placebo arm at a 2-sided significance level of 0.05. Approximately 400 patients were planned to be randomized to this study over approximately 15 months.

There was no planned interim analysis in this study.

Protocol Amendments

The original protocol is dated August 26, 2014. Several changes were implemented and the study started enrollment after Amendment 3, dated November 24, 2014 (the first patient was randomized on December 12, 2014). The study description above reflects the revised study.

In June 12, 2016, the protocol was revised (Amendment Version 4.0) to delete an early PFS analysis.

8.1.4 Study 2013-013-00CH1 (FRESCO): Study Results

Compliance with Good Clinical Practices

The submission (Module 2, Section 2.5) contains a statement that all studies included in the clinical development of fruquintinib were undertaken in accordance with the

standard operating procedures of the Applicant and/or delegated contract research organization, which comply with the principles of Good Clinical Practice for the design, conduct, and analysis of clinical studies.

Financial Disclosure

The submission included a Form 3454 completed by the Applicant. All financial disclosure materials in Module 1.3.4 (Financial Disclosure) were reviewed. There were no financial conflicts present. Refer to Section 20.2 for additional details.

Data Quality and Integrity

The submission was of adequate quality for the clinical and statistical review. The review did not uncover any data integrity issues.

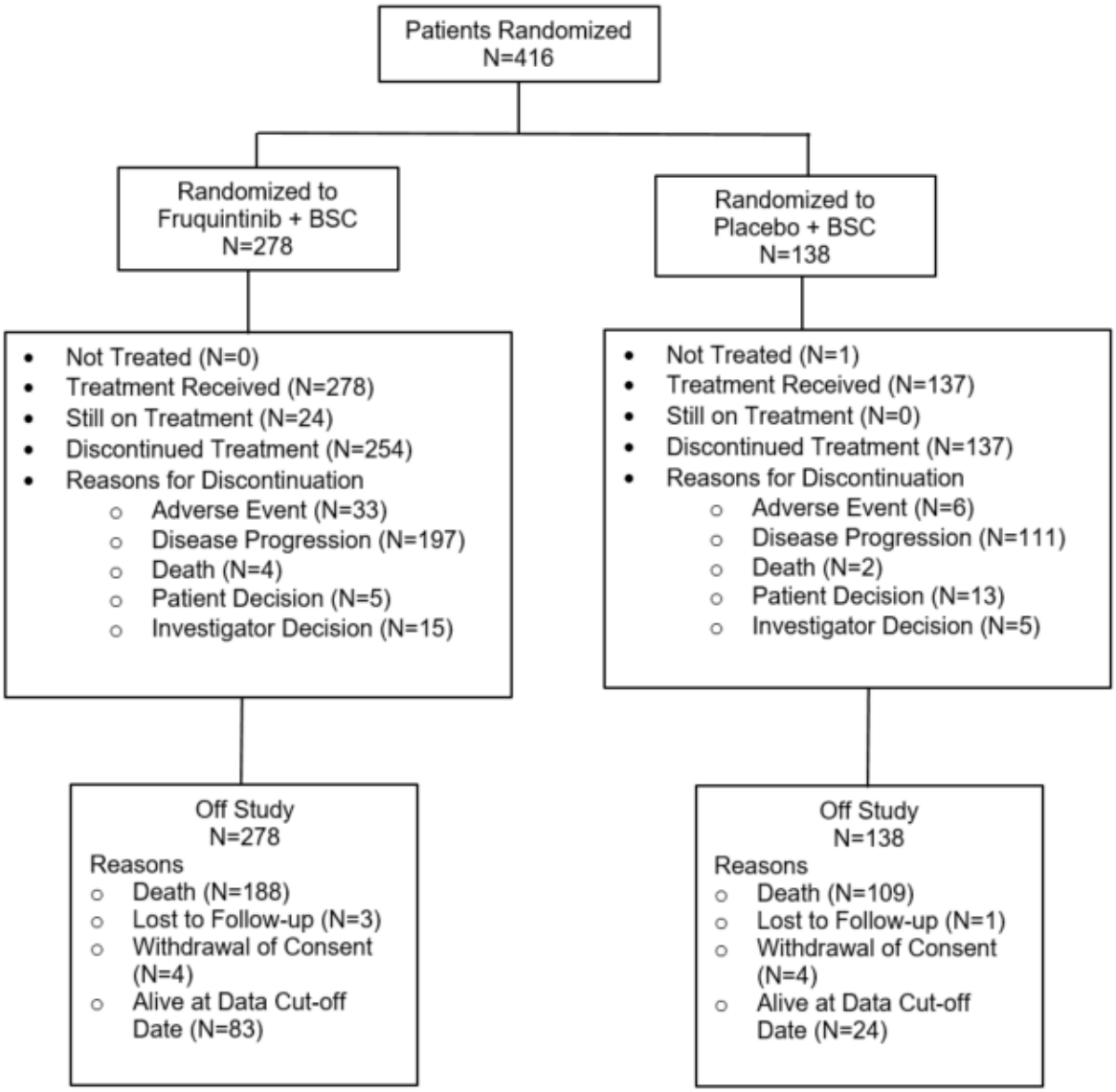
Patient Disposition

FRESCO trial was conducted in China with the first patient enrolled on December 8, 2014; the data cutoff for analysis was January 17, 2017, when a total of 288 deaths were observed.

A total of 416 patients were randomized across 28 sites in China and randomized to treatment with either fruquintinib + BSC (N=278) or placebo + BSC (N=138). All patients but 2 (one per arm) received at least one dose of study treatment. .

As of the data cutoff date, there were 391 (94%) patients who discontinued study treatment: 254 (91%) in the fruquintinib arm and 137 (100%) in the placebo arm. The main reason (74% of patients) for treatment discontinuation was disease progression.

Figure 6: FRESCO - Patient Disposition



Protocol Violations/Deviations

In the FRESCO trial, there were three major protocol violations on the fruquintinib arm: two patients not meeting the 4-week period required between prior therapy and the start of on-study treatment; and one patient who was randomized without confirmation of disease progression with prior irinotecan. On the placebo arm, one patient received prior treatment with another small molecule inhibitor of the VEGF receptor on a clinical trial (violation of inclusion criteria 4 and exclusion criteria 21) and one patient did not meet the 4-week period required between prior therapy and the start of on-study treatment. Additionally, 5 patients on the placebo arm did not complete one cycle of

treatment. Overall, it is unlikely that these protocol violations have a major impact on the interpretability of the data. The reported protocol violations and deviations are unlikely to be a source of bias.

Table 14. FRESCO: Major Protocol Violations

	Fruquintinib + BSC N=278; n (%)	Placebo + BSC N=138; n (%)
Patients excluded from per protocol population	3 (1.1)	8 (5.8)*
Inclusion or exclusion criteria	3 (1.1)	2 (1.4)
Did not complete one cycle of treatment	0	5 (3.6)
Randomized not treated	0	1 (0.7)

*One patient in the placebo arm had two major protocol violations leading to exclusion from the per protocol population.

Demographic Characteristics

Four-hundred sixteen patients from 28 centers in China were randomized. Forty-five percent of all patients were enrolled in 7 centers: sites #3001 (44 patients, 11%), #3007 (29 patients, 7%), #3012 and #3022 (25 patients, 6% each center), #3002, #3017, and #3028 (22 patients, 5% each center). These sites were university-affiliated or specialized cancer centers located in Shanghai, Harbin, Guangzhou, Nantong, Hangzhou, and Hefei. Patient demographics were well balanced between the two treatment arms (Table 15). Median age at randomization was 55 (range: 23 to 75) and 57 (range: 24 to 74) years in the fruquintinib and placebo arms, respectively, a population younger than the median age of diagnosis of mCRC in the US. There also was a male predominance in both arms. Twenty-seven percent of patients had an ECOG PS of 0 and the remaining patients had an ECOG PS of 1.

Table 15. FRESCO: Demographic Characteristics

	Fruquintinib + BSC N=278; n (%)	Placebo + BSC N=138; n (%)	Total N=416; n (%)
Sex			
Female	120 (43.2)	41 (29.7)	161 (38.7)
Male	158 (56.8)	97 (70.3)	255 (61.3)
Age, years			
Median (range)	55 (23,75)	57 (24, 74)	56 (23, 75)
Age Group			
< 65 years old	228 (82.0)	110 (79.7)	338 (81.3)
≥ 65 years old	50 (18.0)	28 (20.3)	78 (18.7)
ECOG PS			
0	77 (27.7)	37 (26.8)	114 (27.4)

1	201 (72.3)	101 (73.2)	302 (72.6)
Race			
Asian	278 (100)	138 (100)	416 (100)
Ethnicity			
Han Chinese	272 (97.8)	135 (97.8)	407 (97.8)
Non-Han Chinese	6 (2.2)	3 (2.2)	9 (2.2)

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The majority of patients in either arm had a left-sided primary tumor with a slightly greater proportion of left-sided tumors in the placebo arm. Liver metastases were present in 185 (67%) patients on the fruquintinib arm and 102 (74%) patients on the placebo arm. A total of 157 (57%) patients on the fruquintinib arm and 74 (54%) patients on the placebo arm had *KRAS* wild-type tumors.

Table 16. FRESCO: Baseline Disease Characteristics

	Fruquintinib + BSC N=278; n (%)	Placebo + BSC N=138; n (%)	Total N=416; n (%)
Primary Tumor Site at Diagnosis			
Left	214 (77.0)	115 (83.3)	329 (79.1)
Right	56 (20.1)	21 (15.2)	77 (18.5)
Right and Left	4 (1.4)	0	4 (1.0)
Unknown/Missing	4 (1.4)	2 (1.4)	6 (1.4)
Duration of Metastatic Disease			
Median (min, max)	16.0 (0.9, 79.0)	17.2 (1.9, 81.6)	16.3 (0.9, 81.6)
< 18 months	163 (58.6)	75 (54.3)	238 (57.2)
≥ 18 months	115 (41.4)	63 (45.7)	178 (42.8)
Metastatic Sites			
Multiple	265 (95.3)	134 (97.1)	399 (95.9)
Single	13 (4.7)	4 (2.9)	17 (4.1)
Liver Metastases Present			
No	93 (33.5)	36 (26.1)	129 (31.0)
Yes	185 (66.5)	102 (73.9)	287 (69.0)
***KRAS* Status**			
Mutant	121 (43.5)	64 (46.4)	185 (44.5)
Wild-type	157 (56.5)	74 (53.6)	231 (55.5)

Per protocol, to be eligible for FRESCO patients must have received prior fluorouracil, oxaliplatin, and irinotecan therapy and all of the patients included on study met this criteria. Approximately 70% of patients in either arm had previously received treatment

with anti-VEGF biological therapy and 25% of *KRAS* wild-type patients had previously received anti-EGFR therapy, which does not appear to be reflective of current standard medical practice in the U.S. where patients would usually receive an anti-VEGF therapy as a part of first- and/or second-line therapy unless contraindicated. Similarly, a relatively low proportion of *KRAS* wild-type patients had previously received anti-EGFR therapy. Table 17 summarizes prior therapies in the FRESCO study.

Table 17. FRESCO: Prior Therapies

	Fruquintinib + BSC N=278; n (%)	Placebo + BSC N=138; n (%)	Total N=416; n (%)
5FU, oxaliplatin, and irinotecan	278 (100)	138 (100)	416 (100)
Prior VEGF inhibitor	194 (69.8)	97 (70.3)	291 (70.0)
KRAS wild-type subpopulation			
N (%)	157 (56.4)	74 (53.6)	231 (55.5)
Prior EGFR Inhibitor	40 (25.4)	17 (22.9)	57 (24.6)

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The median relative dose intensity for fruquintinib and placebo were 100% and 100%, respectively, suggesting that patients were generally compliant with the treatment schedule.

Efficacy Results – Primary Endpoint

As of the data cutoff date, there were a total of 288 deaths observed in the study; 188 (67.6%) deaths in the fruquintinib arm and 108 (78.8%) deaths in the placebo arm. A statistically significant and clinically meaningful prolongation of OS was observed in patients randomized to receive fruquintinib+BSC compared to the placebo arm (OS HR: 0.65 (95% CI: 0.51, 0.83; $p < 0.001$); median OS was 9.3 months in the fruquintinib arm (95% CI: 8.2, 10.5) compared to 6.6 months in the placebo arm (95% CI: 5.9, 8.1).

Results of the OS analysis are summarized below in Table 18 and Figure 7.

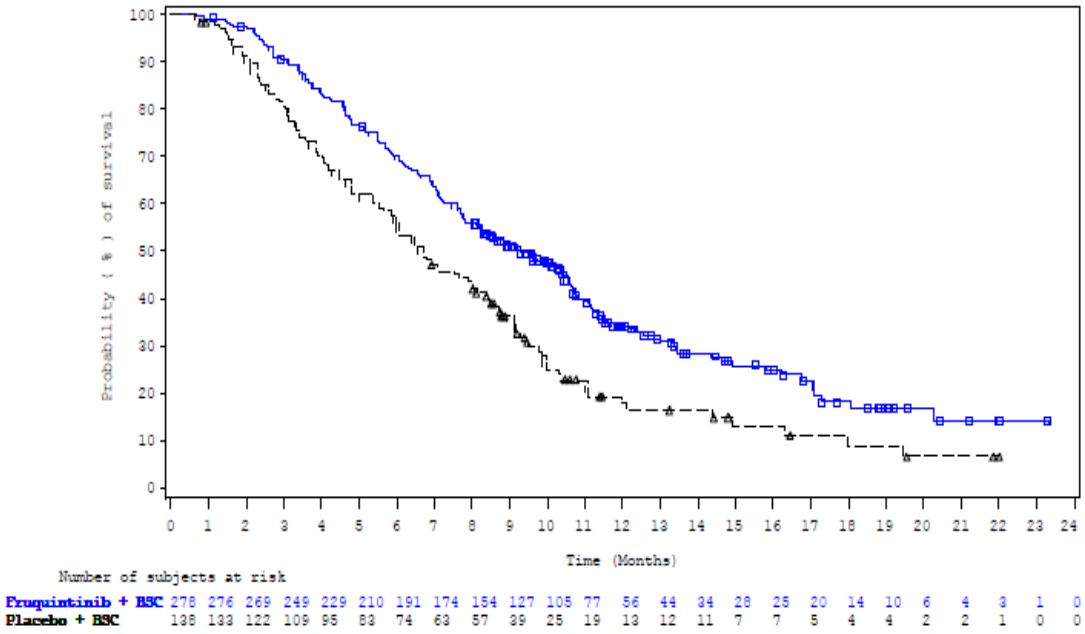
Table 18. FRESCO: OS Analysis Results

	Fruquintinib + BSC N=278	Placebo+ BSC N=138
Number of patients with event (%)	188 (68%)	109 (79%)
Median in months (95% CI)	9.3 (8.2, 10.5)	6.6 (5.9, 8.1)

Adjusted Hazard Ratio[a] (95% CI)	0.65 (0.51, 0.83)
P-Value[b]	<0.001

[a]: Adjusted for stratification factors.
[b]: 2-sided p-value computed from stratified log-rank test.

Figure 7. FRESCO: OS Survival Curves

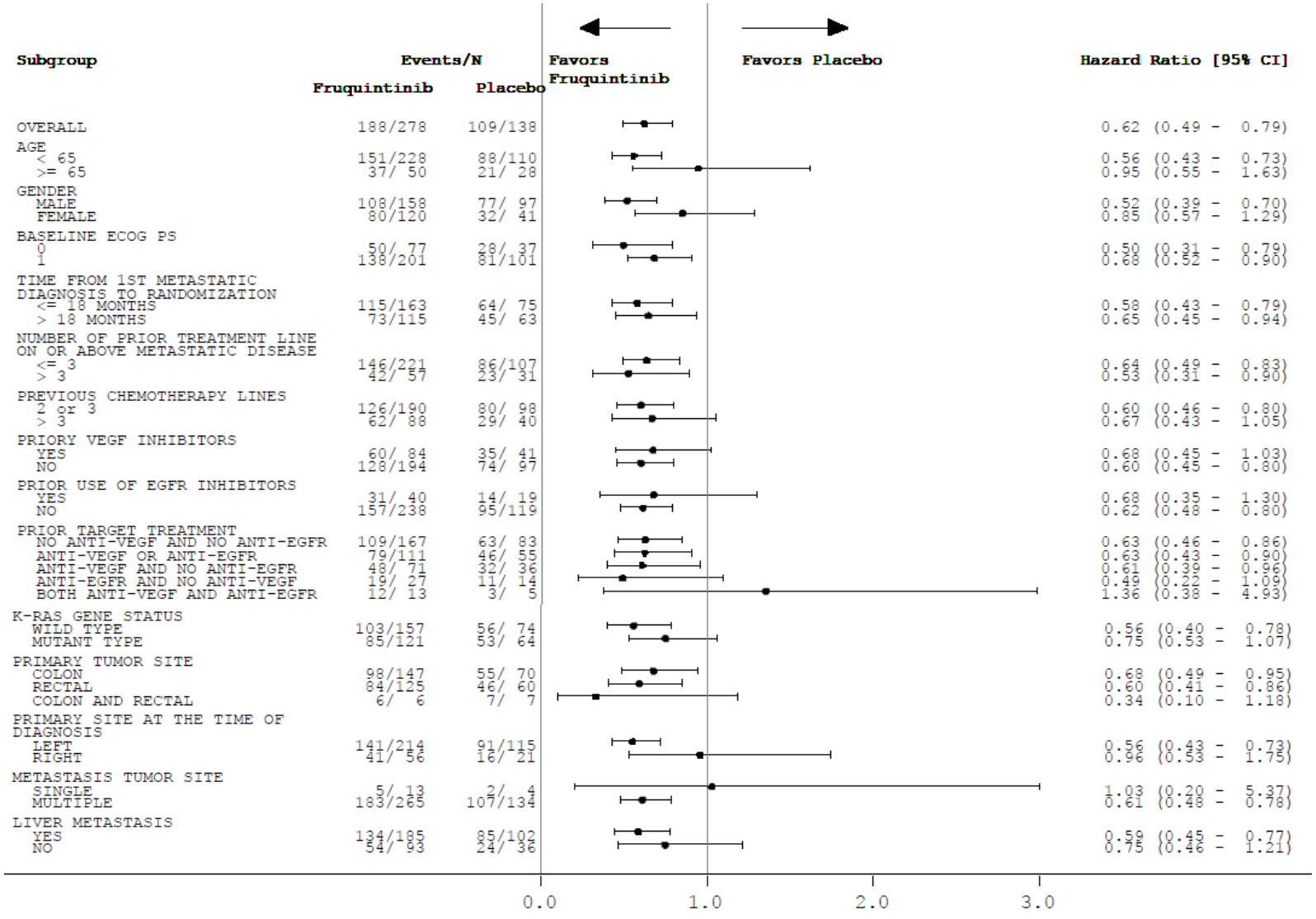


OS Exploratory Subgroup Analysis:

In subgroups with adequate sample size, the OS results (exploratory) were consistent with the overall results.

A forest plot of the OS HR (unstratified) along with number of events in a set of preselected subgroups is presented in Figure 8.

Figure 8. FRESCO: OS Exploratory Subgroup Analysis



Efficacy Results – Secondary and other relevant endpoints

A clinically meaningful improvement in PFS was observed in patients randomized to fruquintinib+BSC arm compared to the placebo arm (PFS HR: 0.26 (95% CI: 0.21, 0.34; nominal p < 0.001); median PFS was 3.71 months in the fruquintinib arm (95% CI: 3.65, 4.63) compared with 1.84 months in the placebo arm (95% CI: 1.81, 1.84). Note that, as stated in Section-8.1.3, there was no clear specification of Type-I error control to test the PFS hypothesis.

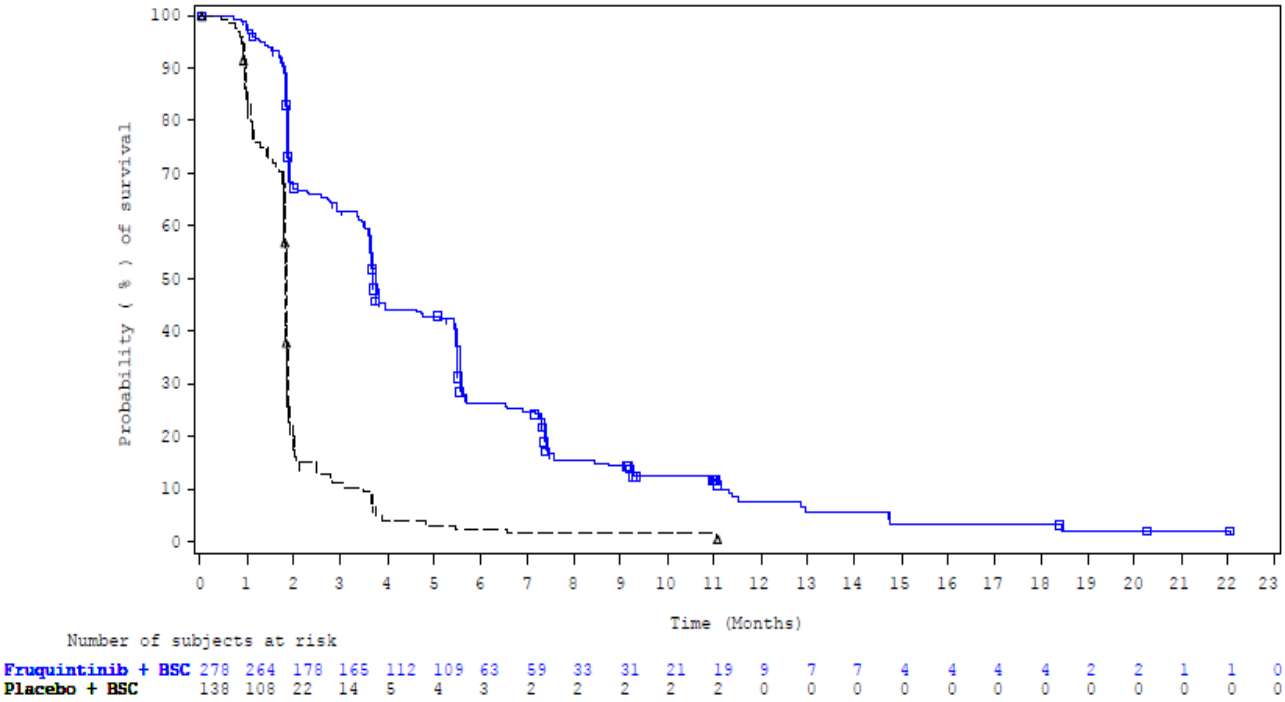
The investigator assessed confirmed ORR was 4.7% (n=13) in the fruquintinib +BSC arm and 0% in the placebo+BSC arm. Among the responders in the fruquintinib+BSC arm 12 patients had a best overall response of partial response and 1 patient had complete response. The median DoR was not estimable in both the arms.

Table 19. FRESCO: PFS and ORR Results

	Fruquintinib + BSC N=278	**Placebo+ BSC N=138**
PFS		
Number of patients with event (%)	235 (85%)	125 (91%)
Median in months (95% CI)	3.7 (3.7,4.6)	1.8 (1.8, 1.8)
Hazard Ratio [a] (95% CI)	0.26 (0.21, 0.34)	
ORR		
# Patients with response, n (%) (95% exact CI)	13 (4.7%) (2.5, 7.9)	0 (0, 2.6)

[a]: Adjusted for stratification factors.

Figure 9.FRESCO: PFS curves



Dose/Dose Response

Only one dose was investigated in the randomized, placebo controlled, clinical trials designed to assess the safety and efficacy of fruquintinib (FRESCO and FRESCO-2); therefore conclusions regarding the effectiveness of lower (or higher) doses cannot be made. Please refer to the clinical pharmacology review for population-PK analyses and exposure-response analyses.

Durability of Response

Durability of response could not be evaluated as only 13 (4.7%) patients on the fruquintinib arm had an objective response. No patients on the placebo arm had an objective response. The effect of fruquintinib appears to be cytostatic and therefore duration of response is not an adequate outcome to assess the benefit of fruquintinib.

Persistence of Effect

Persistence of effect is a term better suited for continuous variables (e.g., hypertension, biomarker assessments, etc.) and is not intended to characterize or compare treatment effects on selected endpoints. Treatment effect and study outcomes are described elsewhere in this section.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Patient reported outcome endpoints were not evaluated in the FRESCO study. No other exploratory endpoints were included in the FRESCO study.

Additional Analyses Conducted on the Individual Trial

Crossover was not allowed for patients in the placebo arm. Subsequent antitumor therapy was received by 118 (42%) patients in the fruquintinib arm and 70 (51%) patients in the placebo arm. This included chemotherapy for 88 (32%) patients in the fruquintinib arm and 60 (43%) of patients in the placebo arm. There were no major imbalances in subsequent therapies received that would have impacted the primary endpoint. Table 20 summarizes post-disease progression therapies.

Table 20. FRESCO: Subsequent Treatment Received

	Fruquintinib + BSC N=278; n (%)	Placebo + BSC N=138; n (%)	Total N=416; n (%)
Subsequent Anti-Tumor Therapy			
Yes	118 (42.4)	70 (50.7)	188 (45.2)
Type of Anti-Tumor Therapy			
Chemotherapy	88 (31.7)	60 (43.5)	148 (35.6)
Radiotherapy	18 (6.5)	6 (4.3)	24 (5.8)
Surgery	12 (4.3)	6 (4.3)	18 (4.3)
Other	42 (15.1)	22 (15.9)	64 (15.4)
Number of Subsequent Anti-Tumor Therapies			
0	150 (57.6)	68 (49.3)	218 (52.4)
1	43 (15.5)	30 (21.7)	73 (17.5)
≥2	75 (27.0)	40 (29.0)	115 (72.6)
Subsequent Use of Targeted Therapies			
Anti-EGFR	12 (4.3)	6 (4.3)	18 (4.3)
Anti-VEGF/VEGFR	34 (12.2)	22 (15.9)	56 (13.5)

8.1.5 Integrated Review of Effectiveness

FDA's independent analyses of the efficacy results for FRESCO-2, in general, concurs with the Applicant's position and analyses of the primary endpoint of OS as well as the secondary endpoints of investigator-assessed PFS and ORR. FRESCO-2 met its primary endpoint of OS and key secondary endpoint of PFS in the intent-to treat population of patients with metastatic colorectal cancer with disease progression after a fluoropyrimidine-, oxaliplatin-, and irinotecan-based therapy, standard of care biological treatment with a VEGFR/R inhibitor, other biologics as determined by biomarker status, and treatment with regorafenib and/or trifluridine/tipiracil, with results that were statistically significant and clinically meaningful. Fruquintinib yields a net favorable risk:benefit profile compared to placebo in the refractory population; median overall survival was 7.4 months in the fruquintinib arm (95% CI: 6.7, 8.2) compared to 4.8

months in the placebo arm (95% CI: 4.8, 5.8), with a hazard ratio of 0.66 (95% CI: 0.55, 0.80; p < 0.001). The median PFS was 3.7 months in the fruquintinib arm (95% CI: 3.5, 38) compared with 1.8 months in the placebo arm (95% CI: 1.8, 1.9), with a hazard ratio of 0.321 (95% CI: 0.267, 0.386; p < 0.001).

Most of the subgroup analyses showed that OS results for subgroups were consistent with the primary result. In addition, patients appeared to benefit regardless of whether they had previously received TAS-102, regorafenib, or both TAS-102 and regorafenib.

The Applicant submitted the results of a second randomized study, FRESCO. Although this study enrolled a different population (patients were not exposed to regorafenib and/or trifluridine/tipiracil and use of biologicals targeting the VEGF/R and EGFR pathways was discretionary and would not be representative of the use of targeted therapy in the US population), the results of FRESCO are supportive of the finding of FRESCO-2. FRESCO results were statistically significant and clinically meaningful. In this supportive study, fruquintinib use yielded a net favorable risk:benefit profile compared to placebo in the treated population, which was refractory to fluoropyrimidine, oxaliplatin-, and irinotecan-based therapy. The median overall survival was 9.3 months in the fruquintinib arm (95% CI: 8.2, 10.5) compared to 6.6 months in the placebo arm (95% CI: 5.9, 8.1), with a hazard ratio of 0.65 (95% CI: 0.51, 0.83; p < 0.001). Similarly, a clinically meaningful prolongation of PFS was observed in patients randomized to fruquintinib; median PFS was 3.71 months in the fruquintinib arm (95% CI: 3.65, 4.63) compared with 1.84 months in the placebo arm (95% CI: 1.81, 1.84), with a hazard ratio of 0.26 (95% CI: 0.21, 0.34). It is important to note that inclusion of FRESCO results (single country outside of US) in labeling were only considered after reviewing the results of FRESCO-2, a multi-regional study that was applicable to the US population.

Due to limitations in the design of FRESCO-2 with respect to PRO assessment and analyses, FDA was not able to conclude that fruquintinib resulted in a clinically meaningful improvement on PROs. No PRO assessments were conducted in the FRESCO study.

8.1.6 Integrated Assessment of Effectiveness

The primary evidence of the effectiveness of fruquintinib for the treatment of patients with refractory metastatic colorectal cancer is derived from an adequate and well controlled, randomized, placebo-controlled trial, FRESCO-2. FRESCO-2 was a placebo-controlled, multiregional trial that met its primary endpoint of OS and key secondary endpoint of PFS in the intent-to treat population of patients with metastatic colorectal cancer with disease progression after a fluoropyrimidine-, oxaliplatin-, and irinotecan-based therapy, standard of care biological treatment with a VEGFR/R inhibitor, other biologics as determined by biomarker status, and treatment with regorafenib and/or trifluridine/tipiracil, with results that were statistically significant and clinically meaningful.

The trial supports the conclusion that fruquintinib resulted in a net favorable risk:benefit profile compared to placebo in the refractory population.

The Applicant submitted a second randomized controlled trial, FRESCO. This trial was conducted in a single country, with a smaller proportion of patients having received anti-EGFR or anti-VEGF biologic and with no patient receiving regorafenib and trifluridine/tipiracil. Like FRESCO-2, FRESCO met its primary endpoint of OS in the intent-to treat population of patients with metastatic colorectal cancer. Given the characteristics of the patients enrolled in the FRESCO study, as a stand-alone study, FRESCO would not have been supportive of registration. However, the results of the study were supportive and consistent with the main results and exploratory subgroup analyses of FRESCO-2, and contributed data showing that although fruquintinib targets VEGFR, the effect of fruquintinib appears to be independent of prior therapy with regorafenib or prior anti-VEGF biologic therapy. Therefore, the review team concluded that broadening the indication beyond the population enrolled in FRESCO-2 (i.e., approving fruquintinib for the treatment of patients with metastatic colorectal cancer with disease progression after treatment with a fluoropyrimidine-, oxaliplatin, irinotecan-based therapy, an anti VEGF/R biologic, and other therapies based on biomarkers *irrespective of prior use of regorafenib and/or trifluridine/tipiracil*) was supported by the data.

Although a multiregional trial, FRESCO-2 did not include sufficient number of underrepresented minorities in the study to adequately characterize the effects of fruquintinib in these patient populations. FDA requested the Applicant to conduct a post-marketing study (for details, refer below to Section 13) to address this deficiency.

8.2 Review of Safety

8.2.1 Safety Review Approach

Although the safety review is focused on the analysis of the FRESCO-2 and FRESCO studies, for completeness and to assist labeling, FDA also reviewed data from the 2012-013-00CH1 study, a double-blind, placebo-controlled randomized controlled study in patients with mCRC. Safety analyses were conducted by treatment arm and includes 911 patients treated with at least one dose of fruquintinib (456, 278, and 47 patients in the FRESCO-2, FRESCO, and 2012-013-00CH1 trials respectively).

Safety presentations of adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation, and laboratory abnormalities are based on all treated patients using a safety window of 30 days after last dose. Any AEs that began within 30 days post treatment discontinuation but became fatal after this time frame were included in the analysis of fatal events.

Fruquintinib is a VEGFR-1, VEGFR-2 and VEGFR-3 inhibitor. Based on the known safety profile of other approved drugs targeting the same pathway (e.g.., axitinib, regorafenib), expected adverse events of special interest (AESIs) include hypertension, hemorrhagic events, arterial thrombotic events, gastrointestinal perforation, palmar-

plantar erythrodysesthesia syndrome (hand-foot syndrome), stomatitis, wound healing difficulty, hepatotoxicity, thyroid dysfunction, and proteinuria.

8.2.2 Review of the Safety Database

Overall Exposure

Four hundred fifty-six patients received at least one dose of fruquintinib and 230 patients received at least one dose of placebo in FRESCO-2. The median duration of treatment was longer in patients receiving fruquintinib: 12 weeks (0 to 82) vs. 7 weeks (0 to 51) in the placebo arm. Table 21 summarizes the overall exposure analysis for FRESCO-2.

Table 21. FRESCO-2: Summary of Treatment Exposure

	Fruquintinib + BSC N=456; n (%)	Placebo + BSC N=230; n (%)
Duration of treatment (weeks)		
Mean (SD)	16.6 (13.57)	7.8 (5.90)
Median (min, max)	12 (0 to 82)	7 (0 to 51)
Duration of Treatment by Category		
≥ 4 weeks	398 (87.3)	171 (74.3)
≥ 8 weeks	294 (64.5)	69 (30.0)
≥ 12 weeks	234 (51.3)	36 (15.7)
≥ 16 weeks	182 (39.9)	20 (8.7)
≥ 20 weeks	143 (31.4)	9 (3.9)
≥ 24 weeks	110 (24.1)	4 (1.7)

These results are consistent with the efficacy results, showing that patients in the fruquintinib arm were treated for longer periods of time reflecting lack of disease progression, while only 30% of patients in the placebo arm continued treatment at least or beyond 8 weeks.

Two hundred seventy-eight patients received at least one dose of fruquintinib and 137 patients received at least one dose of placebo in FRESCO. The median duration of treatment was longer in patients receiving fruquintinib: 15 weeks (0 to 95) in vs. 7 weeks (0 to 48) in the placebo arm. Table 22 summarizes the overall exposure analysis for FRESCO.

Table 22. FRESCO: Summary of Treatment Exposure

	Fruquintinib + BSC N=278; n (%)	Placebo + BSC N=137; n (%)
Duration of treatment (weeks)		
Mean (SD)	20.6 (17.40)	7.4 (6.62)

Median (min, max)	15 (0 to 95)	7 (0 to 48)
Duration of Treatment by Category		
≥ 4 weeks	255 (91.7)	99 (72.2)
≥ 8 weeks	194 (69.8)	29 (21.2)
≥ 12 weeks	166 (59.7)	18 (13.1)
≥ 16 weeks	137 (49.2)	9 (6.6)
≥ 20 weeks	116 (41.7)	4 (2.9)
≥ 24 weeks	82 (29.5)	3 (2.2)

These results are consistent with the efficacy results of FRESCO as well as the exposure analysis of FRESCO-2. In this trial, 70% and 21% of patients continued fruquintinib and placebo respectively at least or beyond 8 weeks.

Adequacy of the safety database:

FDA considers that he safety population of 734 patients receiving fruquintinib and 367 patients receiving placebo in FRESCO-2 and FRESCO was sufficient to characterize the safety profile of fruquintinib for the treatment of patients with refractory mCRC.

Overall, the applicant's monitoring of the clinical safety was adequate and consistent with the standard of care.

8.2.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No issues with safety data quality and integrity have been identified. The submission was complete and of adequate quality for the clinical review. The CRFs and narratives were complete and provided the information needed to supplement the databases.

Categorization of Adverse Events

Adverse events for the FRESCO study were graded according to NCI-CTCAE version 4.03 with adverse events classified and coded using MedDRA version 19.1. Adverse events for the FRESCO-2 study were graded according to NCI-CTCAE version 5.0 with adverse events classified and coded using MedDRA version 25.0.

FDA conducted an audit of the coding of terms in the safety dataset. Verbatim terms for adverse events were accurately coded using the MedDRA dictionary. FDA analyses were conducted irrespective of attribution, and although the numbers may slightly differ from the Applicant's based on use of grouping terms and review strategy, the review team agrees with the general conclusions about the safety and tolerability of fruquintinib.

Routine Clinical Tests

Standard hematology and serum chemistry, amylase, lipase, thyroid stimulating hormone (TSH), free T4 or T3, INR, and proteinuria were assessed on Day 1 of each cycle throughout treatment administration. Additional analytes, including non-study required laboratory tests, were to be performed as clinically indicated or to comply with local regulations.

Laboratory tests were graded using the NCI CTCAE, versions 5.0 and 4.03 in the FRESCO-2 and FRESCO study respectively.

8.2.4 Study 2019-013- GLOB1 (FRESCO-2): Safety Results

Major Safety Results

In FRESCO-2, the majority of patients experienced AEs: 451 patients (99%) on the fruquintinib arm and 213 (93%) patients on the placebo arm. Grade 3-4 AEs occurred more frequently in the fruquintinib arm compared with placebo (61% vs. 45% respectively). The most common Grade 3-4 AE was hypertension, which occurred more frequently on the fruquintinib arm relative to placebo (14% vs. 1%). The proportion of patients with SAEs and fatal AEs was small and similar across arms. Dose interruption was required more often in the fruquintinib arm (47%) than was in the placebo arm (27%). Similarly, dose reductions were implemented more frequently in the fruquintinib arm (24%) relative to the placebo arm (4%). The most common reasons for dose interruptions in the fruquintinib arm were fatigue, palmar-plantar erythrodysesthesia syndrome, and proteinuria. The most common reasons for dose reductions in the fruquintinib arm were palmar-plantar erythrodysesthesia syndrome, fatigue, and hypertension. Table 23 summarizes the major safety results from the FRESCO-2 study.

Table 23. FRESCO-2: Major Safety Results

	Fruquintinib + BSC N=456; n (%)	Placebo + BSC N=230; n (%)
All-Grade TEAEs	451 (98.9)	213 (92.6)
Grade 3-4 TEAEs	277 (60.7)	104 (45.2)
Grade 5	14 (3.1)	10 (4.3)
SAEs	169 (37.1)	89 (38.7)
Patients with AEs leading to treatment interruption	213 (46.7)	62 (27.0)
Patients with AEs leading to dose reduction	110 (24.1)	9 (3.9)
Patients with AEs leading to treatment discontinuation	93 (20.4)	49 (21.3)

Deaths

In the FRESCO-2 study, there were 94 patients (48 patients in the fruquintinib arm and 46 in the placebo arm) who experienced an AE resulting in death within 30 days of the last dose of study medication. This included 3 patients (1 on the fruquintinib arm and 2 on the placebo arm) with AEs that began within 30 days of the last dose, but died at day 32, 33, and 35, respectively, following the last dose of study treatment. Of the documented 94 deaths, 34 of the 48 patients (71%) on the fruquintinib arm and 36 of the 46 patients (78%) on the placebo arm died of reasons considered by the investigator as directly related to the underlying disease of mCRC (e.g., terms included "disease progression" or "tumor invasion"). This left a total of 14 (3.1%) deaths due to AEs on the fruquintinib arm and 10 (4.3%) on the placebo arm. There was one fatal case (0.2%) of intestinal perforation, which is a previously described AE associated with this class of medication. Table 16 summarizes all fatal AEs in the safety population.

There was one event on the fruquintinib arm that was reported only as "death" with a cause unknown in a patient with a bulky mass and extensive metastatic disease who discontinued treatment after 9 days due to an AE of Grade 2 mucosal inflammation. The patient missed several follow-up visits and was unreachable by phone; the date of death was listed in public records 11 days after the last dose of study treatment. Table 24 summarizes the fatal AEs occurring in the FRESCO-2 study.

Table 24. FRESCO-2: Fatal AEs

	Fruquintinib + BSC N=456; n (%)	Placebo + BSC N=230; n (%)
Any Event	**14 (3.1)**	**10 (4.3)**
Cardiac arrest	0	1 (0.4)
Pulmonary embolism	1 (0.2)	0
Acute respiratory distress syndrome	1 (0.2)	0
Pneumothorax	1 (0.2)	0
Dyspnea	0	1 (0.4)
Interstitial lung disease	0	1 (0.4)
Respiratory distress/failure	0	2 (0.8)
Biliary obstruction	1 (0.2)	0
Hepatic function abnormal	0	1 (0.4)
Hepatic failure/encephalopathy	2 (0.4)	1 (0.4)
Pneumonia	3 (0.7)	0
Sepsis/Septic shock	2 (0.4)	0
Covid-19	0	1 (0.4)
Intestinal perforation	1 (0.2)	0
Multiple organ dysfunction syndrome	1 (0.2)	1 (0.4)
Subileus/Intestinal obstruction	1 (0.2)	1 (0.4)

Of note, in the setting of advanced mCRC, the listed AEs are common causes of disease-related deaths, common to both arms, and there is no apparent pattern of

increased risk when patients are being treated with fruquintinib.

Serious Adverse Events

In the FRESCO-2 study, there were 271 SAEs in 157 (34%) patients in the fruquintinib arm and 119 SAEs in 76 (33) patients in the placebo arm. Of note, this analysis differs from the Applicant's analysis, which included events of disease progression and related terms. As disease progression is an outcome and not a drug-related adverse reaction, FDA analysis did not include these events. Notable SAEs in the fruquintinib arm related to the pharmacologic class of the drug include events of hemorrhage (n=10), gastrointestinal perforation (n=9), hypertension (n=8), pulmonary embolism (n=5), and fistula (n=4), The incidence of SAEs was similar in both treatment arms. Table 25 summarizes the serious adverse events observed in the FRESCO-2 study.

Table 25. FRESCO-2: Serious Adverse Events (>1% Incidence)

	Fruquintinib + BSC N=456; n (%)	Placebo + BSC N=230; n (%)
General physical health deterioration	13 (2.9)	7 (3.0)
Hepatotoxicity[1]	11 (2.4)	6 (2.6)
Pneumonia	11 (2.4)	1 (0.4)
Hemorrhage[2]	10 (2.2)	4 (1.7)
Gastrointestinal perforation[3]	9 (2.0)	0
Abdominal pain	8 (1.8)	2 (0.9)
Hypertension[4]	8 (1.8)	0
Intestinal obstruction	7 (1.5)	7 (3.0)
Back pain	6 (1.3)	1 (0.4)
Dyspnea	6 (1.3)	4 (1.7)
Pyrexia	6 (1.3)	2 (0.9)
Urinary tract infection	6 (1.3)	4 (1.7)
Acute kidney injury	5 (1.1)	1 (0.4)
Asthenia	5 (1.1)	0
Pulmonary embolism	5 (1.1)	0
Sepsis	5 (1.1)	0
Small intestinal obstruction	5 (1.1)	1 (0.4)

[1]Hepatotoxicity is a composite term of blood bilirubin increased, hepatic failure, encephalopathy, hepatic encephalopathy, and hepatic function abnormal
[2]Hemorrhage is a composite term of hemorrhage, gastrointestinal hemorrhage, gastric hemorrhage, rectal hemorrhage, upper gastrointestinal hemorrhage, cerebral hemorrhage, hematuria, hematemesis, intermenstrual bleeding, and epistaxis
[3]Gastrointestinal perforation is a composite term of intestinal perforation, small intestinal perforation, gastric perforation, gastrointestinal perforation, large intestine perforation, and rectal perforation
[4]Hypertension is a composite term of hypertension and hypertensive crisis
[5]Fistula is a composite term of fistula, colonic fistula, female genital tract fistula, vesicocutaneous fistula, broncopleural fistula, and enterovesical fistula

Significant Adverse Events

Refer to Section 9.2.6 (Analysis of Submission-Specific Safety Issues).

Dose-Interruptions and Dose-Reductions Due to Adverse Effects

In the FRESCO-2 study, dose modifications were used for 252 (55%) patients on the fruquintinib arm and 66 (29%) patients on the placebo arm. Adverse events leading to dose-interruption occurred 213 (48%) patients in the fruquintinib arm and 62 (27%) patients in the placebo arm . The most common reasons for dose-interruption in the fruquintinib arm included fatigue (7%), palmar-plantar erythrodysesthesia syndrome (6%), and proteinuria (6%). Adverse events leading to dose-reductions occurred in 110 (24%) patients in the fruquintinib arm and 9 (3.9%) patients in the placebo arm. The most common reasons for dose-reductions in the fruquintinib arm included palmar-plantar erythrodysesthesia syndrome (5%), fatigue (4.8%), and hypertension (3.7%). Table 26 summarizes the AEs leading to dose-interruption or dose-reduction that occurred in the FRESCO-2 study.

Table 26. FRESCO-2: AEs Leading to Dose-Interruption or Dose-Reduction

	Fruquintinib + BSC N=456; n (%)	Placebo + BSC N=230; n (%)
Dose-Interruption (>2% Incidence)		
Fatigue[1]	33 (7.2)	3 (0.7)
Palmar-plantar erythrodysesthesia syndrome	29 (6.4)	0
Proteinuria	26 (5.7)	6 (2.6)
Abdominal Pain	16 (3.5)	5 (2.2)
Vomiting	14 (3.1)	6 (2.6)
Hypertension	14 (3.1)	1 (0.4)
Diarrhea	11 (2.4)	0
Dose-Reduction (>1% Incidence)		
Palmar-plantar erythrodysesthesia syndrome	24 (5.2)	0
Fatigue[1]	22 (4.8)	3 (1.3)
Hypertension	17 (3.7)	1 (0.4)
Diarrhea	8 (1.8)	0
Proteinuria	8 (1.8)	1 (0.4)
Blood bilirubin increased	6 (1.3)	0

[1]Fatigue is a composite term that includes asthenia and fatigue.

Dropouts and/or Discontinuations Due to Adverse Effects

In the FRESCO-2 study, 93 (20%) patients in the fruquintinib arm and 40 (17%) patients in the placebo arm discontinued treatment because of an adverse event. The most common reasons for drug discontinuation occurring more frequently in the fruquintinib arm were fatigue (1.5%), proteinuria (0.9%), pulmonary embolism (0.9%), and gastrointestinal perforation (0.9%). While palmar-plantar erythrodysesthesia syndrome was the most common reason for dose-reduction in both the FRESCO-2 and FRESCO studies, relatively few patients discontinued treatment due to palmar-plantar erythrodysesthesia syndrome. Table 27 summarizes the AEs leading to drug discontinuation in the FRESCO-2 study.

Table 27. FRESCO-2: AEs Leading to Drug Discontinuation

	Fruquintinib + BSC N=456; n (%)	Placebo + BSC N=230; n (%)
Drug Discontinuation (>0.5% Incidence)		
Fatigue[1]	7 (1.5)	2 (0.9)
General physical health deterioration	5 (1.1)	5 (2.2)
Proteinuria	4 (0.9)	0
Pulmonary embolism	4 (0.9)	0
Gastrointestinal perforation[2]	4 (0.9)	0
Hemorrhage[3]	3 (0.7)	1 (0.4)
Abdominal pain	3 (0.7)	0
Diarrhea	3 (0.7)	0
Palmar-plantar erythrodysesthesia syndrome	3 (0.7)	0

[1]Fatigue is a composite term that includes asthenia and fatigue.
[2]Gastrointestinal perforation is a composite term that includes gastrointestinal perforation, large intestine perforation, rectal perforation, and small intestinal perforation.
[3]Hemorrhage is a composite term that includes cerebral hemorrhage, gastrointestinal hemorrhage, rectal hemorrhage, and upper gastrointestinal hemorrhage.

Treatment Emergent Adverse Events and Adverse Reactions

In the FRESCO-2 study, the most common AEs (all grades) in the fruquintinib arm were fatigue (53%), hypertension (39%), stomatitis (32%), decreased appetite (27%), abdominal pain (25%), diarrhea (24%), hepatotoxicity (22%), hypothyroidism (21%), palmar-plantar erythrodysesthesia syndrome (19%), proteinuria (18%), and dysphonia (18%). The majority of events were Grade 1-2. The most common Grade ≥ 3 AEs in the fruquintinib arm were hypertension (14%), fatigue (12%), hepatotoxicity (7%), and palmar-plantar erythrodysesthesia syndrome (6%). The incidence of Grade ≥ 3 hypertension with fruquintinib in the FRESCO-2 study (14%) was lower relative to the FRESCO study (23%).

The most common AEs (all grades) in the placebo arm were fatigue (39%), abdominal pain (21%), decreased appetite (18%), hepatotoxicity (12%), vomiting (11%), and

diarrhea (11%). The majority of events in the placebo arm were Grade 1 -2. The most common Grade ≥ 3 AEs in the placebo arm were hepatotoxicity (6%), fatigue (4%), and abdominal pain (3%).

The most common adverse events observed on the fruquintinib are consistent with the class effects that have been observed with other VEGF/R inhibitors. There do not appear to be any new safety signals apparent that have not been observed previously with other drugs in the same class. The most common adverse events observed in the placebo arm are consistent with the underlying disease of metastatic colorectal cancer. Although more patients in the fruquintinib arm experienced hepatotoxicity, Grade ≥ 3 hepatotoxicity was observed with a similar incidence in both arms. Table 28 summarizes the most common AEs reported in FRESCO-2.

Table 28. FRESCO-2: Most Common TEAEs (>10% Incidence, Safety Population)

	Fruquintinib + BSC N=456; n (%)		Placebo + BSC N=230; n (%)	
AE	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**
Fatigue[1]	243 (53.3)	53 (11.6)	89 (38.7)	10 (4.3)
Hypertension[2]	176 (38.6)	65 (14.3)	20 (8.7)	2 (0.9)
Stomatitis[3]	144 (31.6)	11 (2.4)	18 (7.8)	1 (0.4)
Decreased appetite	124 (27.2)	11 (2.4)	41 (17.8)	3 (1.3)
Abdominal Pain[4]	115 (25.2)	15 (3.3)	49 (21.3)	7 (3.0)
Diarrhea[5]	111 (24.3)	17 (3.7)	25 (10.9)	0
Hepatotoxicity[6]	98 (21.5)	32 (7.0)	27 (11.7)	14 (6.1)
Hypothyroidism	94 (20.6)	2 (0.4)	1 (0.4)	0
Palmar-plantar erythrodysesthesia syndrome	88 (19.3)	29 (6.4)	6 (2.6)	0
Proteinuria[7]	80 (17.5)	8 (1.8)	12 (5.2)	2 (0.9)
Dysphonia[8]	80 (17.5)	0	12 (5.2)	0
Constipation	78 (17.1)	2 (0.4)	22 (9.6)	0
Musculoskeletal pain[9]	75 (16.4)	5 (1.1)	17 (7.4)	0
Vomiting	66 (14.5)	7 (1.5)	26 (11.3)	4 (1.7)
Hemorrhage[10]	61 (13.4)	8 (1.8)	21 (9.1)	4 (1.7)
Weight decreased	56 (12.3)	3 (0.7)	20 (8.7)	1 (0.4)
Thrombocytopenia[11]	55 (12.1)	1 (0.2)	5 (2.2)	1 (0.4)
Back pain[12]	53 (11.6)	6 (1.3)	21 (9.1	4 (1.7)
Arthralgia[13]	51 (11.2)	4 (0.9)	10 (4.3)	0
Pyrexia	46 (10.1)	1 (0.2)	22 (9.6)	0

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 5.0 (NCI CTCAE v5)
[1]Fatigue is a composite term that includes fatigue and asthenia
[2]Hypertension is a composite term that includes hypertension, blood pressure increased, blood pressure diastolic increased, diastolic hypertension, and hypertensive crisis

[3]Stomatitis is a composite term that includes stomatitis, mucosal inflammation, apthous ulcer, oral pain, oral dysesthesia, oral discomfort, glossodynia, glossitis, gingival pain, oropharyngeal pain, oropharyngeal discomfort
[4]Abdominal pain is a composite term that includes abdominal pain, abdominal pain lower, abdominal pain upper, abdominal discomfort, and hepatic pain
[5]Diarrhea is a composite term that includes diarrhea, colitis, and enteritis
[6]Hepatotoxicity is a composite term that includes hepatotoxicity, hepatic failure, hepatic cytolysis, hepatic function abnormal, aspartate aminotransferase increased, aspartate aminotransferase abnormal, alanine aminotransferase increased, blood bilirubin increased, bilirubin conjugated increased, hypertransaminasemia, hyperbilirubinemia, hepatitis, liver function test increased, and liver function test abnormal
[7]Proteinuria is a composite term that includes proteinuria, and protein urine present
[8]Dysphonia is a composite term that includes dysphonia and aphonia
[9]Musculoskeletal pain is a composite term that includes musculoskeletal pain, musculoskeletal stiffness, myalgia, musculoskeletal chest pain, non-cardiac chest pain, pain in extremity, bone pain, and neck pain
[10]Hemorrhage is a composite term that includes hemorrhage, conjunctival hemorrhage, eye hemorrhage, anal hemorrhage, gastric hemorrhage, anal hemorrhage, gastric hemorrhage, gastrointestinal hemorrhage, hemorrhoidal hemorrhage, upper gastrointestinal hemorrhage, rectal hemorrhage, post-procedural hemorrhage, stoma-site hemorrhage, cerebral hemorrhage, vaginal hemorrhage, pulmonary hemorrhage, epistaxis, intermenstrual bleeding, gingival bleeding, hemoptysis, hematochezia, hematemesis, and hematuria
[11]Thrombocytopenia is a composite term that includes thrombocytopenia and platelet count decreased
[12]Back pain is a composite term that includes back pain, sacral pain, and spinal pain
[13]Arthralgia is a composite term that includes arthralgia, arthritis, and arthropathy

Laboratory Findings

Laboratory abnormalities (hematology, liver tests, kidney function tests, and electrolytes) in the fruquintinib and placebo arms were primarily Grade 1-2. In FRESCO-2, the most common laboratory abnormalities on the fruquintinib arm were increased triglycerides (53%), cholesterol increased (38%), increased AST (36%), and increased ALT (34%). The most common Grade 3-4 chemistry laboratory abnormalities were increased bilirubin (7%), increased ALT (5%), and increased AST (4.3%).

While there was an increased proportion of patients with increased AST, ALT, or bilirubin in the fruquintinib arm relative to the placebo arm, there was only 1 case in the fruquintinib arm meeting Hy's law criteria and after review of the CRF, it appears unlikely that the case represents drug induced liver injury (see the discussion of hepatoxicity under the section for Adverse Events of Special Interest).

Decreased platelets of any grade occurred in 30% of patients in the fruquintinib arm and in 4.6% of patients on the placebo arm; however, Grade 3-Grade 4 toxicity occurred in only 0.2% of patients on the fruquintinib arm. Decreased platelets is an adverse event that has been observed with VEGF receptor inhibition. Table 29 summarizes the most frequently observed lab abnormalities in FRESCO-2.

Table 29. FRESCO-2: Laboratory Abnormalities Worsening from Baseline Occurring in ≥ 20% of Patients

Laboratory Abnormality	Fruquintinib + BSC (N=456)[1]		Placebo + BSC (N=230)[1]	
	All Grades (%)[2]	Grade 3-4 (%)[2]	All Grades (%)[2]	Grade 3-4 (%)[2]
Chemistry				
Triglycerides Increased	53	2.8	21	1.0
Cholesterol Increased	38	2.1	22	1.9
AST Increased	36	4.3	24	1.9
Albumin Decreased	35	1.6	32	1.4
Sodium Decreased	35	1.1	27	0.9
ALT Increased	34	5	22	1.4
Bilirubin Increased	30	7	21	8
Alkaline Phosphatase Increased	20	1.6	26	0.5
Magnesium Decreased	20	0.5	10	0.5
Hematology				
Lymphocytes Decreased	30	6	32	4.6
Platelets Decreased	30	0.2	4.6	0
aPTT Increased	21	2.7	17	1.5

[1] Graded according to NCI CTCAE version 5.0.
[2] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: fruquintinib (range: 409-444) and placebo (range: 195-216).

Vital Signs

No clinically relevant changes occurred for vital sign indicators other than blood pressure. See section 8.2.5.1 for a discussion of hypertension as an adverse event of special interest.

Electrocardiograms (ECGs)

In the FRESCO-2 study, patients with QTcF > 480 msec or any other factors that prolongs the QTc interval or increases the risk of arrhythmic events were excluded from the study. Patients taking medications with a known risk of causing QT prolongation and/or torsade de pontes were also excluded. ECG assessments (12-lead) were

performed on all patients at baseline and during Cycles 1 to 3 (C1D1, C1D21, C2D21, and C3D21) using standardized equipment. In addition, a continuous 12-lead Holter monitor was used for QTc evaluation during Cycle 1 in a subset of patients. From Cycle 4 onward, ECGs were performed only when clinically indicated.

As summarized in the interdisciplinary review team for cardiac safety studies review uploaded in DAARTS (FDA's Document, Archiving, Reporting, and Regulatory Tracking System) on July 27, 2023, a mean QTc interval prolongation ≥ 20 msec was not observed based on the results of FRESCO-2.

Immunogenicity

Not applicable.

8.2.5 Study 2013-013-00CH1 (FRESCO): Safety Results

Major Safety Results

In the FRESCO study, the majority of patients experienced adverse events: 274 (99%) in the fruquintinib arm and 121 (88%) in the placebo arm. Grade 3-4 AEs occurred more frequently on the fruquintinib arm (58%) than on the placebo arm (18%). The most common Grade 3-4 AE was hypertension, which occurred in 65 (23%) patients on the fruquintinib arm and 3 (2.2%) of patients on the placebo arm. The proportion of patients with fatal AEs was similar in the fruquintinib (2.5%) and placebo (1.5%) arms. Table 30 summarizes the major safety results from the FRESCO study.

Table 30. FRESCO: Major Safety Results

	Fruquintinib + BSC N=278; n (%)	Placebo + BSC N=137; n (%)
All-Grade TEAEs	274 (98.6)	121 (88.3)
Grade 3-4 TEAEs	161 (57.9)	25 (18.2)
Grade 5	7 (2.5)	2 (1.5)
SAEs	43 (15.5)	8 (5.8)
Patients with AEs leading to treatment interruption	98 (35.3)	14 (10.2)
Patients with AEs leading to dose reduction	67 (24.1)	6 (4.4)
Patients with AEs leading to treatment discontinuation	41 (14.7)	7 (5.1)

Deaths

In the FRESCO study, there were 11 patients (9 patients in the fruquintinib arm and 2 in the placebo arm) who experienced an AE resulting in death within 30 days of the last dose of study medication. This included 2 patients on the fruquintinib arm with AEs with the preferred terms of “death” and “sudden death”. The patient whose event was classified as “death” should be re-classified as Grade 5 pneumonia, as he died after being hospitalized for Grade 3 pneumonia, with progression to respiratory distress and subsequent death. Patient (b) (6) was a 64-year-old female, with no history of cardiovascular disease reported, who had metastatic disease to the liver and lungs. The patient lost consciousness and died on Day 42 of study treatment while at home without trauma to head or signs of bleeding (sudden death).

There were a total of 7 (2.5%) fatal AEs on the fruquintinib arm and 2 (1.5%) on the placebo arm. There were two fatal hemorrhages (gastrointestinal hemorrhage and hemoptysis) in the fruquintinib arm while none was reported in the placebo arm. Table 31 summarizes all fatal AEs in the safety population.

Table 31. FRESCO: Fatal AEs

	Fruquintinib + BSC N=278; n (%)	Placebo + BSC N=137; n (%)
Any Event	**7 (2.5)**	**2 (1.5)**
Pulmonary embolism	0	1 (0.7)
Cerebral infarction	1 (0.4)	0
Gastrointestinal hemorrhage	1 (0.4)	0
Hemoptysis	1 (0.4)	0
Bacterial infection	1 (0.4	0
Lower respiratory infection	1 (0.4)	0
Lung infection	1 (0.4)	0
Multiple organ dysfunction	1(0.4)	0
Shock	0	1 (0.7)

As observed in the FRESCO-2 study, the listed AEs are common causes of disease-related deaths.

Serious Adverse Events

In the FRESCO study, 43 (15%) patients in the fruquintinib arm and 7 (5%) patients in the placebo arm experienced SAEs. The majority of events were single occurrences. SAEs of special interest (associated with the pharmacologic class) include hemorrhage (n=6), fistula (n=3), intestinal perforation (n=2), hepatic function abnormal (n=2) hypertension (n=1), urine protein increased (n=1), and palmar-plantar erythrodysesthesia syndrome (n=1). Table 32 summarizes the serious adverse events that occurred in the FRESCO study.

Table 32. FRESCO: Serious Adverse Events (>1% Incidence)

	Fruquintinib + BSC N=278; n (%)	Placebo + BSC N=137; n (%)
Intestinal obstruction	8 (2.9)	1 (0.7)
Hemorrhage[1]	6 (2.2)	0
Fistula[2]	3 (1.1)	0
Lung infection	3 (1.1)	0
Subileus	3 (1.1)	0

[1]Hemorrhage is a composite term of upper gastrointestinal hemorrhage, gastrointestinal hemorrhage, hemoptysis, intestinal hemorrhage, and lower gastrointestinal hemorrhage
[2]Fistula is a composite term of anal fistula, female genital tract fistula, and intestinal fistula

Significant Adverse Events

Refer to Subsection Analysis of Submission-Specific Safety Issues.

Dose Interruptions and Dose-Reductions Due to Adverse Effects

In the FRESCO study, dose modifications were used for 131 (47%) patients on the fruquintinib arm and 18 (13%) patients on the placebo arm. Adverse events leading to dose-interruption occurred 98 (35%) patients in the fruquintinib arm and 14 (10%) patients in the placebo arm. The most common reasons for dose-interruption in the fruquintinib arm included thrombocytopenia (7%), palmar-plantar erythrodysesthesia syndrome (7%), and proteinuria (7%).

Adverse events leading to dose-reductions occurred in 67 (24%) of patients in the fruquintinib arm and 6 (4.4%) patients in the placebo arm. The most common reasons for dose-reductions in the fruquintinib arm included palmar-plantar erythrodysesthesia syndrome (7%), proteinuria (6%), and thrombocytopenia (2.9%). Table 19 summarizes the TEAEs leading to dose interruption or dose-reduction in the FRESCO study.

Table 33. FRESCO: TEAEs Leading to Dose-Interruption or Dose-Reduction

	Fruquintinib + BSC N=278; n (%)	Placebo + BSC N=137; n (%)
Dose-Interruption (>2% Incidence)		
Thrombocytopenia[1]	20 (7.2)	1 (0.7)
Palmar-plantar erythrodysesthesia syndrome	19 (6.8)	0
Proteinuria[2]	18 (6.5)	1 (0.7)
ALT increased	7 (2.5)	1 (0.7)
Diarrhea	6 (2.2)	0
Hypertension	6 (2.2)	0
Dose-Reduction (>1% Incidence)		

Palmar-plantar erythrodysesthesia syndrome	19 (6.8)	0
Proteinuria[2]	16 (5.8)	0
Thrombocytopenia[1]	8 (2.9)	0
Hypertension	7 (2.5)	0
Diarrhea	4 (1.4)	0
Aspartate aminotransferase increased	3 (1.1)	0
Hemorrhage[3]	3 (1.1)	1 (0.7)

[1]Thrombocytopenia is a composite term that includes platelet count decreased and thrombocytopenia.
[2]Proteinuria is a composite term that includes proteinuria and protein urine present.
[3]Hemorrhage is a composite term that includes epistaxis, hematochezia, upper gastrointestinal hemorrhage, and vaginal hemorrhage.

Dropouts and/or Discontinuations Due to Adverse Effects

In the FRESCO study, 41 (15%) patients in the fruquintinib arm and 7 (5%) patients in the placebo arm discontinued treatment because of an AE. The most common reasons for drug discontinuation in the occurring more frequently in the fruquintinib arm were proteinuria (0.9%), hemorrhage, and hepatic function abnormal. Table 34 summarizes the AEs leading to drug discontinuation in the FRESCO study.

Table 34. FRESCO: AEs leading to treatment discontinuation

	Fruquintinib + BSC N=278; n (%)	Placebo + BSC N=137; n (%)
Drug Discontinuation (>0.5% Incidence)		
Proteinuria[1]	9 (3.2)	1 (0.7)
Hemorrhage[2]	4 (1.4)	0
Hepatic function abnormal	4 (1.4)	0
Intestinal obstruction	3 (1.1)	1 (0.7)
Intestinal perforation	2 (0.7)	0

[1]Proteinuria is a composite term that includes proteinuria and protein urine present.
[2]Hemorrhage is a composite term that includes intestinal hemorrhage, lower gastrointestinal hemorrhage, and upper gastrointestinal hemorrhage.

Treatment Emergent Adverse Events and Adverse Reactions

In the FRESCO study, the most common AEs (all grades) in the fruquintinib arm were hypertension (61%), proteinuria (54%), palmar-plantar erythrodysesthesia syndrome (49%), hepatotoxicity (48%), dysphonia (38%), and stomatitis (33%). The most common Grade ≥ 3 AEs in the fruquintinib arm were hypertension (23%), palmar-plantar erythrodysesthesia syndrome (11%), and hepatotoxicity (8%).

The most common AEs (all grades) in the placebo arm were proteinuria (29%), hepatotoxicity (26%), abdominal pain (18%), hypertension (17%), hemorrhage (14%), and decreased appetite (14%). Patients with Grade 1 proteinuria were allowed to be enrolled, and the majority of proteinuria events were Grade 1. The most common Grade ≥ 3 AEs in the placebo arm were hepatotoxicity (8%) and hypertension (2%).

The most common adverse events observed on the fruquintinib are consistent with the class effects that have been observed with VEGF/R inhibitors. There do not appear to be any new safety signals apparent that have not been observed previously with other drugs in the same class. The most common adverse events observed in the placebo arm are generally consistent with the underlying disease of metastatic colorectal cancer. As observed in FRESCO-2, although more patients in the fruquintinib arm in FRESCO experienced hepatotoxicity, the proportion of patients with Grade ≥ 3 hepatotoxicity was similar both arms. Table 35 summarizes the most common AEs in FRESCO (8%).

Table 35. FRESCO: Most Common TEAEs (>10% Incidence, Safety Population)

	Fruquintinib + BSC N=278; n (%)		Placebo + BSC N=137; n (%)	
AE	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**
Hypertension[1]	170 (61.2)	65 (23.4)	23 (16.8)	3 (2.2)
Proteinuria[2]	149 (53.6)	12 (4.3)	39 (28.5)	0
Palmar-plantar erythrodysesthesia syndrome	137 (49.3)	30 (10.8)	4 (2.9)	0
Hepatotoxicity[3]	133 (47.8)	21 (7.6)	35 (25.5)	11 (8.0)
Dysphonia	105 (37.8)	0	2 (1.5)	0
Stomatitis[4]	92 (33.1)	2 (0.7)	4 (2.9)	0
Abdominal pain[5]	81 (29.1)	11 (4.0)	24 (17.5)	2 (1.5)
Hemorrhage[6]	77 (27.7)	5 (1.8)	19 (13.9)	0
Diarrhea[7]	71 (25.5)	10 (3.6)	8 (5.8)	0
Blood TSH increased	71 (25.5)	0	3 (2.2)	0
Fatigue[8]	68 (24.5)	7 (2.5)	18 (13.1)	2 (1.5)
Decreased appetite	68 (24.5)	6 (2.2)	19 (13.9)	1 (0.7)
Thrombocytopenia[9]	58 (20.9)	11 (4.0)	4 (2.9)	0
Weight decreased	58 (20.9)	4 (1.4)	12 (8.8)	0
Musculoskeletal pain[10]	58 (20.9)	6 (2.2)	8 (5.8)	2 (1.5)
Hypothyroidism	46 (16.5)	0	3 (2.2)	0
Occult blood positive	46 (16.5)	0	11 (8.0)	0
Back pain[11]	43 (15.5)	5 (1.8)	8 (5.8)	0
Constipation	41 (14.7)	0	13 (9.5)	2 (1.5)
Cough	41 (14.7)	0	15 (10.9)	0
Pyrexia	31 (11.2)	1 (0.4)	9 (6.6)	0

Blood alkaline phosphatase increased	31 (11.2)	3 (1.1)	13 (9.5)	1 (0.7)
White blood cell count decreased	29 (10.4)	0	4 (2.9)	1 (0.7)
Blood LDH increased	28 (10.1)	1 (0.4)	6 (4.4)	0

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 5.0 (NCI CTCAE v5)
[1]Hypertension is a composite term that includes hypertension, pre-hypertension, and blood pressure increased
[2]Proteinuria is a composite term that includes proteinuria and protein urine present
[3]Hepatotoxicity is a composite term that includes liver injury, hepatic function abnormal, aspartate aminotransferase increased, alanine aminotransferase increased, alanine aminotransferase abnormal, blood bilirubin increased, bilirubin conjugated increased, and hyperbilirubinemia.
[4]Stomatitis is a composite term that includes stomatitis, mouth ulceration, apthous ulcer, oral mucosal blistering, oral pain, oral discomfort, oral dysesthesia, gingival pain, gingival swelling, gingival ulceration, oropharyngeal pain, oropharyngeal discomfort
[5]Abdominal pain is a composite term that includes abdominal pain, abdominal pain lower, abdominal pain upper, abdominal discomfort, epigastric discomfort, and hepatic pain
[6]Hemorrhage is a composite term that includes hemorrhage, anal hemorrhage, hematochezia, hemorrhoid hemorrhage, intestinal hemorrhage, gastrointestinal hemorrhage, lower gastrointestinal hemorrhage, upper gastrointestinal hemorrhage, anastomotic hemorrhage, stoma site hemorrhage, hematuria, hemorrhage urinary tract, and hemoptysis
[7]Diarrhea is a composite term that includes diarrhea, colitis, and frequent bowel movements
[8]Fatigue is a composite term that includes fatigue and asthenia
[9]Thrombocytopenia is a composite term that includes thrombocytopenia and platelet count decreased
[10]Musculoskeletal pain is a composite term that includes musculoskeletal pain, myalgia, musculoskeletal chest pain, non-cardiac chest pain, pain in extremity, bone pain, neck pain, musculoskeletal discomfort, and musculoskeletal stiffness
[11]Back pain is a composite term that includes back pain and spinal pain

Laboratory Findings

Laboratory abnormalities (hematology, liver tests, kidney function tests, and electrolytes) in the fruquintinib and placebo arms were primarily Grade 1-2. In FRESCO, the most common laboratory abnormalities on the fruquintinib arm were creatinine increased (87%), glucose increased (43%), AST increased (42%), ALP increased (40%), and bilirubin increased (39%). The most common Grade 3 or Grade 4 chemistry laboratory abnormalities were urate increased (26%), bilirubin increased (4.7%), ALP increased (4.3%), and AST increased (3.6%).

As expected, the most common hematology laboratory abnormality in the fruquintinib arm was decreased platelets (29% and 6% of patients in the fruquintinib arm and placebo arm respectively). Grade 3 or Grade 4 decreased platelets occurred in only 3.6% of patients on the fruquintinib arm and 0.6% of patients on the placebo arm. The observed thrombocytopenia may have contributed to the greater proportion of patients with hemorrhage in the fruquintinib arm (28%) relative to the placebo arm (14%).

Table 36. FRESCO: Laboratory Abnormalities Worsening from Baseline Occurring in ≥ 20% of Patients

Laboratory Abnormality	Fruquintinib + BSC (N=278)[1]		Placebo + BSC (N=137)[1]	
	All Grades[1] (%)[2]	Grade 3[1] or 4 (%)[2]	All Grades[1] (%)[2]	Grade 3[1] or 4 (%)[2]
Chemistry				
Creatinine Increased	87	0.7	75	1.5
Glucose Increased	43	1.1	31	3.0
AST Increased	42	3.6	31	1.5
Alkaline Phosphatase Increased	40	4.3	34	6
Bilirubin Increased	39	4.7	34	8
ALT Increased	33	2.2	18	1.5
Sodium Decreased	33	6	31	5
Urate Increased	26	26	22	22
Calcium Decreased	25	0.4	13	0
Potassium Decreased	22	1.8	15	2.3
Hematology				
Platelets Decreased	29	3.6	6	0.7
Hemoglobin Decreased	23	0.7	33	4.5

[1] Graded according to NCI CTCAE version 4.03.
[2] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: FRUZAQLA (range: 257-277) and placebo (range: 126-134).

Vital Signs

No clinically relevant changes occurred for vital sign indicators other than blood pressure. See section 8.2.5.1 for a discussion of hypertension as an adverse event of special interest.

Electrocardiograms (ECGs)

Refer to Section 9.2.4 above (interdisciplinary review team for cardiac safety studies review). Fruquintinib does not cause a mean increase in QTc interval > 20 milliseconds (ms) at the proposed recommended dosage.

Immunogenicity

Not applicable.

8.2.6 Analysis of Submission-Specific Safety Issues

The incidence of the AESIs appears consistent with the pharmacologic class. With the exception of hypertension, most AEs were Grade 1 or Grade 2. Palmar-plantar erythrodysesthesia syndrome, a known effect of small molecules inhibiting VEGFR, was among the most common reasons for dose modifications in the FRESCO-2 study. Serious complications such as Grade ≥ 3 gastrointestinal perforation of fistula did occur more frequently with fruquintinib (2.6%) than with placebo (0.9%). One (0.2%) patient in the fruquintinib arm experienced a case of Grade 4 posterior reversible encephalopathy syndrome (PRES).

Table 37. FRESCO-2: Adverse Events of Special Interest

	Fruquintinib + BSC N=456; n (%)		Placebo + BSC N=230; n (%)	
AE	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**
Hypertension[1]	176 (38.6)	65 (14.3)	20 (8.7)	2 (0.9)
Stomatitis[2]	142 (31.1)	10 (2.2)	18 (7.8)	1 (0.4)
Thyroid dysfunction[3]	135 (27.0)	2 (0.4)	4 (1.7)	0
Hepatotoxicity[4]	98 (21.5)	32 (7.0)	27 (11.7)	14 (6.1)
Palmar-plantar erythrodysesthesia syndrome	88 (19.3)	29 (6.4)	6 (2.6)	0
Proteinuria[5]	80 (17.5)	8 (1.8)	12 (5.2)	2 (0.9)
Dysphonia[6]	80 (17.5)	0	12 (5.2)	0
Hemorrhage[7]	61 (13.4)	8 (1.8)	21 (9.1)	4 (1.7)
Rash[8]	25 (5.5)	0	8 (3.5)	1 (0.4)
Gastrointestinal perforation or fistula[9]	16 (3.5)	12 (2.6)	2 (0.9)	2 (0.9)
Thrombotic Events[10]	17 (3.7)	11 (2.4)	4 (1.7)	1 (0.4)
Left Ventricular Dysfunction[11]	5 (1.1)	3 (0.7)	1 (0.4)	1 (0.4)
Wound healing difficulty[12]	1 (0.2)	0	0	0
Posterior reversible encephalopathy syndrome	1(0.2)	1 (0.2)	0	0

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 5.0 (NCI CTCAE v5)

[1]Hypertension is a composite term that includes hypertension, blood pressure increased, blood pressure diastolic increased, diastolic hypertension, and hypertensive crisis
[2]Stomatitis is a composite term that includes stomatitis, mucosal inflammation, apthous ulcer, oral pain, oral dysesthesia, oral discomfort, glossodynia, glossitis, gingival pain, oropharyngeal pain, oropharyngeal discomfort
[3]Thyroid dysfunction is a composite term for hypothyroidism, hyperthyroidism, thyroid disorder, thyroxine free decreased, tri-iodothyronine increased, and blood TSH increased
[4]Hepatotoxicity is a composite term that includes hepatotoxicity, hepatic failure, hepatic cytolysis, hepatic function abnormal, aspartate aminotransferase increased, aspartate aminotransferase abnormal, alanine aminotransferase increased, blood bilirubin increased, bilirubin conjugated increased, hypertransaminasemia, hyperbilirubinemia, hepatitis, liver function test increased, and liver function test abnormal
[5]Proteinuria is a composite term that includes proteinuria, and protein urine present
[6]Dysphonia is a composite term that includes dysphonia and aphonia
[7]Hemorrhage is a composite term that includes hemorrhage, conjunctival hemorrhage, eye hemorrhage, anal hemorrhage, gastric hemorrhage, anal hemorrhage, gastric hemorrhage, gastrointestinal hemorrhage, hemorrhoidal hemorrhage, upper gastrointestinal hemorrhage, rectal hemorrhage, post-procedural hemorrhage, stoma-site hemorrhage, cerebral hemorrhage, vaginal hemorrhage, pulmonary hemorrhage, epistaxis, intermenstrual bleeding, gingival bleeding, hemoptysis, hematochezia, hematemesis, and hematuria
[8]Rash is a composite term that includes rash, rash erythematous, rash macular, rash maculopapular, and rash pruritis
[9]Gastrointestinal perforation or fistula is a composite term that includes gastrointestinal perforation, gastric perforation, intestinal perforation, small intestine perforation, large intestine perforation, and rectal perforation
[10]Thrombotic events is a composite term that includes pulmonary embolism, portal vein thrombosis, device-related thrombosis hepatic vein thrombosis, deep vein thrombosis, venous thrombosis, thrombosis, vena cava thrombosis, cerebrovascular accident, cerebral infarction, pulmonary artery occlusion and acute myocardial infarction
[11]Left ventricular dysfunction is a composite term that includes cardiac failure, cardiac failure congestive, and left ventricular dysfunction.
[12]Wound healing difficulty is a composite term that includes only the term wound dehiscence

In the FRESCO study, overall, a greater proportion of patients experienced AESIs than did in the FRESCO-2 study. Among the most notable differences between the two studies was the difference in the incidence of palmar-plantar erythrodysesthesia syndrome (49% and 19% in FRESCO and FRESCO-2 respectively) in patients treated with fruquintinib arm. The potential role of a more diverse population in the decreased incidence of palmar-plantar erythrodysesthesia in FRESCO-2 cannot be explored with the existing data and the reasons for the difference remain unclear. .

Table 38. FRESCO: Adverse Events of Special Interest

	Fruquintinib + BSC N=278; n (%)		Placebo + BSC N=137; n (%)	
AE	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**
Hypertension[1]	170 (61.2)	65 (23.4)	23 (16.8)	3 (2.2)
Proteinuria[2]	149 (53.6)	12 (4.3)	39 (28.5)	0
Palmar-plantar erythrodysesthesia syndrome	137 (49.3)	30 (10.8)	4 (2.9)	0

Hepatotoxicity[3]	133 (47.8)	21 (7.6)	35 (25.5)	11 (8.0)
Dysphonia	105 (37.8)	0	2 (1.5)	0
Stomatitis[4]	92 (33.1)	2 (0.7)	4 (2.9)	0
Hemorrhage[5]	77 (27.7)	5 (1.8)	19 (13.9)	0
Thyroid dysfunction[6]	67 (24.1)	0	9 (6.6)	0
Rash[7]	25 (9.0)	0	2 (1.5)	0
GI perforation or fistula[8]	6 (2.2)	5 (1.8)	1 (0.7)	0
Thrombotic events[9]	3 (1.1)	1 (0.4)	1 (0.7)	0
Left ventricular dysfunction[10]	3 (1.1)	1 (0.4)	1 (0.7)	0

[1]Hypertension is a composite term that includes hypertension, pre-hypertension, and blood pressure increased
[2]Proteinuria is a composite term that includes proteinuria and protein urine present
[3]Hepatotoxicity is a composite term that includes liver injury, hepatic function abnormal, aspartate aminotransferase increased, alanine aminotransferase increased, alanine aminotransferase abnormal, blood bilirubin increased, bilirubin conjugated increased, and hyperbilirubinemia.
[4]Stomatitis is a composite term that includes stomatitis, mouth ulceration, apthous ulcer, oral mucosal blistering, oral pain, oral discomfort, oral dysesthesia, gingival pain, gingival swelling, gingival ulceration, oropharyngeal pain, oropharyngeal discomfort
[5]Hemorrhage is a composite term that includes hemorrhage, anal hemorrhage, hematochezia, hemorrhoid hemorrhage, intestinal hemorrhage, gastrointestinal hemorrhage, lower gastrointestinal hemorrhage, upper gastrointestinal hemorrhage, anastomotic hemorrhage, stoma site hemorrhage, hematuria, hemorrhage urinary tract, and hemoptysis
[6]Thyroid dysfunction is a composite term that includes hypothyroidism, hyperthyroidism, thyroid disorder, thyroid disfunction abnormal, thyroid hormones increased, thyroxine decreased, thyroxine free decreased, thyroxine increased, thyroxine free increased, tri-iodothyronine decreased, tri-iodothyronine increased, tri-iodothyronine free decreased, tri-iodothyronine increased
[7]Rash is a composite term that includes rash and rash maculopapular
[8]GI perforation or fistula is a composite term that includes only the term intestinal perforation
[9]Thrombotic events is a composite term that includes pulmonary embolism, venous thrombosis, venous thrombosis limb, cerebrovascular accident, and cerebral infarction
[10]Left ventricular dysfunction is a composite term that includes left ventricular dysfunction and left ventricular hypertrophy

Hypertension

Both the FRESCO-2 and FRESCO studies excluded patients with uncontrolled hypertension, defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg despite optimal medical management. In the FRESCO-2 trial, hypertension was reported as an AE in 38.6% and 8.7% of patients on the fruquintinib and placebo arms, respectively; 14.3% and 0.9% of patients on the fruquintinib and placebo arms, respectively had Grade ≥3 events. In the FRESCO trial, hypertension

was reported as an AE in 61.2% and 16.8% of patients on the fruquintinib and placebo arms, respectively; 23.4% and 2.2% of patients on the fruquintinib and placebo arms, respectively had Grade ≥3 events.

Based on blood pressure assessment data, Grade 3 hypertension occurred in 117 (26%) patients in the fruquintinib arm and 9 (3.9%) patients in the placebo in the FRESCO-2 study and 57 (21%) patients in the fruquintinib arm and 6 (4.4%) in the placebo arm in the FRESCO study. CTCAE includes treatment received in the categorization of the severity of hypertension. As expected, based on blood pressure analysis, elevated blood pressure was observed more frequently that the incidence reported as an AE. The results of the analysis in both fruquintinib arms are similar; differences in blood pressure across the placebo arms are likely multifactorial and there is inherent variability across clinical trials that could contribute to these differences. An analysis of hypertension based on blood pressure assessments throughout treatment is included in Table 25.

Table 39. Evaluation of Hypertension Based on Blood Pressure Assessments

	FRESCO-2		FRESCO	
	Fruquintinib + BSC N=456; n (%)	**Placebo + BSC N=230; n (%)**	**Fruquintinib + BSC N=278; n (%)**	**Placebo + BSC N=137; n (%)**
Any Grade: SBP ≥ 120 mmHg or DBP ≥ 80 mmHg	437 (95.8)	188 (81.7)	272 (97.8)	121 (88.3)
Grade 1: SBP 120-139 mmHg or DBP 80 – 89 mmHg	126 (27.6)	96 (41.7)	90 (32.4)	89 (65.0)
Grade 2: SBP 140-159 mmHg or DBP 90 – 99 mmHg	194 (42.5)	83 (36.1)	125 (45.0)	26 (19.0)
Grade 3: SBP ≥ 160 mmHg or DBP ≥ 100 mmHg	117 (25.7)	9 (3.9)	57 (20.5)	6 (4.4)

Hemorrhagic Events

Hemorrhages were reported in 61 (13%) and 21 (9%) patients on the fruquintinib and placebo arms, respectively, in the FRESCO-2 trial. Events were mostly Grade 1-2. The most common event was epistaxis, which occurred in 18 (3.9%) patients on the fruquintinib arm and 3 (1.3%) on the placebo arm. Grade ≥ 3 hemorrhage occurred in 8 (1.8%) patients on the fruquintinib arm and 4 (1.7%) on the placebo arm. No fatal events of hemorrhage occurred on the FRESCO-2 trial.

In the FRESCO trial, hemorrhage was reported in 77 (28%) and 19 (14%) of patients on the fruquintinib and placebo arms, respectively. Like in the FRESCO-2 trial, events of hemorrhage were mostly Grade 1-2. The most common event was epistaxis, which occurred in 25 (9%) patients on the fruquintinib arm and 2 (1.5%) patients on the placebo arm. Grade ≥ 3 hemorrhage occurred in 5 (1.8%) patients on the fruquintinib arm including two fatal events. There were no events of Grade ≥ 3 hemorrhage on the placebo arm.

Arterial Thrombotic Events
Few events of arterial thrombotic events were observed in FRESCO-2 and FRESCO. Events in FRESCO-2 included transient ischemic attack (n=1), acute myocardial infarction (n=1), and cerebral infarction (n=1) in the fruquintinib arm and . cerebrovascular accident (n=1) in the placebo arm. No fatal events of arterial thrombosis occurred on the FRESCO-2 trial. In the FRESCO trial, arterial thrombotic events were reported in 3 patients in the fruquintinib arm (cerebrovascular accident, transient ischemic attack, and fatal cerebral infarction. No arterial thrombotic events were reported in the placebo arm in FRESCO.

Gastrointestinal Perforation
Gastrointestinal perforation occurred in 10 (2.2%) and 0% of patients on the fruquintinib and placebo arms, respectively, in the FRESCO-2 trial, including one fatal event. On the FRESCO trial, gastrointestinal perforation of any grade occurred in 2 (0.7%) patients, all in the fruquintinib arm. No fatal events of gastrointestinal perforation occurred on the FRESCO trial.

Wound Healing
Impairment of wound healing has been associated with other inhibitors of the VEGF/R pathway. A single case (0.2%) of wound dehiscence (Grade 2) occurred in the fruquintinib arm on the FRESCO-2 study. No events of impaired wound healing were reported on the FRESCO trial.

Hepatotoxicity
The most common AEs were liver transaminases or increased bilirubin; these findings are consistent with FDA's review of the laboratory datasets. Although increased transaminases and bilirubin were more frequently observed in the fruquintinib arms, most of these were Grade 1-2. Table 39 and Table 40 summarize the laboratory assessment of liver abnormalities from FRESCO-2 and FRESCO, respectively.

Table . FRESCO-2: Laboratory Assessment of Liver Abnormalities

Laboratory Abnormality	FRUZAQLA (N=456)[1]		Placebo (N=230)[1]	
	All Grades[1] (%)[2]	Grade 3[1] or 4 (%)[2]	All Grades[1] (%)[2]	Grade 3[1] or 4 (%)[2]
AST or ALT Increased	39	6	27	2.8
Bilirubin Increased	30	7	21	8
Alkaline Phosphatase Increased	20	1.6	26	0.5

[1] Graded according to NCI CTCAE version 5.0.
[2] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: FRUZAQLA (range: 441-443) and placebo (range: 214-216).

Table 40. FRESCO: Laboratory Assessment of Liver Abnormalities

Laboratory Abnormality	FRUZAQLA (N=278)[1]		Placebo (N=137)[1]	
	All Grades[1] (%)[2]	Grade 3[1] or 4 (%)[2]	All Grades[1] (%)[2]	Grade 3[1] or 4 (%)[2]
AST or ALT Increased	43	4.3	30	2.2
Bilirubin Increased	39	4.7	34	8
Alkaline Phosphatase Increased	40	4.3	34	6

[1] Graded according to NCI CTCAE version 4.03.
[2] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: FRUZAQLA (range: 276-277) and placebo (range: 134-134).

Since the majority of patients in FRESCO-2 and FRESCO (72%) had liver metastases, assessment of hepatotoxicity can be confounded. To evaluate the potential for drug-induced liver injury, analyses of adverse events in the hepatobiliary disorders system organ class (SOC) and the laboratory dataset was performed accounting for status of liver metastatic disease. One patient met the criteria for Hy's law based upon laboratory criteria. The patient had LFT values within normal limits at the end of his treatment (Day 21) and 58 days after, his LFTs were elevated with AST of 171 u/L (5-33 u/L), ALT of 270 u/L (5-45 u/L), and the total bilirubin was 4.8 mg/dL (0.2-1.0 mg/dL). Given the short-half-life of fruquintinib ($T_{1/2}$ ~42 hours), the timeline of this event would preclude conclusions of relatedness to study drug.

In the FRESCO-2 trial, adverse events in the hepatobiliary disorders SOC occurred more frequently in patients with liver metastases. Among patients with liver metastatic disease, 63 (19%) patients in the fruquintinib arm and 29 (19%) patients in the placebo arm had a liver-related AE. There were 2 (0.6%) and 2 (1.3%) fatal liver-related events in the fruquintinib and placebo arms respectively. AEs in hepatobiliary disorders SOC in patients without liver metastasis were not life-threatening. Results of FDA's analysis are summarized in Table 42.

Table 41. FRESCO-2: Liver-Related Toxicities

	Fruquintinib + BSC N=456; n (%)		Placebo + BSC N=230; n (%	
	Patients with Liver metastasis (N=335)	Patients without Liver Metastasis (N=121)	Patients with Liver metastasis (N=155)	Patients without Liver Metastasis (N=75)
Any Event	63 (18.8)	6 (5.0)	29 (18.7)	0
Grade 3	18 (5.4)	3 (2.5)	10 (6.5)	0

Grade 4	2 (0.6)	0	1 (0.6	0
Grade 5	2 (0.6)	0	2 (1.3)	0
Laboratory assessments				
AST or ALT >3x ULN*	79 (23.6)	13 (10.7)	38 (24.5)	5 (6.7)
Total Bili. > 2 x ULN	43 (12.8)	5 (4.1)	24 (15.5)	0
AST or ALT >3x and Bili. > 2x ULN	24 (7.2)	3 (2.5)	17 (11.0)	0
Hy's Law lab. Criteria**	0	1 (0.8)	3 (1.9)	0

Similarly, in the FRESCO trial, adverse events in the hepatobiliary disorders SOC occurred more frequently in patients with liver metastases. Table 43 summarizes the analysis of liver-related AEs and lab abnormalities in the FRESCO trial. There was one event in the fruquintinib arm that met the laboratory criteria for Hy's law but is highly confounded by prior liver-directed radiotherapy and simultaneous assessment of liver metastatic disease progression. Results of FDA's analysis are summarized in Table 43.

Table 42. FRESCO: Liver Related Toxicities

	Fruquintinib + BSC N=278; n (%)		**Placebo + BSC N=137; n (%)**	
	Patients with Liver metastasis (N=185)	Patients without Liver Metastasis (N=93)	Patients with Liver metastasis (N=102)	Patients without Liver Metastasis (N=35)
Any Event	30 (16.2)	7 (7.5)	7 (6.9)	1 (2.9)
Grade 3	10 (5.4)	2 (2.2)	2 (2.0)	0
Grade 4	5 (2.7)	1 (1.1)	0	0
Grade 5	0	0	0	0
Laboratory assessments				
AST or ALT >3x ULN*	28 (15.1)	3 (3.2)	8 (7.8)	1 (2.9)
Total Bili. > 2 x ULN	30 (16.2)	1 (1.1)	10 (9.8)	1 (2.9)
AST or ALT >3x and Bili. > 2x ULN	14 (7.6)	0	1 (1.0)	1 (2.9)

Hy's Law lab. Criteria**	1 (0.5)	0	0	0

As summarized above, the most common liver lab abnormalities and liver-related AEs were increased AST and ALT, or increased total bilirubin, and these events were more frequently reported in the fruquintinib arms. However, the analysis based on presence of liver metastatic disease shows that the incidence of these AEs and laboratory abnormalities were similar between the fruquintinib and placebo treatment arms. An increased risk for fatal or drug-induced liver injury meeting Hy's law criteria was not observed in FRESCO-2 or FRESCO; however, there is a modest increase in the risk of hepatic toxicity (consistent with the pharmacologic class), which can be mitigated through adequate monitoring. The product labeling has been revised accordingly.

Thyroid Dysfunction
In the FRESCO-2 study, thyroid dysfunction (preferred terms: hypothyroidism, hyperthyroidism, thyroid disorder, thyroxine free decreased, tri-iodothyronine increased, and blood TSH increased) occurred in 135 (27%) patients on the fruquintinib arm and 4 (1.7%) patients on the placebo arm. Grade ≥ 3 thyroid dysfunction occurred in two (0.4%) patients on the fruquintinib arm and no patients on the placebo arm.

In the FRESCO trial, thyroid dysfunction (hypothyroidism, hyperthyroidism, thyroid disorder, thyroid function abnormal, thyroid hormones increased, thyroxine decreased, thyroxine free decreased, thyroxine increased, thyroxine free increased, tri-iodothyronine decreased, trio-iodothyronine increased, trio-iodothyronine free decreased, tri-iodothyronine free increased) occurred in 67 (24%) patients on the fruquintinib arm and 9 (7%) patients on the placebo arm. There were no Grade ≥ 3 AEs on either treatment arm.

Proteinuria
Proteinuria was reported as an AE in 80 (18%) and 12 (5%) patients on the fruquintinib and placebo arms, respectively, in the FRESCO-2 trial. Grade ≥ 3 events occurred in 8 (1.8%) and 2 (0.9%) patients on the fruquintinib and placebo arms, respectively. In the FRESCO trial, proteinuria occurred in 149 (54%) and 39 (28%) patients on the fruquintinib and placebo arms, respectively. Grade ≥ 3 events occurred in 12 (4.3%) patients, all in the fruquintinib arm. Review of urine protein testing from the FRESCO-2 study show a higher incidence of proteinuria. The study allowed enrollment of patients with Grade 1 proteinuria. Patients in the fruquintinib arm had higher incidence of Grade 2 proteinuria (23% and 4.4% in the fruquintinib and placebo arms respectively). Grade 3 proteinuria was infrequent (Table 44).

Table 43. FRESCO-2: Proteinuria

	Fruquintinib + BSC N=456; n (%)	**Placebo + BSC N=230; n (%)**

Preferred Term	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Proteinuria	126 (27.6)	105 (23.0)	5 (1.1)	60 (26.1)	20 (4.4)	0

8.2.7 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Patient-reported tolerability was not adequately assessed. For example, symptoms related to dysphonia or palmar-plantar erythrodysesthesia syndrome were not assessed using patient-reported outcomes. Therefore, tolerability assessment using PROs could not be performed by FDA.

8.2.8. Safety Analyses by Demographic Subgroups

There were no major differences in AEs by sex. For both males and females, treatment with fruquintinib arm resulted in an increased incidence of AEs. Table 45 summarizes the major safety outcomes by sex.

Table 44. FRESCO-2: Major Safety Outcomes by Sex

	Fruquintinib + BSC Male N=245; n (%)	Fruquintinib + BSC Female N=216; n (%)	Placebo + BSC Male N=140; n (%)	Placebo + BSC Female N=90; n (%)
Any Grade AEs	238 (97.1)	213 (98.6)	127 (90.7)	86 (95.6)
Grade ≥ 3 AEs	147 (59.2)	139 (64.4)	68 (48.6)	48 (53.3)
SAEs	93 (38.0)	76 (35.2)	58 (41.4)	31 (34.4)
Dose-Interruption	115 (46.9)	98 (45.4)	36 (25.7)	26 (28.9)
Dose-Reduction	47 (19.2)	63 (29.2)	2 (1.4)	7 (7.8)
Drug-Discontinuation	45 (18.4)	48 (22.2)	29 (20.7)	20 (22.2)

There were no major differences in AEs by age. Table 46 summarizes the major safety outcomes by age group (<65 and ≥ 65 years old).

Table 45. FRESCO-2: Major Safety Outcomes by Age

	Fruquintinib + BSC < 65 years N=247; n (%)	Fruquintinib + BSC ≥ 65 years N=214; n (%)	Placebo + BSC < 65 years N=119; n (%)	Placebo + BSC ≥ 65 years N=111; n (%)
Any Grade AEs	240 (97.2)	211 (98.6)	108 (90.8)	105 (94.6)
Grade ≥ 3 AEs	153 (61.9)	133 (62.1)	53 (44.5)	63 (56.8)
SAEs	93 (37.7)	76 (35.5)	41 (34.5)	48 (43.2)
Dose-Interruption	108 (43.7)	105 (49.1)	29 (24.4)	33 (29.7)

Dose-Reduction	57 (23.1)	53 (24.8)	5 (4.2)	4 (3.6)
Drug-Discontinuation	44 (17.8)	49 (22.9)	24 (20.2)	25 (22.5)

A total of 33 Black or African-American patients have been treated across a variety of doses in the development program for fruquintinib. A total of 21 Black or African-American patients with mCRC have been treated with the dosing regimen used in FRESCO and FRESCO-2, 5 mg PO QD for 3 weeks on/1 week of fruquintinib. Only 13 (2.8%) Black or African American patients were treated on the pivotal, randomized, double-blind FRESCO-2 study and none were treated on the FRESCO study. Hypertension, proteinuria, and hand-foot skin reaction were among the most common AEs among all racial groups, but given the small number of Black or African-American patients, the data is not sufficient to adequately characterize the safety. Refer to Section 13 for FDA's request for additional studies to characterize the safety of fruquintinib in underrepresented minorities. Table 47 summarizes the major safety outcomes by race.

Table 46. FRESCO-2: Major Safety Outcomes by Race

	Asian N=42; n (%)	**Black N=13; n (%)**	**White N=364; n (%)**	**Other N=37; n (%)**
Any Grade AEs	41 (97.6)	13 (100)	360 (98.9)	37 (100)
Grade ≥ 3 AEs	29 (69.0)	9 (69.2)	222 (61.0)	26 (70.3)
SAEs	18 (42.9)	7 (53.8)	129 (35.4)	15 (40.5)
Dose-Interruption	20 (47.6)	5 (38.5)	175 (48.1)	13 (35.1)
Dose-Reduction	20 (47.6)	3 (23.1)	78 (21.4)	9 (24.3)
Drug-Discontinuation	7 (16.7)	3 (23.1)	73 (20.1)	10 (27.0)

A total of 35 Hispanic patients have been treated across a variety of doses in the development program for fruquintinib. A total of 22 Hispanic patients with mCRC have been treated with the dosing regimen used in FRESCO-2 and FRESCO. Only 20 (4.3%) Hispanic patients received treatment with fruquintinib on the FRESCO-2 study. Given the limited number of patients, the data is not sufficient to adequately characterize the safety. Refer to Section 13 for FDA's request for additional studies to characterize the safety of fruquintinib in underrepresented minorities. Table 48 summarizes the major safety outcomes by ethnicity.

Table 47. FRESCO-2: Major Safety Outcomes by Ethnicity

	Hispanic N=20; n (%)	**Non-Hispanic N=405; n (%)**	**Not Reported N=36; n (%)**
Any Grade AEs	19 (95.0)	397 (98.0)	35 (97.2)
Grade ≥ 3 AEs	11 (55.0)	251 (62.0)	24 (66.7)
SAEs	7 (35.0)	149 (36.8)	13 (36.1)
Dose-Interruption	4 (20.0)	199 (49.1)	10 (27.0)
Dose-Reduction	4 (20.0)	95 (23.5)	11 (29.7)

Drug-Discontinuation	6 (30.0)	76 (18.8)	11 (29.7)

8.2.9 Specific Safety Studies/Clinical Trials

Not applicable.

8.2.10 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Not applicable.

Human Reproduction and Pregnancy

No pregnancies occurred during the FRESCO-2 or FRESCO studies. There is no information to report for use of fruquintinib in pregnancy or lactation.

Pediatrics and Assessment of Effects on Growth

Not applicable.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

8.2.11 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Study 2018-013-00CH2 (NCT04005066) is an open-label, parallel, observational study in cancer patients in China (b) (4) The goal of this study is to further characterize the safety of fruquintinib in a larger size population. As of September 3rd, 2022, a total of 3003 patients were enrolled in 2 cohorts and exposed to fruquintinib, a cohort of patients with mCRC treated in accordance with the fruquintinib package insert and a second cohort of patients with other indications suitable for treatment according to investigator's judgment. According to the Summary of Clinical Safety provided by the applicant, no new safety findings have been identified from the fruquintinib post-marketing study and the safety data are consistent with the established safety profile of fruquintinib.

8.2.12 Integrated Assessment of Safety

The FRESCO-2 study showed a (generable) manageable safety profile among adult patients with refractory unresectable or metastatic CRC which is considered acceptable given the OS benefit observed with fruquintinib. The types of adverse events observed are generally consistent with the known safety profile of inhibitors of the VEGF pathway.

No new safety risks were identified. When they occurred, Grade 3 or 4 events were generally manageable with standard of care and/or dose modifications. The incidence of SAEs and fatal events was similar between the fruquintinib and placebo arms suggesting that most of these events were due to the underlying disease.

Adverse events leading to dose reduction occurred in 24% of patients in the fruquintinib arm, but the median relative dose intensity was 92% indicating that most patients were able to receive the intended dose of fruquintinib over their treatment duration. Although a heavily pretreated, refractory population, 51% of patients remained on treatment with fruquintinib for at least 12 weeks and 24% of patients remained on treatment at least 24 weeks, which is consistent with the effect observed in PFS.

Safety findings from the FRESCO study supported and corroborated those of the FRESCO-2 study with no new safety signals identified.

8.3 Statistical Issues

There were no major statistical issues encountered while reviewing this application. Please refer below for conclusion related to efficacy assessments.

8.4 Conclusions and Recommendations

The clinical and statistical review teams determined that the evidence submitted provides substantial evidence of the effectiveness of fruquintinib for the treatment of patients with metastatic colorectal cancer with disease progression after treatment with a fluoropyrimidine, oxaliplatin, irinotecan, a VEGF inhibitor, and if eligible, an anti-EGFR monoclonal antibody.

The primary support for the effectiveness of fruquintinib for this indication was derived from the results of a multicenter, double-blind, placebo-controlled randomized trial, FRESCO-2. In addition of being refractory to standard of care with chemotherapy and monoclonal antibodies treatment, patients enrolled in FRESCO-2 received prior treatment with regorafenib and/or tipiracil/trifluridine. The major efficacy outcome measure was OS for patients randomized to fruquintinib or placebo. Treatment continued until unacceptable toxicity or disease progression. No crossover from placebo arm to fruquintinib arm was allowed.

The HR for OS was 0.66 (95% CI: 0.55, 0.80; p<0.001) with a median OS of 7.4 months (95% CI: 6.7, 8.2) in the fruquintinib arm and 4.8 months (95% CI: 4.0, 5.8) for the placebo arm. The PFS HR was 0.32 (95% CI: 0.27, 0.39; p<0.001) with a median PFS was 3.7 months (95% CI: 3.5, 3.8) in the fruquintinib arm and 1.8 months (95% CI: 1.8, 1.9) in the placebo arm. FRESCO-2 demonstrated a modest but clinically meaningful, statistically significant improvement in OS. Secondary endpoints, subgroup analyses, and sensitivity analyses were consistent with results for OS and conformed the

robustness of the study results. The safety profile observed in patients receiving fruquintinib on the FRESCO-2 study was consistent with the class effects of inhibition of the VEGF receptors and was manageable with dose modifications and supportive care in most patients.

In support of the FRESCO-2 study, the Applicant submitted a second randomized, double-blind placebo-controlled study, FRESCO. The main differences between FRESCO-2 and FRESCO are that FRESCO was conducted entirely in China, the study was conducted before regorafenib and trifluridine/tipiracil were available and the use of monoclonal antibodies targeting VEGF and EGFR was permitted but not mandated, which resulted in a population that was (previously) treated differently that the standard of care for the treatment in the US.

The HR for OS in FRESCO was 0.65 (95% CI: 0.51, 0.83; p<0.001) with a median OS of 9.3 months (95% CI: 8.2, 10.5) in the fruquintinib arm and 6.6 months (95% CI: 5.9, 8.1) in the placebo arm. The PFS HR was 0.26 (95% CI: 0.21, 0.34) with a median PFS was 3.7 months (95% CI: 3.7, 4.6) in the fruquintinib arm and 1.8 months (95% CI: 1.8, 1.8) in the placebo arm. The safety profile observed in patients receiving fruquintinib on the FRESCO study was consistent with the class effects of inhibition of the VEGF receptors and was manageable with dose-modifications and supportive care in most patients. Ultimately, this study demonstrated a similar magnitude of effect on OS to that which was observed in the later-line FRESCO-2 study. While this FDA approval is based primarily on the FRESCO-2 study, FRESCO provided supportive evidence to extend the indication to patients with no prior treatment with regorafenib and/or trifluridine/tipiracil.

While FRESCO-2 was a multiregional trial, it did not include sufficient number of underrepresented minorities in the study to adequately characterize the effects of fruquintinib in these patient populations. FDA requested the Applicant to conduct a post-marketing study to address this deficiency.

The review team concluded that the overall risk:benefit assessment favored approval of fruquintinib for the treatment of patients with metastatic colorectal cancer with disease progression after treatment with a fluoropyrimidine, oxaliplatin, irinotecan, a VEGF inhibitor, and if eligible, an anti-EGFR monoclonal antibody. The demonstrated improvement in survival for patients randomized to fruquintinib compared to patients randomized to placebo in combination with chemotherapy SOC is clinically meaningful, statistically significant, and supported by subgroup analyses in FRESCO-2. The adverse reaction profile observed in patients receiving fruquintinib is consistent with the adverse reaction profiles observed in the same pharmacological class and the disease setting. The risks of fruquintinib are acceptable considering the life-threatening nature of refractory metastatic colorectal cancer.

X Sirisha L Mushti

Primary Statistical Reviewer

X Joyce Cheng

Statistical Team Leader

X

Primary Clinical Reviewer

X

Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

No advisory committee was convened for this supplemental application as the application did not raise any issues that warranted the committee's input.

10 Pediatrics

Fruquintinib was not studied in pediatric patients with advanced or metastatic colorectal cancer as this disease occurs mainly in adults and rarely in children. Under IND 131038 an initial pediatric study plan (iPSP) was submitted on April 10, 2020. Although VEGFR is a molecular target of interest for pediatric studies, based on the lack of activity observed in pediatric clinical studies with agents with the same mechanism of action as fruquintinib, FDA agreed with the planned request for waiver of pediatric studies and issued a letter agreeing to this plan on July 7, 2020.

An agreed PSP was submitted on August 28, 2020, and FDA issued an agreement letter on September 18, 2020.

The NDA contains a request for a waiver of pediatric studies with fruquintinib, which will be granted.

12 Risk Evaluation and Mitigation Strategies (REMS)

No REMS have been requested. The pharmacological class has been extensively used in cancer patients and the review did not uncover new safety signals. The risks of fruquintinib can be managed with standard of care monitoring and labeling recommendations.

13 Postmarketing Requirements and Commitment

Takeda agreed to the following clinical postmarketing commitment (PMC).

Conduct a clinical study to further characterize the clinical effects of fruquintinib, including pharmacokinetics (PK), activity, blood pressure assessments, and safety events of palmar-plantar erythrodysesthesia in an underrepresented minority population.

Draft Protocol Submission:	05/2024
Final Protocol Submission:	09/2024
Study Completion:	03/2028
Final Report Submission:	12/2028

FDA PMC/PMR Checklist for Trial Diversity and U.S. Population Representativeness

The following were evaluated and considered as part of FDA's review:		**Is a PMC/PMR needed?**
□	The patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication.	X Yes __ No
□	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g. race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	X Yes __ No
□	Other considerations (e.g.: PK/PFS), if applicable:	__ Yes X No

14 Division Director (DHOT)

X

15 Division Director (OCP)

X

16 Division Director (OB) Comments

X

17 Division Director (Clinical) Comments

I agree with the approval recommendations made by the review teams with respect to this NDA.

X Steven Lemery, M.D., M.H.S.

18 Office Director (or designated signatory authority) Comments

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X _____

19 Appendices

19.1 References

Biller L, Schrag D. Diagnosis and Treatment of Metastatic Colorectal Cancer A Review. JAMA. 2021;325(7):669-685
Dekker E, Tanis P, Vleugels, Kasi P, Wallace M. Colorectal Cancer. The Lancet, V34, 10207, p1467-1480, 2019.
Siegel R, Jakubowski C, Fedewa S, Davis An, Azad N. Colorectal Cancer in the Young: Epidemiology, Prevention, Management. American Society of Clinical Oncology Educational Book 40 (April 21, 2020) e75-e88.
Siegel R, Sandeep Wagle N, Cercek A, Smith R, Jemal A. Colorectal cancer statistics, 2023. CA V73,3 May/June 2023: 233-254
Surveillance, Epidemiology and End Results Program (SEER): Cancer Stat Facts: Colorectal Cancer. Colorectal Cancer — Cancer Stat Facts
Venook A, Niedwiezcki, Lenz H, Innocenti F, Fruth B. et al. Effect of First-Line Chemotherapy Combined With Cetuximab or Bevacizumab on Overall Survival in Patients With *KRAS* Wild-Type Advanced or Metastatic Colorectal Cancer. *JAMA*. 2017;317(23):2392-2401

19.2 Financial Disclosure

Disclosure of financial interests of the investigators who conducted the FRESCO-2 and FRESCO were provided, including statements of due diligence (FDA forms 3454) in cases where the Sponsor was unable to obtain a signed form from the investigator.

During the period of interest (FRESCO-2 study conduct + 1 year afterward), (b) (6), a FRESCO-2 investigator at site number (b) (6) received a total of (b) (6) These payments represented remuneration for consulting services provided by (b) (6) to HUTCHMED, including participation in advisory boards and review of a variety of clinical documents for surufatinib and fruquintinib. A total of (b) (6) ((b) (6)% of the study population) were enrolled in (b) (6) center (site # (b) (6)).

As FRESCO-2 was a multicenter randomized study with a primary endpoint of overall survival, it is unlikely that a potential bias was introduced by payments associated with investigators in this clinical site.

Covered Clinical Study: 2019-013- GLOB1 (FRESCO-2)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1520		

Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 29		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): Study 2013-013-00CH1 (FRESCO)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 258		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0		

Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 6		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

19.3 Nonclinical Pharmacology/Toxicology

Not Applicable

19.4 OCP Appendices (Technical documents supporting OCP recommendations)

Summary of bioanalytical method validation and performance

Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

Yes, plasma and urine concentrations of the active parent, fruquintinib and the major metabolite, M11, were measured in the clinical pharmacology and biopharmaceutics studies. At steady-state, the mean M11-to-fruquintinib ratio was approximately 30% for Cmax and $AUC_{0\text{-}24h}$. In vitro, M11 was 10-fold less potent against VEGFR-2 compared to fruquintinib. M11 is not considered as an active metabolite based on its potent against VEGFR-2 and exposure.

For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

The total plasma concentrations of fruquintinib (HMPL-013) and M11 (HM5025423) were measured in the clinical trials. This was appropriate due to the constant plasma protein binding of fruquintinib. The average fraction unbound (fu) value in human plasma proteins of fruquintinib was approximately 5 % and was independent of concentrations (1 to 10 μM). The fu value of M11 was approximately 2% at the concentration of 1 μM.

What bioanalytical methods are used to assess concentrations?
Methods HMPHPP and HM13HPP are used for analysis of human plasma samples as described in Table 49. In method HMPHPP, concentrations were calculated with a $1/x^2$ linear regression over a concentration range of 0.5 to 1000 ng/mL with 8 calibration standards. In method HM13HPP, concentrations were calculated with a $1/x^2$ linear regression over a concentration range of 1 to 750 ng/mL with 8 calibration standards.

Table 48. Bioanalytical method and validation parameters

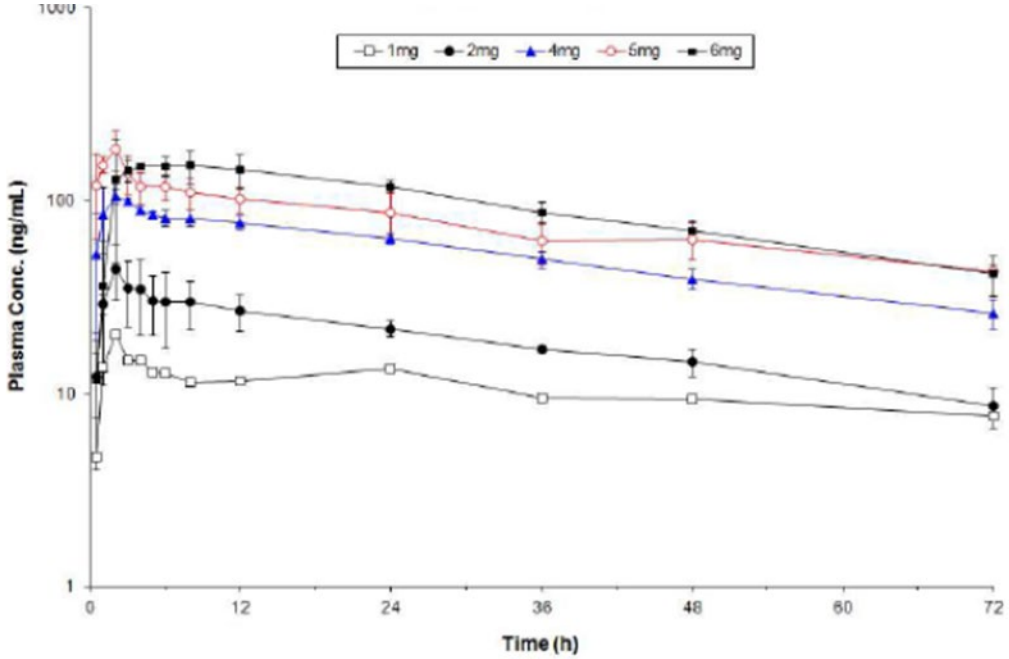
Validation Parameter	Validation at (b) (4) (b) (4)	Validation at (b) (4) (b) (4)	Validation at (b) (4) (b) (4)
Method ID	HMPHPP	HM13HPP	
Calibration range	0.5 to 1000 ng/mL	1.0 to 750 ng/mL	
Analytes	HMPL-013 M2 (HM5012569) M7 (HM5013199)	HMPL-013 M9 (HM5234093) M11 (HM5025423)	
Inter-run precision (CV)	≤ 8.2%	≤ 8.6%	≤ 9.9%
Inter-run bias	-0.4% to 4.0%	-5.2% to 2.2%	-2.3% to 2.0%
Stability in plasma	26 hours at wet ice 192 days at -10°C to -30°C 192 days at -60°C to -80°C	25 hours at RT 820 days at -10°C to -30°C 1226 days at -60°C to -80°C	Not performed Performed at Covance Shanghai
Studies supported	2009-013-00CH1, 2012-013-00CH2, 2012-013-00CH3, 2013-013-00CH2	2014-013-00CH5, 2015-013-00US1	2019-013-GLOB1, 2020-013-00US1, 2020-013-00US2, 2021-013-00US1[a], 2021-013-00US2[a], 2021-013-00US3[a]

Abbreviations: CV = coefficient of variation; RT = room temperature.
[a] Topline PK report only will be submitted in the application.
(Source: Table 4 in 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods)

Clinical PK

Fruquintinib PK following single and multiple QD dose administration was characterized in Study 2009-013-00CH1, conducted in China in patients with cancer. Mean plasma concentration-time data of fruquintinib after single dose are shown in Figure 10. The summary statistics of PK parameters of fruquintinib after single dose are presented in Table 50. and multiple QD dose on Day 1, Day 14 and Day 28 are presented in Table 51. After 14 days of dosing with 1 to 6 mg fruquintinib, accumulation was observed, with accumulation of $AUC_{0\text{-}24h}$ values ranging between 2 and 4 across the dose range studied.

Figure 10. Mean (SD) plasma concentration versus time profiles of fruquintinib after single dose.



(Source: Figure 2 in Pharmacokinetic Study Report of Study Protocol No. 2009-013-00CH1)

Table 49. Summary of the plasma pharmacokinetic parameters of fruquintinib after single dose

Dose	mg	1*		2 (n=3)		4 (n=3)		5 (n=3)		6 (n=3)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
λ_z	1/h	0.0106	-	0.0188	0.0067	0.0185	0.0028	0.0145	0.0023	0.0208	0.0063
$t_{1/2}$	h	65.1	-	39.7	11.8	37.9	5.3	48.5	7.3	35.2	9.1
T_{max}	h	2	-	2.0	0.0	2.0	1.0	1.5	0.9	4.7	3.1
C_{max}	ng/mL	20.2	-	44.5	14.2	111.0	9.2	195.3	34.2	182.0	22.6
$AUC_{0\text{-}72h}$	h*ng/mL	759	-	1353	87	3832	243	5495	992	6672	303
$AUC_{0\text{-}\infty}$	h*ng/mL	1450	-	1887	172	5266	664	8417	907	8885	966
V_z/F	L	64.8	-	60.0	13.4	41.5	2.1	42.2	9.5	34.0	6.7
CL/F	mL/min	11.5	-	17.8	1.7	12.8	1.6	10.0	1.1	11.3	1.2
$AUMC_{0\text{-}\infty}$	h*h*ng/mL	139034	-	109714	41605	291644	73028	576304	75108	469068	151763
$MRT_{0\text{-}\infty}$	h	95.9	-	57.1	17.9	54.8	7.0	68.9	10.3	52.0	12.0
$AUC_{0\text{-}12h}$	h*ng/mL	152	-	360	101	988	71	1445	235	1576	92
$AUC_{0\text{-}24h}$	h*ng/mL	303	-	651	140	1832	99	2575	457	3152	292

* Only 1 subject was in 1 mg group; thus, the mean actually referred to the value from that subject and the SD could not be calculated.

(Source: Table 3 in Applicant's Pharmacokinetic Study Report of Study Protocol No. 2009-013-00CH1)

Table 50. Summary of the plasma pharmacokinetic parameters of fruquintinib after QD dose

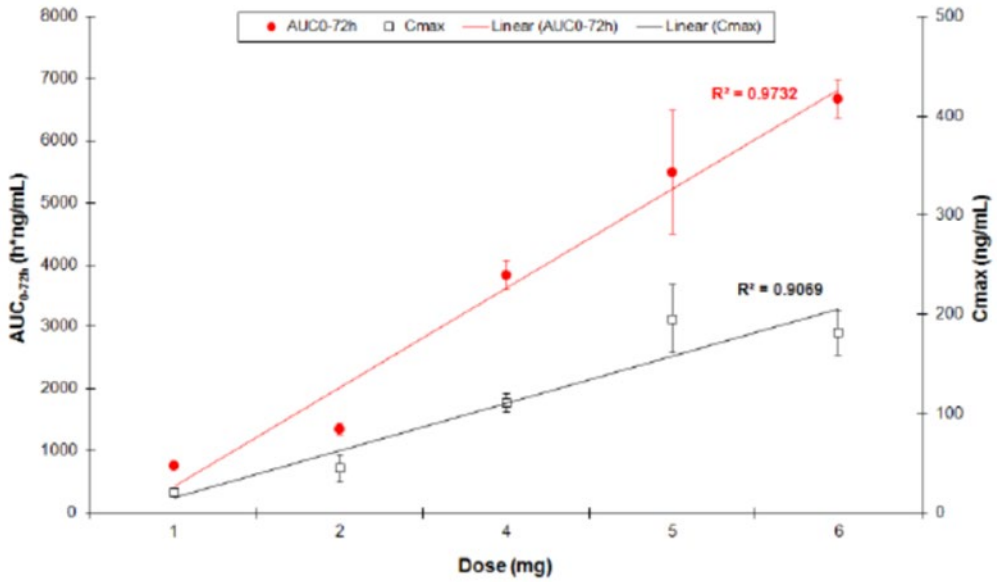
Dose			1mg*			2mg			4#			5mg			6mg**	
Day	PK Parameters	Unit	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
1	AUC_{0-12h}	h*ng/mL	1	178	-	3	379	77	16	932	248	3	1337	109	3	1798	293
	AUC_{0-24h}	h*ng/mL	1	341	-	3	723	139	16	1749	402	3	2534	299	3	3594	497
	C_{max}	ng/mL	1	16.3	-	3	41.2	7.8	16	96.9	26.5	3	150.7	30.1	3	185.0	32.5
	C_{min}	ng/mL	1	12.8	-	3	11.2	10.2	16	54.2	25.2	3	56.7	48.7	3	56.4	50.8
	T_{max}	h	1	4	-	3	3.0	1.7	16	3.2	2.4	3	3.0	1.7	3	5.7	5.7
	T_{min}	h	1	12	-	3	3.0	4.4	16	12.3	10.4	3	4.3	6.7	3	8.7	13.3
14	R-AUC***		1	4.0	-	3	3.1	0.7	16	3.0	0.6				2	2.5	0.7
	AUC_{0-12h}	h*ng/mL	1	718	-	3	1130	93	16	2741	643	3	4080	678	2	5135	600
	AUC_{0-24h}	h*ng/mL	1	-	-	-	-	-	13	5212	1227	3	7784	1539	2	9230	1215
	C_{ss}	ng/mL	1	55.3	-	-	-	-	13	217.1	51.1	3	324.3	64.1	2	384.6	50.6
	C_{max}	ng/mL	1	82.1	-	3	108.6	14.9	16	289.9	61.1	3	397.7	43.7	2	508.0	63.6
	C_{min}	ng/mL	1	52.8	-	3	76.0	18.4	16	181.5	49.5	3	295.0	69.8	2	307.5	78.5
	DF	%	1	53.0	-	-	-	-	13	56.3	22.3	3	33.9	18.1	2	52.8	10.8
	T_{max}	h	1	1	-	3	3.0	1.7	16	5.1	7.9	3	1.0	0.0	2	4.0	0
	T_{min}	h	1	8	-	3	0	0	16	7.5	9.7	3	12.0	0.0	2	12.0	17.0
28	R-AUC***		1	4.1	-	3	3.1	0.6	16	3.0	0.5	3	3.1	0.4	2	2.2	0.2
	AUC_{0-12h}	h*ng/mL	1	695	-	3	1172	126	16	2806	569	3	2678	1378	2	4344	338
	AUC_{0-24h}	h*ng/mL	1	1413	-	3	2226	294	16	5119	1008	3	5086	2687	2	8109	563
	C_{ss}	ng/mL	1	58.9	-	3	92.8	12.2	16	213.3	42.0	3	211.9	112.0	2	337.9	23.5
	C_{max}	ng/mL	1	69.3	-	3	114.7	19.4	16	295.1	70.4	3	280.0	158.7	2	424.0	14.1
	C_{min}	ng/mL	1	50.4	-	3	73.6	11.3	16	181.3	41.1	3	180.5	106.9	2	272.5	6.4
	DF	%	1	32.1	-	3	43.7	7.9	16	53.8	24.6	3	48.0	7.4	2	44.7	3.0
	T_{max}	h	1	24	-	3	3.3	4.0	16	1.5	1.3	3	2.0	1.7	2	4.0	0
	T_{min}	h	1	12	-	3	8.0	13.9	16	10.6	9.6	3	12.0	12.0	2	6.0	8.5

*Only 1 subject was in 1 mg group; thus, the mean actually referred to the value from that subject and the SD could not be calculated.
**Since subjects withdrew from the 6 mg group, there were only 2 cases of multiple dosing data
***accumulative ratio of exposure at the steady state was obtained by calculating ratio between AUC in an dosing interval (24 hours) at steady state and AUC in the same dose interval after first dosing. AUC_{0-12h} was used for the subjects without AUC_{0-24h};
#AUC_{0-24h} from 3 subjects in 4 mg group on day 14 was not available.

(Source: Table 5 in Pharmacokinetic Study Report of Study Protocol No. 2009-013-00CH1)

In Study 2009-013-00CH1, plasma fruquintinib exposure increased linearly in patients with cancer over the dose range of 1 to 6 mg after single dose (Figure 11) and multiple QD doses (Figure 12).

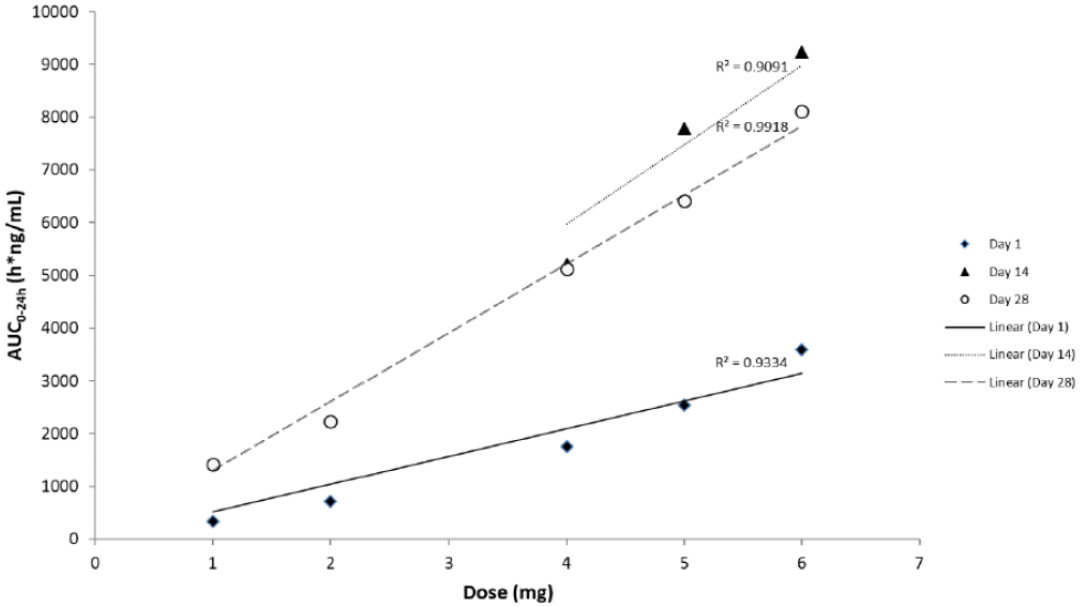
Figure 11. Linear Regression Plot of Fruquintinib Exposure Versus Dose After Single Doses



Abbreviations: $AUC_{0\text{-}72h}$=area under the plasma concentration-time curve from time 0 to 72 hours; Cmax=maximum plasma concentration; R^2=correlation coefficient

(Source: Figure 6 in 2.7.2 Summary of Clinical pharmacology Studies)

Figure 12. Linear Regression Plot of Fruquintinib Exposure Versus Dose After Single Does and Multiple QD Doses



Abbreviations: $AUC_{0\text{-}24h}$=area under the plasma concentration-time curve from time 0 to 24 hours; R^2=correlation coefficient

(Source: Figure 7 in 2.7.2 Summary of Clinical pharmacology Studies)

Dose proportionality was also observed in Study 2015-013-00US1 where patients with cancer received multiple doses of fruquintinib 3 and 5 mg QD 3/1, **Table 52**.

Table 51. Summary of the plasma pharmacokinetic parameters of fruquintinib after QD dose

Analyte	Day	Parameter	Unit	Cohort GeoLSM				GeoLSM Ratio	90% CI
				3 mg Dose Normalized to 5 mg	(n)	5 mg	(n)		
Fruquintinib	1	AUC_{0-24}	h•ng/mL	1486.87	7	1192.79	94	1.25	0.82, 1.90
		C_{max}	ng/mL	86.99	7	89.36	94	0.97	0.77, 1.22
	14	AUC_{0-24}	h•ng/mL	6156.68	5	5408.86	82	1.14	0.85, 1.53
		C_{max}	ng/mL	330.08	5	270.99	82	1.22	0.92, 1.62

(Source: Table 5 in 2.7.2 Summary of Clinical pharmacology Studies)

Population PK Analysis

Executive Summary

The sponsor is seeking approval of fruquintinib, an oral tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFRs)-1, -2, and -3, for the treatment of adult patients with colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild-type, an anti-EGFR therapy. The key pharmacometrics findings are summarized below:

Population PK Analysis

- Body weight (36-158 kg), coadministration of PPIs (proton pump inhibitor), health status (healthy vs. cancer), sex, age (18-82 yrs.), ECOG , race (Japanese vs. Chinese vs. other races), ethnicity, albumin, tumor type, mild or moderate renal impairment (CLCR from 32.6 to < 90 mL/min), mild hepatic impairment, and concomitant administration of H2A (H2 antagonist) were found to have no clinically meaningful impact. The fruquintinib dose adjustment in patients with mild and moderate renal impairment or mild - hepatic impairment is not required.

Safety E-R Analysis

- Higher model-predicted fruquintinib steady-state maximum plasma concentration (CmaxSS) was associated with a higher probability of Grade 3-4 dermatological toxicity.
- Compared to the QD 3/1 regimen, the QD continuous regimen was associated with higher probabilities of Gr3+ dermatological toxicity, any grade hemorrhage, and Grade 3-4 proteinuria.

- There was no trend of positive E-R relationships with fruquintinib or M11 exposure identified for any grade dermatological toxicity, any grade or Grade 3-4 hypertension, any grade or Grade 3-4 hepatic function abnormal, any grade proteinuria, and Grade 3-4 hemorrhage.

Efficacy E-R Analysis

- There was no trend of a positive relationship between OS and fruquintinib steady-state minimum plasma concentration (CminSS) derived based on the starting dose or adjusted for relative dose intensity (RDI) following the 5 mg QD 3/1 regimen in Studies 2019-013-GLOB1 and 2015-013-00US1 Cohort B.
- There was a (nominally) statistically significant trend of ER relationship between exposure (CminSS) and progression-free survival (PFS) in Study 2019-013-GLOB1. But given the context of a lack of an E-R relationship for OS, this observation may not be clinically meaningful.

Review Summary

The primary objectives of the Applicant's analysis were to develop a population PK model for fruquintinib, an oral tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFRs)-1, -2, and -3, and M11 (a major metabolite[1]).

The Applicant's PopPK analysis for fruquintinib is acceptable to support the current submission as outlined in Table 53. The Applicant's final PopPK model adequately described the fruquintinib and M11 concentrations, in which PopPK parameter estimates were estimated with acceptable precision as indicated by the relative standard errors (RSE) for total clearance (CL, 1.2%, RSE), volume of distribution in central compartment (V, 0.9% RSE), absorption lag time (Lag, 1.1 % RSE) and absorption rate constant (Ka, 7.6 % RSE). The goodness-of-fit plots showed a good agreement between the observed and the individual predicted concentrations without any obvious bias over time or predicted concentrations. The prediction-corrected visual predictive check plots showed a good agreement between the observed and the simulated concentrations. The Applicant's analyses were verified by the reviewer, with no significant discordance identified.

Table 52. Specific Comments on Applicant's Final Population PK model

Utility of the final model			**Reviewer's Comments**
Support applicant's proposed	**Intrinsic factor**	Body weight, coadministration of PPIs (proton pump inhibitor)	The applicant's recommendation that there is

[1] *population-pk-and-exposure-response-final-analysis-report, Page 20 (link).*

labeling statements about intrinsic and extrinsic factors		and healthy status (healthy vs cancer) were identified as (nominally) statistically significant covariates and not considered clinically meaningful.	no dose adjustment based on intrinsic factors is acceptable.
	Extrinsic factor	NA	NA
Derive exposure metrics for Exposure-response analyses	CminSS, CmaxSS, AUCave[2]		The applicant's final model is generally acceptable for generating exposure metrics for exposure-response analyses (Table 58).

PopPK model development

Data

There are six clinical studies: 2009-013-00CH1 (a dose finding study in patients with advanced solid tumors including CRC); 2015-013-00US1 (a dose finding study in patients with mCRC); 2012-013-00CH3 (a randomized study comparing two different dosing regimens in patients with mCRC); 2020-013-00US1 and 2020-013-00US2 (studies assessing the effect of rabeprazole and itraconazole respectively on the PK of fruquintinib), and the randomized controlled study in patients with refractory mCRC, Study 2019-013-GLOB1 (Table 54). PK sampling for fruquintinib was performed in all 6 studies, and PK sampling for metabolite M11 was performed in Studies 2019-013-GLOB1,2015-013-00US1, 2020-013-00US1, and 2020-013-00US2. The safety E-R analysis pooled data from all 4 studies in patients with cancer (2019-013-GLOB1, 2009-013-00CH1, 2012-013-00CH3, and 2015-013-00US1) and the efficacy E-R analyses included patients with mCRC from study 2019-013-GLOB1 and Cohort B of 2015-013-00US1. Summary of baseline demographic covariates was shown in Table 55 and summary of concomitant administration was shown in Table 56.

Plasma concentration results with missing or uncertain corresponding dosing data along with all subsequent concentration samples were excluded from the analysis, unless enough time had elapsed for the missing/uncertain dosing records to have a negligible impact on the PK samples. Samples with missing date information that could not be imputed using dosing and nominal time information were excluded. When all values of a continuous demographic covariate were missing for an analysis subject, the median value in the analysis dataset was an imputed value. Missing categorical covariates were

[2] AUCave: average daily area under the plasma concentration-time curve over the 4-week cycle at steady state

imputed with the most common covariate category. If the proportion of subjects completely missing a covariate was greater than 20%, that covariate was not included in the population PK analysis.

In the PK analysis, plasma concentration samples that were below the assay lower limit of quantification (BLQ) were excluded from the analysis. Subjects with no observations above the assay lower limit of quantification were excluded from the analysis, shown in Table 57.

Reviewer comments:
The PopPK model with excluded BLQ samples, which were treated by the M3 method[3], has similar parameter estimates with those of the Applicant's final PopPK model. Therefore, the Applicant's final model was acceptable.

[3] Beal SL. Ways to fit a PK model with some data below the quantification limit. J Pharmacokinet Pharmacodyn 2001 Oct;28:481–504.

Table 53. Summary of Clinical Study Designs

Study Description	Phase	Drug Dose and Regimen	Subject Population/ Planned Subject Number	PK Sampling Scheme
2009-013-00CH1 Dose escalation A Single-Center, Open-Label, Dose Escalation Phase 1 Clinical Study of Fruquintinib for Treatment of Advanced Malignant Solid Tumors	1	*Single-dose study*: Fruquintinib capsule, PO 1 mg (N = 1) 2 mg (N = 3) 4 mg (N = 3) 5 mg (N = 3) 6 mg (N = 3) *Multiple-dose study*: Fruquintinib capsule, PO 1 mg QD continuous (N = 1) 2 mg QD continuous (N = 3) 4 mg QD continuous (N = 16) 5 mg QD continuous (N = 3) 6 mg QD continuous (N = 3) 5 mg QD 3/1 (N = 8) 6 mg QD 3/1 (N = 6)	Patients with advanced malignant solid tumors N = 40	PK sampling for fruquintinib *Single-dose study*: Predose and 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, and 72 hrs postdose of fruquintinib *Multiple-dosing study*: QD continuous: Days 1, 14, and 28: Predose (-10 min) and 1, 4, 8, and 12 hrs after postdose of fruquintinib Days 2, 3, and 7: Predose (-10 min) and postdose of fruquintinib Days 15, 29, and 56 (follow-up visit): Predose (-10 min) QD 3/1: Days 1, 21, 29, 42, and 49: Predose (-10 min) and 1, 2, 4, 8, and 12 hrs after postdose of fruquintinib Days 2, 22, 23, 30, 43, 50, and 51: Predose (-10 min) of fruquintinib
2012-013-00CH3 A Phase 1b, Randomized, Open-Label Study for Comparing Two Different Dosing Regimens of Fruquintinib as Third-Line or Up Therapy for Advanced CRC in Patients Who Had Failed With Standard Therapy	1/1b	Randomized comparison stage: Fruquintinib capsule 4 mg, PO, QD continuous dosing or fruquintinib capsule 5 mg, PO, QD 3/1 Expansion stage: Fruquintinib capsule 5 mg QD 3/1.	Patients with advanced CRC who had failed with standard therapy N = 62 as total of randomized comparison stage (N = 40) and the expansion stage (N = 22).	PK sampling for fruquintinib 4 mg QD continuous dosing: Days 1 and 21[a]: Predose (-10 min) and 1, 2, 4, and 8 hrs postdose of fruquintinib Days 2 and 22[a]: Predose (-10 min) Days 28, 42, 56, 70, and 84[b]: Predose (-10 min) and 1, 2, 4, and 8 hrs postdose of fruquintinib Days 29, 43, 57, 71, and 85[a]: Predose (-10 min) 5 mg QD 3/1: Days 1 and 21: Predose (-10 min) and 1, 2, 4, and 8 hrs postdose of fruquintinib

Study Description	Phase	Drug Dose and Regimen	Subject Population/ Planned Subject Number	PK Sampling Scheme
				Days 2 and 22: Predose (-10 min) Day 14 after continuous administration with reduced dose: Predose (-10 min) and 1, 2, 4, and 8 hrs postdose of fruquintinib Day 15 after continuous administration with reduced dose: Predose (-10 min)
2015-013-00US1 A Multi Center, Open-Label, Phase 1/1b Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Anticancer Activity of Fruquintinib in Patients With Advanced Solid Tumors	1/1b	Fruquintinib capsule 5 mg PO, QD 3/1 for every 28-day treatment cycle until end of treatment.	Patients with advanced solid tumors N = 128 as total of dose escalation phase (N = 12) and dose expansion phase (N = 116). Approximately 30 patients from mBC Cohorts D and E will not be included in the analysis.	PK sampling for fruquintinib and M11 *Dose escalation phase and Cohort A of dose expansion phase*: Cycle 1 Days 1, 14, and 21: Predose and 1, 2, 4, and 8 hrs postdose of fruquintinib Cycle 1 Days 2, 15, and 22: Predose *Cohort B, C, D, and E of the dose expansion phase*: Cycle 1 Days 1 and 14: Predose and 1, 2, 4, and 8 hrs postdose of fruquintinib Cycle 1 Days 2 and 15: Predose

Study Description	Phase	Drug Dose and Regimen	Subject Population/ Planned Subject Number	PK Sampling Scheme
2019-013-GLOB1 (FRESCO-2) A Global, Multicenter, Randomized, Placebo-Controlled Phase 3 Trial to Compare the Efficacy and Safety of Fruquintinib Plus Best Supportive Care to Placebo Plus Best Supportive Care in Patients With Refractory Metastatic Colorectal Cancer	3	Fruquintinib or placebo capsule 5 mg PO, QD continuous, 3 weeks on, 1 week off (4-week cycles) If dose adjustment is required, 1 mg fruquintinib or placebo capsules will be used.	Patients with refractory metastatic CRC N = 687 randomized 2:1 (fruquintinib plus BSC:placebo plus BSC).	PK sampling for fruquintinib and M11 *Dense PK sampling*[b]: Cycle 1 Days 1 and 21: Predose and 1, 2, 3, and 4 hrs postdose of fruquintinib Cycle 2 Day 1, Cycle 3 Day 1, Cycle 5 Day 1, and every other cycle thereafter: Predose Cycle 2 Day 21 and Cycle 3 Day 21: Predose and 2 hrs postdose of fruquintinib *Sparse PK sampling*[b]: Cycle 1 Days 1 and 21, Cycle 2 Day 21, and Cycle 3 Day 21: Predose and 2 hrs postdose of fruquintinib Cycle 2 Day1, Cycle 3 Day 1, Cycle 5 Day 1, and every other cycle thereafter: Predose
2020-013-00US1 A Phase 1 Open-Label, 3-Period, Randomized 2-Sequence Study to Evaluate the Effect of Food and Rabeprazole, a Proton Pump Inhibitor, on the PK of Fruquintinib in Healthy Subjects	1	Treatment sequence 1: Fruquintinib 5 mg single dose: Fed on Day 1, fasted on Day 15 and Day 29 Treatment sequence 2: Fruquintinib 5 mg single dose: Fasted on Day 1, fed on Day 15, fasted on Day 29 All subjects: Day 23 – Day 29: Rabeprazole 40 mg QD continuous.	Healthy Subjects N = 14 Randomized in 1:1 ratio for 1 of the 2 possible treatment sequences	PK sampling for fruquintinib and M11 Predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, and 168 hrs after each fruquintinib dose in each period[c]

Study Description	Phase	Drug Dose and Regimen	Subject Population/ Planned Subject Number	PK Sampling Scheme
2020-013-00US2 A Phase 1, Open-Label, 2-Part, 2-Period Fixed-Sequence Crossover Study to Assess the Effect of Itraconazole, a Strong CYP3A Inhibitor, and the Effect of Rifampin, a Strong CYP3A Inducer, on the PK of Fruquintinib in Healthy Subjects	1	Part A Days 1 and 19: Fruquintinib 5 mg single dose Days 15 to 25: Itraconazole 200 mg BID on Day 15 and QD on Days 16 to 25 Part B Days 1 and 15: Fruquintinib 5 mg single dose Days 8 to 21: Rifampin 600 mg QD continuous	Healthy subjects N = 28	PK sampling for fruquintinib and M11 Predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, and 168 hrs after each fruquintinib dose in each period[c]

[a] If the dose was adjusted to 2 or 3 mg before Day 21, PK sampling was not performed on Day 21 or Day 22 but was performed predose and up to 24 hours postdose of the first follow-up visit (one of Day 28, Day 42, Day 56, Day 70, or Day 84) after continuous administration for 14 days.
[b] Dense PK was performed in a subset of 120 subjects in the study; sparse sampling was performed in all other patients.
[c] In Studies 2020-013-00US1 and 2020-013-00US2, only PK samples collected when fruquintinib is administered alone will be included in the population PK analysis.
Notes: "3/1" refers to "3-week continuous dosing with 1-week break (3 on/1 off)" dosage regimen.
BID = twice daily; BSC = best supportive care; CRC = colorectal cancer; CYP3A = cytochrome P450 3A; mBC = metastatic breast cancer; N = number of subjects; PK = pharmacokinetic(s); PO = per oral; QD = once daily

Source: population-pk-and-exposure-response-final-analysis-report, Page 30 (link).

Table 54. Summary of Baseline Demographic Covariates for Analysis

Covariate	2009-013-00CH1 (N = 40)	2012-013-00CH3 (N = 40)	2015-013-00US1 (N = 101)	2019-013-GLOB1 (N = 334)	2020-013-00US1 (N = 14)	2020-013-00US2 (N = 28)	Overall (N = 557)
Sex							
Female	22 (55.0%)	12 (30.0%)	49 (48.5%)	155 (46.4%)	1 (7.1%)	5 (17.9%)	244 (43.8%)
Male	18 (45.0%)	28 (70.0%)	52 (51.5%)	179 (53.6%)	13 (92.9%)	23 (82.1%)	313 (56.2%)
Race							
White	0 (0%)	0 (0%)	85 (84.2%)	250 (74.9%)	8 (57.1%)	16 (57.1%)	359 (64.5%)
Black	0 (0%)	0 (0%)	9 (8.9%)	12 (3.6%)	2 (14.3%)	6 (21.4%)	29 (5.2%)
Asian	40 (100%)	40 (100%)	4 (4.0%)	48 (14.4%)	3 (21.4%)	5 (17.9%)	140 (25.1%)
Hawaiian/Pacific Islander	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (7.1%)	0 (0%)	1 (0.2%)
Multiple	0 (0%)	0 (0%)	0 (0%)	2 (0.6%)	0 (0%)	1 (3.6%)	3 (0.5%)
Other	0 (0%)	0 (0%)	3 (3.0%)	3 (0.9%)	0 (0%)	0 (0%)	6 (1.1%)
Missing	0 (0%)	0 (0%)	0 (0%)	19 (5.7%)	0 (0%)	0 (0%)	19 (3.4%)
Ethnicity							
Hispanic or Latino	0 (0%)	0 (0%)	5 (5.0%)	14 (4.2%)	1 (7.1%)	8 (28.6%)	28 (5.0%)
Not Hispanic or Latino	40 (100%)	40 (100%)	95 (94.1%)	297 (88.9%)	13 (92.9%)	20 (71.4%)	505 (90.7%)
Missing	0 (0%)	0 (0%)	1 (1.0%)	23 (6.9%)	0 (0%)	0 (0%)	24 (4.3%)
Health Status							
Healthy	0 (0%)	0 (0%)	0 (0%)	0 (0%)	14 (100%)	28 (100%)	42 (7.5%)
Patient	40 (100%)	40 (100%)	101 (100%)	334 (100%)	0 (0%)	0 (0%)	515 (92.5%)
Tumor Type							
Colorectal Cancer	12 (30.0%)	39 (97.5%)	85 (84.2%)	334 (100%)	0 (0%)	0 (0%)	470 (84.4%)
Other	28 (70.0%)	1 (2.5%)	16 (15.8%)	0 (0%)	0 (0%)	0 (0%)	45 (8.1%)
No Tumor	0 (0%)	0 (0%)	0 (0%)	0 (0%)	14 (100%)	28 (100%)	42 (7.5%)

Covariate	2009-013-00CH1 (N = 40)	2012-013-00CH3 (N = 40)	2015-013-00US1 (N = 101)	2019-013-GLOB1 (N = 334)	2020-013-00US1 (N = 14)	2020-013-00US2 (N = 28)	Overall (N = 557)
NCI Liver Dysfunction Category							
Normal	40 (100%)	40 (100%)	79 (78.2%)	222 (66.5%)	14 (100%)	26 (92.9%)	421 (75.6%)
Mild	0 (0%)	0 (0%)	22 (21.8%)	109 (32.6%)	0 (0%)	2 (7.1%)	133 (23.9%)
Moderate	0 (0%)	0 (0%)	0 (0%)	2 (0.6%)	0 (0%)	0 (0%)	2 (0.4%)
Missing	0 (0%)	0 (0%)	0 (0%)	1 (0.3%)	0 (0%)	0 (0%)	1 (0.2%)
Renal Impairment Category							
Normal	26 (65.0%)	25 (62.5%)	66 (65.3%)	179 (53.6%)	14 (100%)	27 (96.4%)	337 (60.5%)
Mild	12 (30.0%)	15 (37.5%)	31 (30.7%)	118 (35.3%)	0 (0%)	1 (3.6%)	177 (31.8%)
Moderate	2 (5.0%)	0 (0%)	4 (4.0%)	36 (10.8%)	0 (0%)	0 (0%)	42 (7.5%)
Missing	0 (0%)	0 (0%)	0 (0%)	1 (0.3%)	0 (0%)	0 (0%)	1 (0.2%)
Eastern Cooperative Oncology Group Performance Status Score							
0	10 (25.0%)	8 (20.0%)	36 (35.6%)	151 (45.2%)	14 (100%)	28 (100%)	247 (44.3%)
1	30 (75.0%)	32 (80.0%)	65 (64.4%)	183 (54.8%)	0 (0%)	0 (0%)	310 (55.7%)
Country							
Rest of the World	0 (0%)	0 (0%)	101 (100%)	289 (86.5%)	14 (100%)	28 (100%)	432 (77.6%)
China	40 (100%)	40 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	80 (14.4%)
Japan	0 (0%)	0 (0%)	0 (0%)	45 (13.5%)	0 (0%)	0 (0%)	45 (8.1%)

Source: \Deliverables\Analysis\Development\POPPK\EDA\EDA_FRUQ_POPPK_02FEB2023_allstudies.html
N = number of subjects; NCI = National Cancer Institute; PK = pharmacokinetic

	2009-013-00CH1 (N = 40)	2012-013-00CH3 (N = 40)	2015-013-00US1 (N = 101)	2019-013-GLOB1 (N = 334)	2020-013-00US1 (N = 14)	2020-013-00US2 (N = 28)	Overall (N = 557)
Age (years)							
Mean (SD)	54.5 (11.2)	54.2 (12.5)	58.6 (10.2)	62.5 (10.1)	40.9 (7.97)	39.3 (10.4)	58.9 (12.0)
Median [Min, Max]	56.0 [18.0, 70.0]	56.5 [21.0, 70.0]	59.0 [34.0, 77.0]	64.0 [25.0, 82.0]	42.5 [27.0, 52.0]	37.5 [20.0, 55.0]	61.0 [18.0, 82.0]
Baseline Body Weight (kg)							
Mean (SD)	60.7 (11.7)	65.9 (13.0)	84.3 (21.3)	73.7 (17.3)	76.7 (8.81)	76.3 (10.9)	74.3 (18.1)
Median [Min, Max]	59.0 [36.0, 95.0]	64.0 [40.0, 101]	83.5 [44.8, 135]	73.0 [40.1, 158]	76.2 [59.5, 93.9]	75.1 [49.8, 101]	73.0 [36.0, 158]
Baseline Body Mass Index (kg/m^2)							
Mean (SD)	22.8 (3.73)	23.6 (3.51)	28.7 (6.81)	25.9 (5.27)	25.2 (2.01)	25.8 (2.46)	26.0 (5.43)
Median [Min, Max]	22.5 [16.0, 35.3]	22.6 [16.7, 31.2]	27.8 [17.8, 48.2]	25.2 [16.1, 56.7]	25.6 [20.7, 27.8]	25.9 [19.2, 28.6]	25.2 [16.0, 56.7]
Missing	0 (0%)	0 (0%)	6 (5.9%)	2 (0.6%)	0 (0%)	0 (0%)	8 (1.4%)
Creatinine Clearance (mL/min)							
Mean (SD)	104 (33.2)	110 (38.5)	106 (32.4)	96.3 (34.7)	120 (19.7)	125 (22.5)	102 (34.5)
Median [Min, Max]	103 [45.2, 205]	104 [60.8, 223]	105 [42.2, 212]	92.6 [32.6, 293]	118 [95.1, 157]	127 [79.3, 160]	97.9 [32.6, 293]
Missing	0 (0%)	0 (0%)	0 (0%)	1 (0.3%)	0 (0%)	0 (0%)	1 (0.2%)
Alanine Aminotransferase (IU/L)							
Mean (SD)	20.0 (10.4)	22.9 (13.0)	27.1 (18.8)	27.9 (23.6)	33.4 (16.4)	28.8 (17.4)	27.0 (21.0)
Median [Min, Max]	16.4 [7.30, 55.0]	17.2 [6.70, 54.6]	21.0 [7.00, 105]	21.0 [2.00, 170]	27.5 [18.0, 70.0]	22.0 [11.0, 88.0]	21.0 [2.00, 170]

	2009-013-00CH1 (N = 40)	2012-013-00CH3 (N = 40)	2015-013-00US1 (N = 101)	2019-013-GLOB1 (N = 334)	2020-013-00US1 (N = 14)	2020-013-00US2 (N = 28)	Overall (N = 557)
Alkaline Phosphatase (IU/L)							
Mean (SD)	104 (56.8)	119 (49.5)	153 (113)	207 (197)	79.3 (23.8)	69.6 (18.7)	173 (168)
Median [Min, Max]	91.5 [43.0, 370]	106 [50.1, 272]	118 [34.0, 743]	145 [33.0, 1830]	77.0 [54.0, 134]	64.5 [38.0, 114]	120 [33.0, 1830]
Aspartate Aminotransferase (IU/L)							
Mean (SD)	23.7 (7.21)	26.2 (8.99)	33.7 (18.7)	36.7 (25.8)	29.8 (6.29)	34.8 (17.3)	34.2 (22.4)
Median [Min, Max]	21.4 [13.2, 43.7]	26.6 [12.3, 53.5]	29.0 [13.0, 106]	29.0 [8.00, 220]	28.5 [20.0, 43.0]	30.0 [19.0, 102]	28.0 [8.00, 220]
Missing	0 (0%)	0 (0%)	0 (0%)	2 (0.6%)	0 (0%)	0 (0%)	2 (0.4%)
Total Bilirubin (umol/L)							
Mean (SD)	10.3 (4.39)	10.6 (4.01)	9.52 (4.91)	10.5 (5.53)	12.6 (5.87)	12.5 (4.72)	10.4 (5.24)
Median [Min, Max]	9.35 [3.20, 20.6]	10.1 [5.20, 22.3]	8.55 [3.42, 30.8]	8.76 [2.57, 38.0]	12.0 [3.42, 23.9]	11.1 [5.13, 23.9]	9.30 [2.57, 38.0]
Total Protein (g/L)							
Mean (SD)	69.3 (5.10)	74.6 (4.80)	72.1 (6.32)	72.3 (7.29)	68.9 (4.70)	67.9 (3.42)	71.9 (6.75)
Median [Min, Max]	69.1 [59.2, 80.0]	74.5 [64.2, 89.0]	72.0 [52.0, 94.0]	72.0 [7.40, 94.0]	69.0 [59.0, 77.0]	68.0 [61.0, 75.0]	72.0 [7.40, 94.0]
Missing	0 (0%)	0 (0%)	0 (0%)	9 (2.7%)	0 (0%)	0 (0%)	9 (1.6%)
Albumin (g/L)							
Mean (SD)	42.4 (4.29)	42.8 (4.25)	39.7 (4.26)	39.2 (5.22)	46.0 (1.84)	46.8 (2.45)	40.3 (5.20)
Median [Min, Max]	42.3 [29.9, 50.3]	43.5 [33.5, 50.0]	40.0 [28.0, 50.0]	40.0 [20.0, 50.0]	45.5 [43.0, 50.0]	47.0 [42.0, 52.0]	41.0 [20.0, 52.0]

Source: \Deliverables\Analysis\Development\POPPK\EDA\EDA_FRUQ_POPPK_02FEB2023_allstudies.html
ECOG = Eastern Cooperative Oncology Group; Max = maximum; Min = minimum; N = number of subjects; PK = pharmacokinetic; SD = standard deviation

Source: population-pk-and-exposure-response-final-analysis-report, Page 64-67 (link).

Table 55. Summary of Concomitant Administration in Subjects Included the Population PK Analysis Dataset

	2009-013-00CH1 (N = 40)	2012-013-00CH3 (N = 40)	2015-013-00US1 (N = 101)	2019-013-GLOB1 (N = 334)	2020-013-00US1 (N = 14)	2020-013-00US2 (N = 28)	Overall (N = 557)
PPI Coadministration							
PPI Absent	40 (100%)	40 (100%)	86 (85.1%)	238 (71.3%)	14 (100%)	28 (100%)	446 (80.1%)
PPI Present	0 (0%)	0 (0%)	15 (14.9%)	96 (28.7%)	0 (0%)	0 (0%)	111 (19.9%)
H2 Antagonist Coadministration							
H2A Absent	40 (100%)	40 (100%)	97 (96.0%)	294 (88.0%)	14 (100%)	28 (100%)	513 (92.1%)
H2A Present	0 (0%)	0 (0%)	4 (4.0%)	40 (12.0%)	0 (0%)	0 (0%)	44 (7.9%)
CYP3A4 Inhibitor							
None	39 (97.5%)	40 (100%)	99 (98.0%)	325 (97.3%)	14 (100%)	28 (100%)	545 (97.8%)
Moderate Inhibitor	1 (2.5%)	0 (0%)	2 (2.0%)	8 (2.4%)	0 (0%)	0 (0%)	11 (2.0%)
Strong Inhibitor	0 (0%)	0 (0%)	0 (0%)	1 (0.3%)	0 (0%)	0 (0%)	1 (0.2%)
CYP3A4 Inducer							
Inducer Absent	40 (100%)	40 (100%)	101 (100%)	334 (100%)	14 (100%)	28 (100%)	557 (100%)
Inducer Present	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Source: \Deliverables\Analysis\Development\POPPK\EDA\EDA_FRUQ_POPPK_02FEB2023_allstudies.html
CYP3A4 = cytochrome P450 3A4; H2A = H2 antagonist; N = number of subjects who received at least 1 coadministration; PK = pharmacokinetic; PPI = proton pump inhibitor

Source: population-pk-and-exposure-response-final-analysis-report, Page 68 (link).

Table 56. Summary of Available Data and Data Included in the Population PK Analysis

Parameter	2009-013-00CH1	2012-013-00CH3	2015-013-00US1	2019-013-GLOB1 (FRESCO-2)	2020-013-00US1	2020-013-00US2	Total
Number of Fruquintinib Subjects							
$N_{subj,all}$	40	40	101	338	14	28	561
$N_{subj,analysis}$	40	40	101	334	14	28	557
Number of Fruquintinib Observations							
N_{obs}	1198	449	1098	3174	469	469	6857
$N_{obs,excluded}$ (%)	9 (0.8%)	0 (0%)	0 (0%)	11 (0.3%)	0 (0%)	0 (0%)	20 (0.3%)
N_{obsBLQ} (%)	10 (0.8%)	0 (0%)	6 (0.5%)	126 (4.1%)	27 (5.8%)	0 (0%)	169 (2.5%)
$N_{obs,analysis}$	1179	449	1092	3037	442	469	6668
Number of M11 Subjects							
$N_{subj,all}$	0	0	101	338	14	28	481
$N_{subj,analysis}$	0	0	100	318	14	28	460
Number of M11 Observations							
N_{obs}	-	-	1098	3174	469	469	5210
$N_{obs,excluded}$ (%)	-	-	0 (0%)	11 (0.3%)	0 (0%)	0 (0%)	11 (0.2%)
N_{obsBLQ} (%)	-	-	252 (23.0%)	618 (19.5%)	104 (22.2%)	89 (19.0%)	1063 (20.4%)
$N_{obs,analysis}$	-	-	846	2545	365	380	4136

Source: \Deliverables\Analysis\Development\For report\miscellaneous-calculations-forReport.html
Notes: The lower limit of quantification of fruquintinib and M11 was 1.0 ng/mL.

Source: population-pk-and-exposure-response-final-analysis-report, Page 62 (link).

Base model

The base model is a one-compartment PK model with absorption lag time (tlag), first-order absorption, and first-order elimination.

Inter-individual variability was modelled assuming a log-normal distribution for patient level random effects. The inter-individual variability was considered for total body clearance of drug (CL), volume of distribution for central compartment (V2), absorption rate constant (ka), volume of distribution of compartment (V4) for metabolite M11 and total clearance of metabolize (CLM).

Intra-individual variability was tested as combined additive and proportional error model on the dependent variable.

Model evaluation and selection were based on the point estimates of PK parameters, their respective relative standard errors and standard statistical criteria of goodness-of-fit such as a decrease in the minimum objective function value (OFV), successful model convergence, and diagnostic prediction-corrected visual predictive check (pcVPC).

Covariate analysis

Covariate parameters were taken into search as follows:

- CL/F: albumin, body weight, CLCR (creatinine clearance), ECOG (Eastern Cooperative Oncology Group) status, NCI (National Cancer Institute) hepatic impairment category, race (Asian versus Black versus White/other/missing), and tumor type
- Apparent clearance of M11 (CLM/F): albumin, body weight, CLCR, NCI hepatic impairment category, race, and tumor type
- Fruquintinib bioavailability (F1): race, sex, and tumor type fruquintinib first-order absorption rate constant (Ka): concomitant administration with PPIs (proton pump inhibitor), race, and tumor type
- V/F: body weight, health status, and race
- Apparent volume of distribution of M11 (VM/F): body weight, albumin, and race
- The effect of NCI hepatic impairment category on CLM/F was not statistically significant in the univariate screening step, but it was included in the stepwise covariate search to enable a formal investigation of the potential impact of organ impairment on M11 PK

Source: population-pk-and-exposure-response-final-analysis-report, Page 84 (link).

Software and estimation methods
Data manipulation, visualization, and simulations were conducted using R version 4.2.0, a data analysis language suitable for use in regulated environments. Population PK analyses were conducted using NONMEM® version 7.4.3.

20.4.3.2.2 Final Model

The parameter estimates for the final PopPK model are listed in Table 58 and the schematic of the final PopPK model for fruquintinib and M11 is shown in Figure 13. The goodness-of-fit plots for the final model are shown in Figure 14. The pcVPC plot for the final covariate model with all data is shown in Figure 15. The impact of body weight, health status, and coadministration of PPI on the population PK model parameters into effects on fruquintinib and M11 exposures were shown by forest plots for steady-state area under the plasma concentration-time curve (AUCSS, Figure 16).

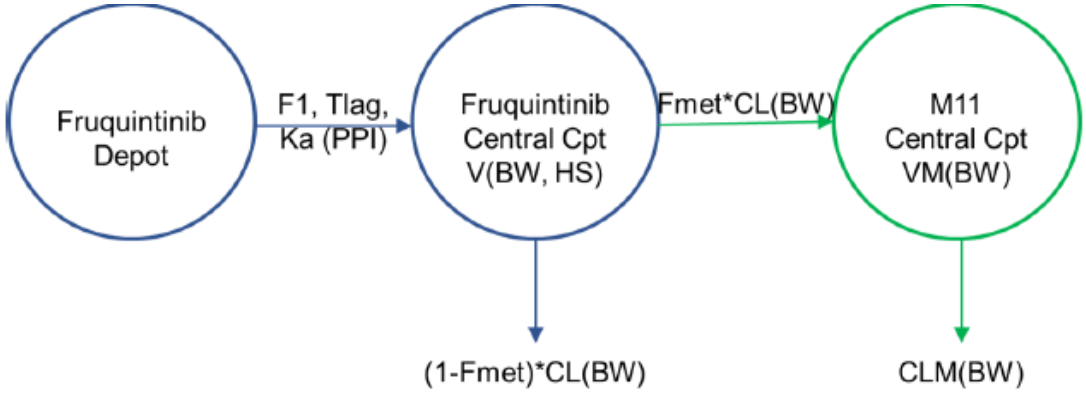
The PK of fruquintinib after oral administration was described by a 1-compartment model with first-order absorption, absorption lag time, and first-order elimination and M11 PK connected to the central compartment of fruquintinib by a single metabolite compartment with linear elimination of M11. The conversion from fruquintinib to M11 was assumed to be 7.25%.

- Fruquintinib PK was found to be dose proportional because dose-dependency of bioavailability over the dose range in the analysis dataset (1 to 6 mg) was excluded during model development.
- CL/F, CLM/F, V/F, and VM/F increased with increasing body weight.
- Fruquintinib Ka was 60.7% lower with coadministration of PPIs, and fruquintinib V/F was 9.08% lower in healthy subjects compared to patients with cancer.
- The magnitudes of the covariate effects due to body weight, coadministration of PPIs, and health status on fruquintinib exposures were minor (< 20%) and not considered clinically meaningful, shown in Figure 16.
- No effects on the PK of fruquintinib or M11 were identified based on sex, age (18.0 to 82.0 years), ECOG performance status score, race (Japanese versus Chinese versus other races, Figure 17), ethnicity (Figure 18), albumin, tumor type (CRC or other tumor types), mild or moderate renal impairment (CLCR from 32.6 to < 90 mL/min), mild hepatic impairment based on NCI hepatic impairment categorization, and concomitant administration of H2A.
- The data were insufficient for an assessment of the impact of moderate and severe hepatic impairment, severe renal impairment, and coadministration of CYP3A4-modifying drugs on fruquintinib or M11 PK.

Reviewer comments:
There are enough subjects in mild and moderate renal or mild hepatic impairment sub-groups. So based on the PopPK model, there is no dose adjustment for mild or moderate renal impairment, and mild hepatic impairment. A dedicated PK study,[4] used to evaluate the effect of moderate hepatic impairment (Child-Pugh Class B) on the PK of fruquintinib after the administration of a single oral dose in subjects who do not have cancer, indicated that there was no clinically significant difference in exposure to fruquintinib and M11 in subjects with moderate hepatic impairment compared with historical data in healthy subjects; however, insufficient numbers of patients were studied to make formal recommendations regarding the safety of exposing patients with moderate hepatic impairment to fruquintinib.

[4] Hepatic impairment report page 19 (link)

Figure 13. Schematic of the Final Population PK Model for Fruquintinib and M11



BW = body weight; CL = fruquintinib clearance; CLM = M11 clearance; Cpt = compartment; F1 = fruquintinib bioavailability; Fmet = fraction of fruquintinib metabolized to M11; HS = health status; Ka = fruquintinib first-order absorption rate constant; PPI = proton pump inhibitor; Tlag = absorption lag time; V = fruquintinib volume of distribution; VM = M11 volume of distribution

Source: population-pk-and-exposure-response-final-analysis-report, Page 88 (link).

Table 57. Population Pharmacokinetic Parameter Estimates for Final Models

Parameter	Estimate	%RSE	95% CI	Shrinkage (%)
Typical Values				
CL/F (L/h)	0.808	1.2	0.789, 0.827	
V/F (L)	50.4	0.9	49.5, 51.3	

Parameter	Estimate	%RSE	95% CI	Shrinkage (%)
Ka (1/h)	2.52	7.6	2.15, 2.90	
Lag Time (h)	0.463	1.1	0.453, 0.473	
CLM/F (L/h)	0.161	2.2	0.154, 0.169	
VM/F (L)	11.7	3.3	10.9, 12.4	
Covariate Effects				
CL/F ~ Body Weight Exponent	0.430	12.1	0.328, 0.532	
CLM/F ~ Body Weight Exponent	1.06	9.0	0.873, 1.25	
Ka ~ PPI Fractional Change	-0.607	11.0	-0.739, -0.476	
V/F ~ Body Weight Exponent	0.924	3.9	0.853, 0.995	
V/F ~ Healthy Subject Fractional Change	-0.0908	26.7	-0.138, -0.0434	
VM/F ~ Body Weight Exponent	1.28	11.0	1.00, 1.56	
Residual Variability				
Fruquintinib Proportional Error %CV	19.9	1.2	19.4, 20.4	8.5
Fruquintinib Additive Error SD (ng/mL)	4.50	4.1	4.14, 4.86	
M11 Proportional Error %CV	19.5	1.4	18.9, 20.0	
M11 Additive Error SD (ng/mL)	0.551	4	0.509, 0.594	
Between-Subject Variability				
BSV CL/F %CV	26.2	3.5	24.3, 28.0	8.3
Corr (CL/F, V/F)	0.295	10.9		
BSV V/F %CV	16.3	4.9	14.6, 17.8	19.4
Corr (CL/F, CLM/F)	0.563	4.9		
Corr (V/F, CLM/F)	0.167	19.7		
BSV CLM/F %CV	49.3	3.5	45.5, 53.0	10.6
Corr (CL/F, VM/F)	0.413	6.8		
Corr (V/F, VM/F)	0.495	6.4		
Corr (CLM/F, VM/F)	0.708	4.4		
BSV VM/F %CV	75.3	3.7	68.4, 82.0	12.5
BSV Ka %CV	247	4.4	201, 299	21.0

Source: \Deliverables\Analysis\Development\POPPK\Modeling-update-28DEC2022\Simultaneous\Final Model Parameter Estimate Table and Forest Plots.docx

Notes: Typical values correspond to a patient with cancer weighing 73 kg and not taking any PPIs. Shrinkage is reported only for residual and BSV parameters. BSV %CV is calculated as sqrt(exp(Ω – 1)), where Ω is the BSV variance.

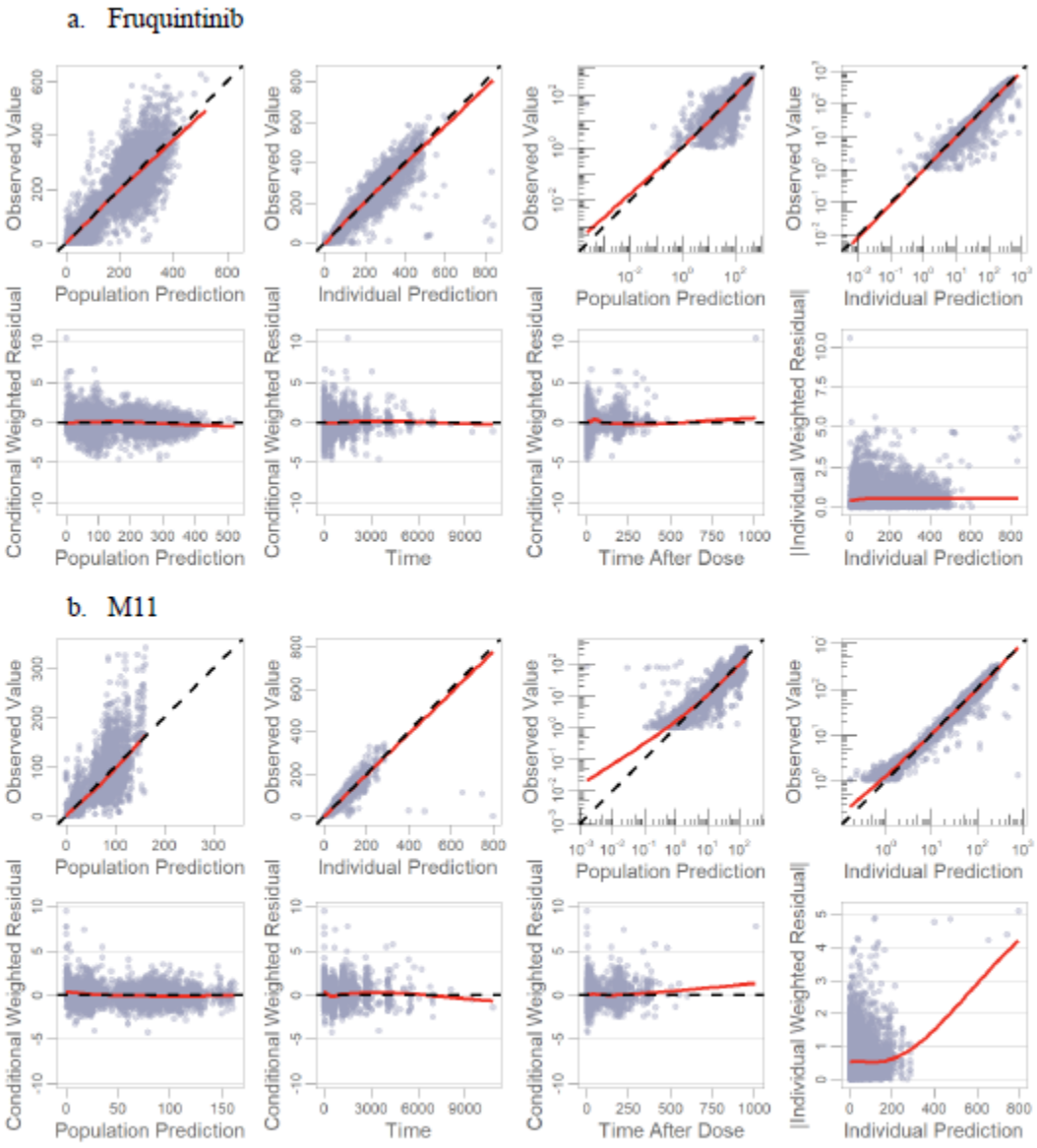
%CV = percent coefficient of variation; %RSE = percent relative standard error; BSV = between-subject variability; CI = confidence interval; CL/F = apparent clearance of fruquintinib; CLM/F = apparent clearance of M11; Corr = correlation; Ka = first-order absorption rate constant; PPI = proton pump inhibitor; SD = standard deviation; V/F = apparent volume of distribution of fruquintinib; VM/F = apparent volume of distribution of M11

Source: population-pk-and-exposure-response-final-analysis-report, Page 86 (link).

Review comments:

*Although the definition of %CV (%CV=sqrt(exp(Ω-1)) in the report appears not to be correct, which should be %CV=sqrt(exp(Ω)-1)*100, the calculation of %CV in the report is right.*

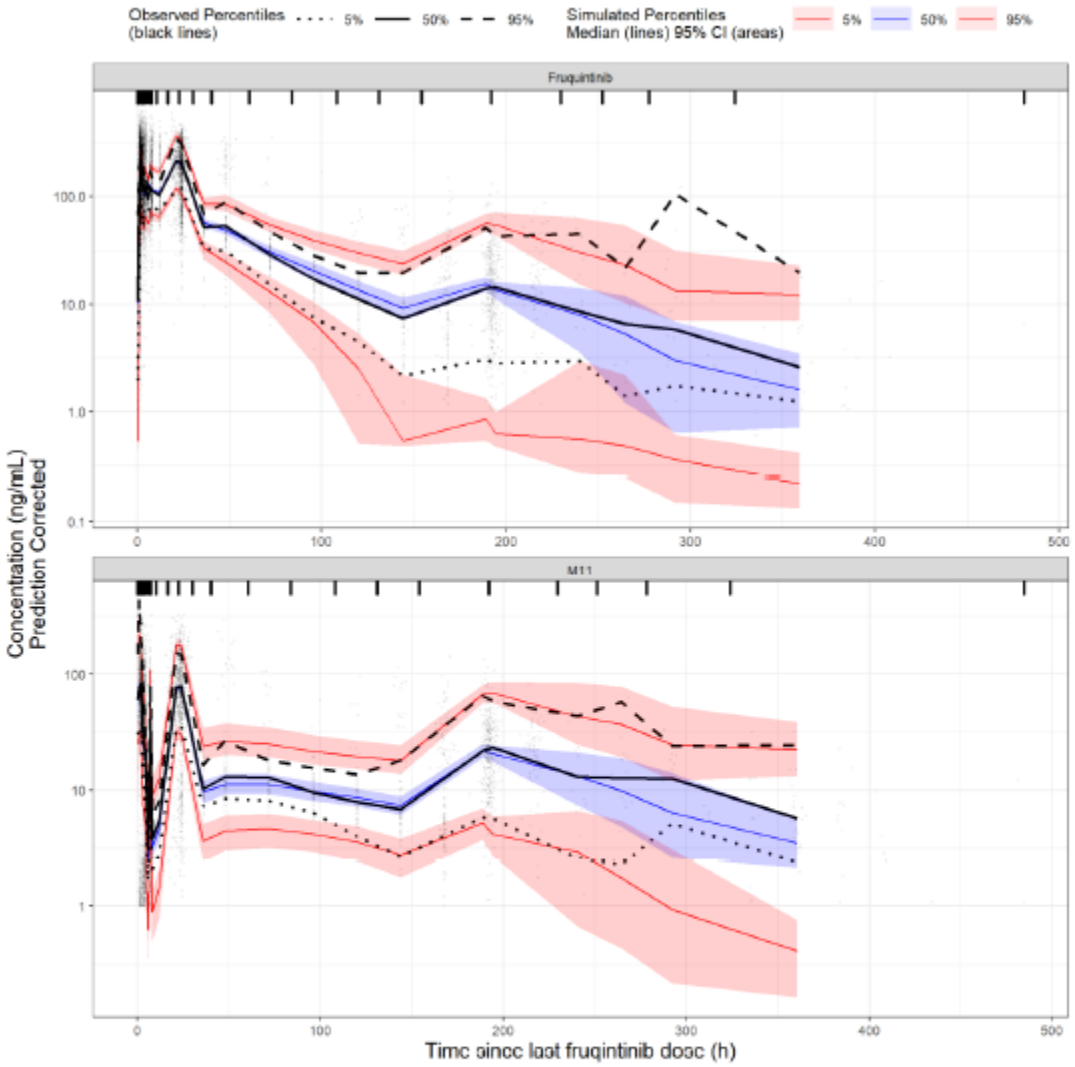
Figure 14. Goodness-of-fit plots for final covariate model



Source: \Deliverables\Analysis\Development\POPPK\Modeling-update-28DEC2022\scripts\Simultaneous_GOF_run_final_cov_noCL/FMALB_fullblock_woKA_noF1SEX.html
Notes: Gray points represent individual data points. Black lines represent the line of unity for observation versus prediction plots, y = 0 for the conditional weighted residual plots, and a straight line passing through the 25th and 75th percentiles of the standardized residuals and the same percentiles of a standard normal distribution for the quantile-quantile plot. Red lines represent LOESS regression lines.
LOESS = locally estimated scatterplot smoothing

Source: population-pk-and-exposure-response-final-analysis-report, Page 90 (link).

Figure 15. Visual Predictive Check of the Final Population PK Model



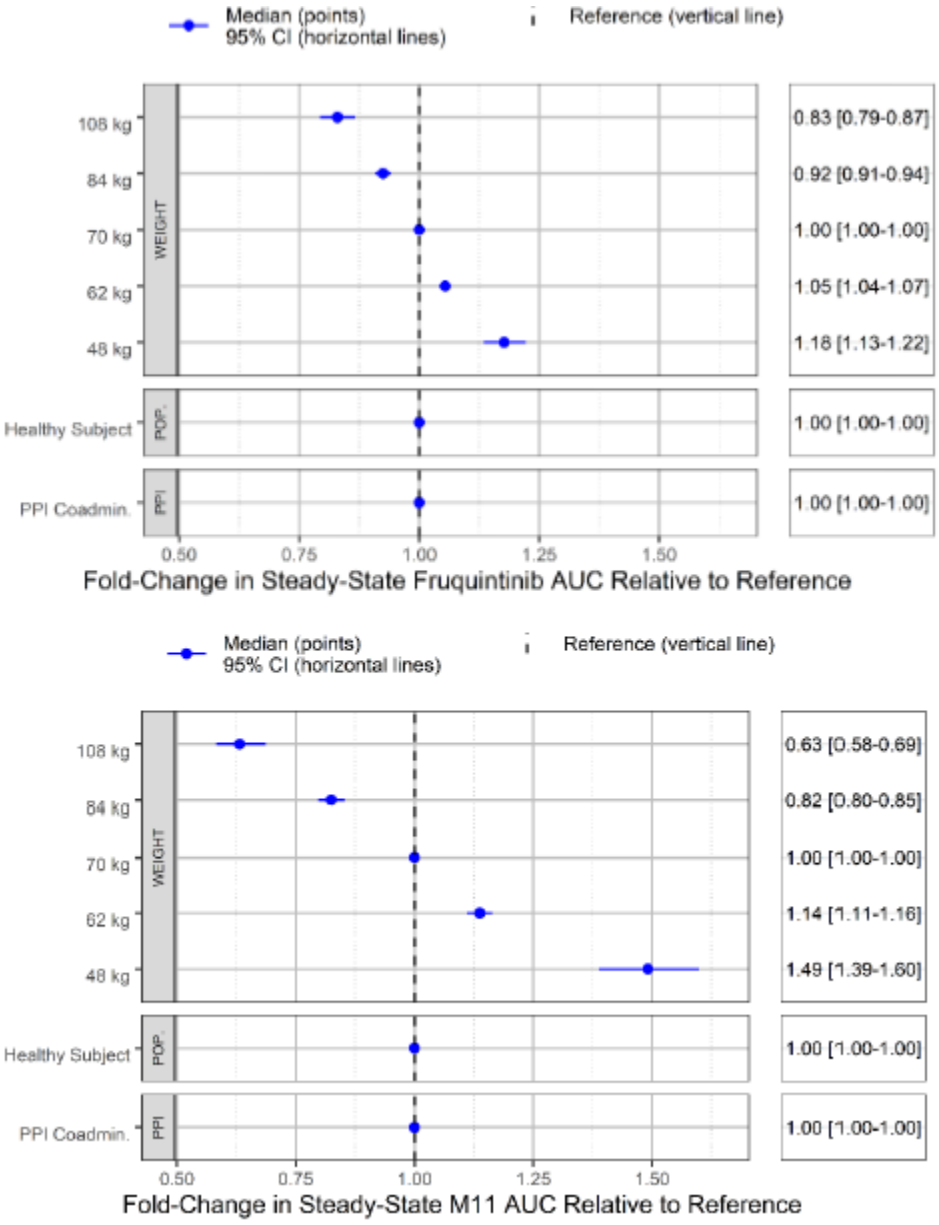
Source: \Deliverables\Analysis\Development\POPPK\Modeling-update-28DEC2022\scripts\Simultaneous_GOF_run_final_cov_noCL/FMALB_fullblock_woKA_noF1SEX_06JAN2023.html

Notes: Black dots are observed data points; the black solid line is the observed median; the black dotted and dashed lines are the observed p5 and p95, respectively. The blue-shaded region is the 95% PI of the simulated median, and red-shaded regions are the 95% PI of the simulated p5 and p95. One sparsely sampled data point at TAD > 500 from fruquintinib and 7 sparsely sampled data points at TAD > 500 from M11 were excluded from figure for better visualization.

CI = confidence interval; p5 = 5th percentile; p95 = 95th percentile; PI = prediction interval; PK = pharmacokinetic; TAD = time after dose

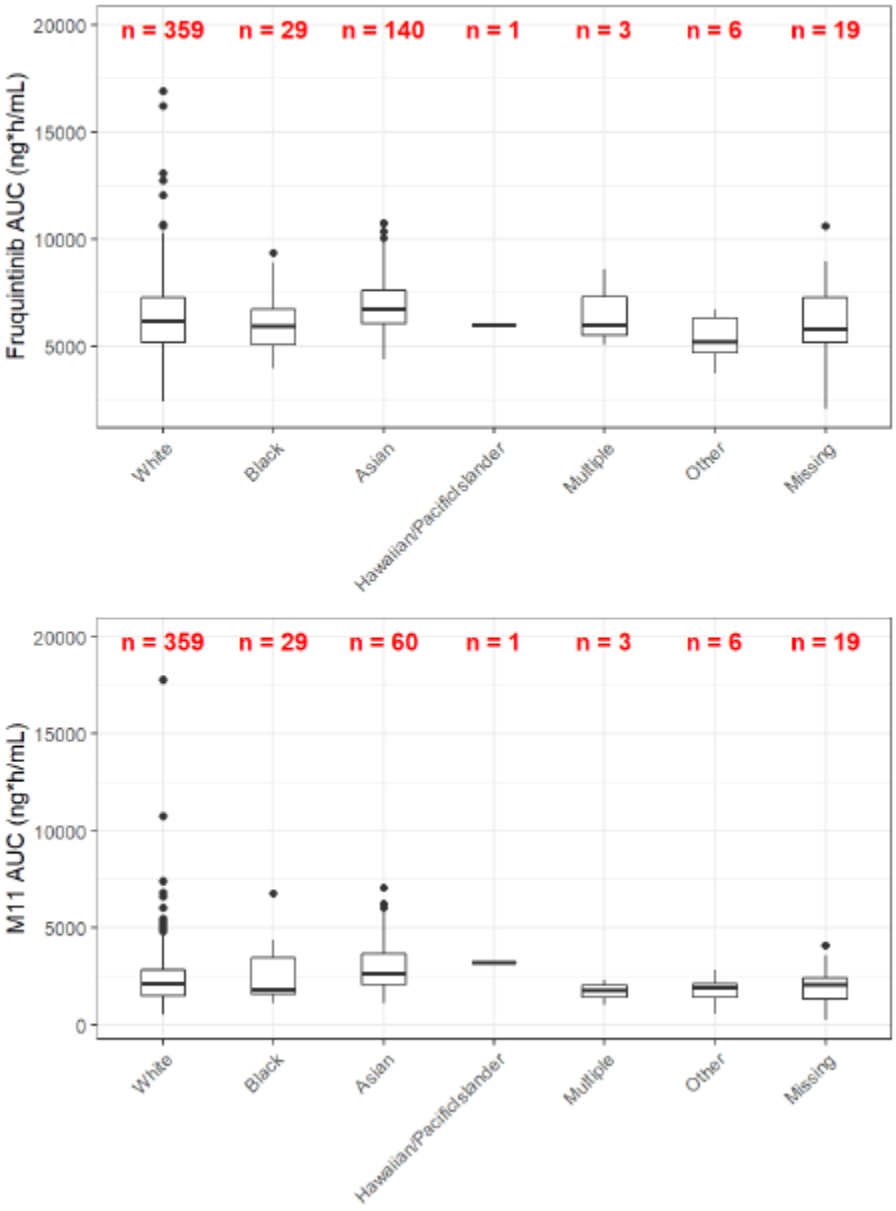
Source: population-pk-and-exposure-response-final-analysis-report, Page 91 (link).

Figure 16. Covariate Effects on Steady-State Fruquintinib and M11 AUC



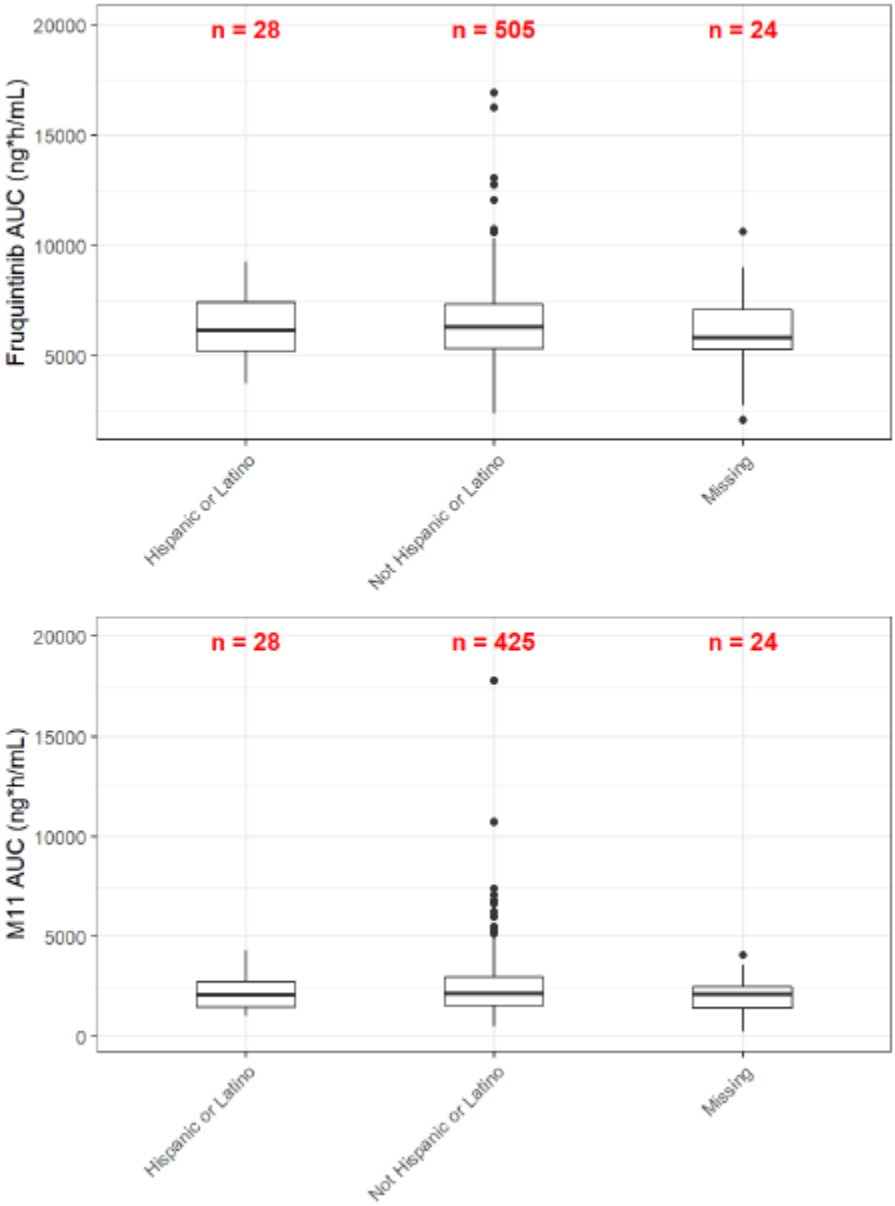
Source: pk-and-exposure-response-final-analysis-report, Page 93 (link).

Figure 17. Relationship Between Model-Predicted Fruquintinib and M11 Steady-State AUC Following 5 mg QD Continuous Dosing and Race



Source: population-pk-and-exposure-response-final-analysis-report, Page 99 (link).

Figure 18. Relationship Between Model-Predicted Fruquintinib and M11 Steady-State AUC Following 5 mg QD Continuous Dosing and Ethnicity



Source: population-pk-and-exposure-response-final-analysis-report, Page 100 (link).

Reviewer comments:

The body weights (108 and 48 kg) in the forest plots are the 95% and 5% quantile values of body weights of PopPK dataset. Overall, tested intrinsic factors including body weight were found to have no clinically meaningful impact on fruquintinib exposure.

Exposure-response (E-R) analysis

The primary objectives of applicant's E-R analysis were to:

- To characterize the relationship between fruquintinib exposure and efficacy (OS and PFS) in patients with mCRC.
- To explore the relationship between fruquintinib and M11 exposures and safety.

Regimens of fruquintinib (QD) continuous, and QD 3/1 and AUC_{ave} were used for both the safety and efficacy E-R analyses. The safety E-R analysis explored the relationships between fruquintinib exposure, M11 exposure, and combined fruquintinib + M11 exposure (adjusted for molecular weight differences) and safety endpoints of interest. Meanwhile, efficacy E-R analyses investigated only fruquintinib exposure because M11 does not have clinically meaningful contribution to the total pharmacological activity of fruquintinib at therapeutic exposures (M11 potency was 10 times lower than that of fruquintinib and the mean metabolite-to-parent AUC ratio was approximately 0.3 at steady state).

The E-R analyses were performed under the assumption that there were sufficient events for a meaningful analysis. p-Values lower than 0.05 were considered (nominally) statistically significant as no correction for multiple statistical testing was implemented. The nature of the current analyses was purely exploratory and considered hypothesis-generating. Thus, the estimates of the parameters of interest, 95% confidence intervals (CIs), and p-values were determined to assist in evaluating the E-R relationships and therefore should be cautiously interpreted.

E-R analysis for safety

Fruquintinib and M11 are associated with adverse events (AEs); therefore, fruquintinib, M11, and combined fruquintinib + M11 exposures were investigated. In addition to AUC_{ave} and C_{maxSS}, C_{maxSS} +regimen (QD continuous versus QD 3/1) was also included as an exposure measure to account for differences due to regimen. Because M11 PK data were available only for the QD 3/1 regimen (study 2019-013-GLOB1 and 2015-013-00US1), C_{maxSS} + regimen for M11 and combined fruquintinib + M11 were not included in any of the safety E-R analyses.

The E-R analysis for safety was based on data from all 4 patient studies (Studies 2019-013-GLOB1, 2015-013-00US1, 2009-013-00CH1, and 2012-013-00CH3) who had both exposure and AE data, with a range of fruquintinib doses (1 to 6 mg) and 2 different regimens (QD continuous versus QD 3/1).

The summary of covariates stratified by studies was shown in Table 59. Most patients (65%) were White, and the majority of patients (53.8%) were males. The median (range) age was 61(18 to 82) years old, and the median baseline body weight was 72.4 (36.0 to 158) kg.

A summary of frequencies of the selected AEs of special interest in each study is presented in Table 60. Grade ≥ 3proteinuria and Grade ≥ 3 hemorrhage had low

frequencies (≤ 2.7%), while any grade dermatological toxicity and any grade hypertension had relatively high frequencies across studies (approximately 44%).

Table 58. Covariate Summary Statistics for Patients Included in the Safety E-R Analysis

	2009-013-00CH1 (N = 40)	2012-013-00CH3 (N = 40)	2015-013-00US1 (N = 101)	2019-013-GLOB1 (N = 334)	Overall (N = 515)
Age (y)					
Mean (SD)	54.5 (11.2)	54.2 (12.5)	58.6 (10.2)	62.5 (10.1)	60.5 (10.8)
Median (%CV)	56.0 (20.5)	56.5 (23.1)	59.0 (17.4)	64.0 (16.2)	61.0 (17.9)
[Min, Max]	[18.0, 70.0]	[21.0, 70.0]	[34.0, 77.0]	[25.0, 82.0]	[18.0, 82.0]
Sex					
Female	22 (55.0%)	12 (30.0%)	49 (48.5%)	155 (46.4%)	238 (46.2%)
Male	18 (45.0%)	28 (70.0%)	52 (51.5%)	179 (53.6%)	277 (53.8%)
Body Weight (kg)					
Mean (SD)	60.7 (11.7)	65.9 (13.0)	84.3 (21.3)	73.7 (17.3)	74.1 (18.6)
Median (%CV)	59.0 (19.3)	64.0 (19.8)	83.5 (25.2)	73.0 (23.5)	72.4 (25.0)
[Min, Max]	[36.0, 95.0]	[40.0, 101]	[44.8, 135]	[40.1, 158]	[36.0, 158]
Race					
Asian	40 (100%)	40 (100%)	4 (4.0%)	48 (14.4%)	132 (25.6%)
Black or African American	0 (0%)	0 (0%)	9 (8.9%)	12 (3.6%)	21 (4.1%)
Other	0 (0%)	0 (0%)	3 (3.0%)	3 (0.9%)	6 (1.2%)
White	0 (0%)	0 (0%)	85 (84.2%)	250 (74.9%)	335 (65.0%)
Multiple	0 (0%)	0 (0%)	0 (0%)	2 (0.6%)	2 (0.4%)
Not Reported	0 (0%)	0 (0%)	0 (0%)	16 (4.8%)	16 (3.1%)
Unknown	0 (0%)	0 (0%)	0 (0%)	3 (0.9%)	3 (0.6%)
Country					
China	40 (100%)	40 (100%)	0 (0%)	0 (0%)	80 (15.5%)
Rest of World	0 (0%)	0 (0%)	101 (100%)	289 (86.5%)	390 (75.7%)
Japan	0 (0%)	0 (0%)	0 (0%)	45 (13.5%)	45 (8.7%)
ECOG Performance Status Score					
0--- Fully Active	9 (22.5%)	8 (20.0%)	36 (35.6%)	151 (45.2%)	204 (39.6%)
1--- Restricted Activity	31 (77.5%)	32 (80.0%)	65 (64.4%)	183 (54.8%)	311 (60.4%)

	2009-013-00CH1 (N = 40)	2012-013-00CH3 (N = 40)	2015-013-00US1 (N = 101)	2019-013-GLOB1 (N = 334)	Overall (N = 515)
Prior Therapy With TAS-102 and/or Regorafenib					
None	40 (100%)	40 (100%)	0 (0%)	0 (0%)	80 (15.5%)
Both	0 (0%)	0 (0%)	15 (14.9%)	131 (39.2%)	146 (28.3%)
Missing	0 (0%)	0 (0%)	59 (58.4%)	6 (1.8%)	65 (12.6%)
Regorafenib	0 (0%)	0 (0%)	8 (7.9%)	30 (9.0%)	38 (7.4%)
TAS-102	0 (0%)	0 (0%)	19 (18.8%)	167 (50.0%)	186 (36.1%)
RAS Status					
Missing	40 (100%)	40 (100%)	35 (34.7%)	0 (0%)	115 (22.3%)
Mutant	0 (0%)	0 (0%)	46 (45.5%)	208 (62.3%)	254 (49.3%)
Wild Type	0 (0%)	0 (0%)	20 (19.8%)	126 (37.7%)	146 (28.3%)
Duration of Metastatic Disease					
Missing	40 (100%)	40 (100%)	0 (0%)	0 (0%)	80 (15.5%)
≤ 18 Months	0 (0%)	0 (0%)	24 (23.8%)	25 (7.5%)	49 (9.5%)
> 18 Months	0 (0%)	0 (0%)	77 (76.2%)	309 (92.5%)	386 (75.0%)
Alanine Aminotransferase (IU/L)					
Mean (SD)	20.8 (10.9)	22.9 (13.0)	27.1 (18.8)	27.9 (23.6)	26.8 (21.3)
Median (%CV)	17.3 (52.3)	17.2 (56.6)	21.0 (69.3)	21.0 (84.4)	21.0 (79.5)
[Min, Max]	[8.10, 55.0]	[6.70, 54.6]	[7.00, 105]	[2.00, 170]	[2.00, 170]
Aspartate Aminotransferase (IU/L)					
Mean (SD)	24.3 (10.2)	26.2 (8.99)	33.7 (18.7)	36.7 (25.8)	34.3 (23.0)
Median (%CV)	21.1 (42.2)	26.6 (34.3)	29.0 (55.4)	29.0 (70.4)	28.0 (67.1)
[Min, Max]	[10.9, 68.0]	[12.3, 53.5]	[13.0, 106]	[8.00, 220]	[8.00, 220]
Missing	0 (0%)	0 (0%)	0 (0%)	2 (0.6%)	2 (0.4%)
Total Bilirubin (μmol/L)					
Mean (SD)	10.9 (3.83)	10.6 (4.01)	9.29 (5.13)	10.5 (5.53)	10.3 (5.24)
Median (%CV)	10.1 (35.3)	10.1 (37.9)	8.55 (55.2)	8.76 (52.8)	8.70 (51.0)
[Min, Max]	[5.30, 20.6]	[5.20, 22.3]	[0.400, 30.8]	[2.57, 38.0]	[0.400, 38.0]
Regimen					
QD 3/1	14 (35.0%)	20 (50.0%)	101 (100%)	334 (100%)	469 (91.1%)
QD	26 (65.0%)	20 (50.0%)	0 (0%)	0 (0%)	46 (8.9%)
Fruquintinib Average Daily AUC (ng•h/mL)					
Mean (SD)	5760 (1970)	5290 (1160)	4200 (1170)	4990 (1360)	4920 (1420)
Median (%CV)	5490 (34.3)	5080 (21.9)	3920 (27.8)	4850 (27.1)	4820 (28.9)
[Min, Max]	[1430, 9720]	[3750, 8570]	[1790, 7940]	[1560, 12700]	[1430, 12700]

	2009-013-00CH1 (N = 40)	2012-013-00CH3 (N = 40)	2015-013-00US1 (N = 101)	2019-013-GLOB1 (N = 334)	Overall (N = 515)
Fruquintinib Steady-State C_{max} (ng/mL)					
Mean (SD)	317 (116)	300 (58.8)	268 (71.8)	320 (81.5)	308 (83.6)
Median (%CV)	322 (36.4)	296 (19.6)	251 (26.7)	308 (25.5)	302 (27.1)
[Min, Max]	[66.8, 610]	[204, 449]	[132, 493]	[108, 838]	[66.8, 838]
Fruquintinib Steady-State C_{min} (ng/mL)					
Mean (SD)	223 (84.2)	208 (43.5)	197 (58.9)	233 (69.8)	223 (68.8)
Median (%CV)	232 (37.8)	200 (20.9)	183 (29.9)	225 (29.9)	217 (30.8)
[Min, Max]	[52.3, 425]	[115, 321]	[70.6, 387]	[58.3, 610]	[52.3, 610]

Source: HMPI-PMX-FRUQ-2785— Project Data\Deliverables\Analysis\Development\ER\efficacy\ fruq-efficacyER_Final_startingdose_21FEB2023_UpdatedSurvPredictions.html
Note: The fruquintinib exposure measures have not been dose normalized.
%CV = percent coefficient of variation; AUC = area under the plasma concentration-time curve; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; ECOG = Eastern Cooperative Oncology Group; Max = maximum; Min = minimum; N = number of patients; QD = once daily; RAS = rat sarcoma virus; SD = standard deviation

Source: population-pk-and-exposure-response-final-analysis-report, Page 105 (link).

Table 59. Summary of Frequencies of Adverse Events of Special Interest Stratified by Study

	2009-013-00CH1 (N = 40)	2012-013-00CH3 (N = 40)	2015-013-00US1 (N = 101)	2019-013-GLOB1 (N = 334)	Overall (N = 515)
Any Grade Dermatological Toxicity					
No	5 (12.5%)	5 (12.5%)	61 (60.4%)	216 (64.7%)	287 (55.7%)
Yes	35 (87.5%)	35 (87.5%)	40 (39.6%)	118 (35.3%)	228 (44.3%)
Gr3+ Dermatological Toxicity					
No	32 (80.0%)	33 (82.5%)	95 (94.1%)	312 (93.4%)	472 (91.7%)
Yes	8 (20.0%)	7 (17.5%)	6 (5.9%)	22 (6.6%)	43 (8.3%)
Any Grade Hypertension					
No	22 (55.0%)	17 (42.5%)	40 (39.6%)	209 (62.6%)	288 (55.9%)
Yes	18 (45.0%)	23 (57.5%)	61 (60.4%)	125 (37.4%)	227 (44.1%)
Gr3+ Hypertension					
No	33 (82.5%)	32 (80.0%)	73 (72.3%)	286 (85.6%)	424 (82.3%)
Yes	7 (17.5%)	8 (20.0%)	28 (27.7%)	48 (14.4%)	91 (17.7%)
Any Grade Hepatic Function Abnormal					
No	25 (62.5%)	18 (45.0%)	65 (64.4%)	253 (75.7%)	361 (70.1%)
Yes	15 (37.5%)	22 (55.0%)	36 (35.6%)	81 (24.3%)	154 (29.9%)

	2009-013-00CH1 (N = 40)	2012-013-00CH3 (N = 40)	2015-013-00US1 (N = 101)	2019-013-GLOB1 (N = 334)	Overall (N = 515)
Gr3+ Hepatic Function Abnormal					
No	37 (92.5%)	34 (85.0%)	94 (93.1%)	304 (91.0%)	469 (91.1%)
Yes	3 (7.5%)	6 (15.0%)	7 (6.9%)	30 (9.0%)	46 (8.9%)
Any Grade Proteinuria					
No	20 (50.0%)	16 (40.0%)	56 (55.4%)	267 (79.9%)	359 (69.7%)
Yes	20 (50.0%)	24 (60.0%)	45 (44.6%)	67 (20.1%)	156 (30.3%)
Gr3+ Proteinuria					
No	36 (90.0%)	38 (95.0%)	100 (99.0%)	327 (97.9%)	501 (97.3%)
Yes	4 (10.0%)	2 (5.0%)	1 (1.0%)	7 (2.1%)	14 (2.7%)
Any Grade Hemorrhage					
No	30 (75.0%)	19 (47.5%)	75 (74.3%)	291 (87.1%)	415 (80.6%)
Yes	10 (25.0%)	21 (52.5%)	26 (25.7%)	43 (12.9%)	100 (19.4%)
Gr3+ Hemorrhage					
No	39 (97.5%)	39 (97.5%)	97 (96.0%)	327 (97.9%)	502 (97.5%)
Yes	1 (2.5%)	1 (2.5%)	4 (4.0%)	7 (2.1%)	13 (2.5%)

Source: \Deliverables\Analysis\Development\ER\safety\ER_safety_binary20230126_v2.html
Gr3+ = Grade 3 or higher; N = number of patients

Source: population-pk-and-exposure-response-final-analysis-report, Page 107 (link).

Safety Basic E-R models

The AICs (Akaike information criterion) and LRT (likelihood ratio test) p-values from logistic regression analyses for all exposure measures are assessed for all of the safety endpoints. The AEs showed statistically significant E-R relationships with fruquintinib model-predicted exposure measures shown in Table 61:

Table 60. Statistically Significant Safety Exposure-Response Relationships Based on Logistic Regression Analysis With Only Exposure Measures

Safety Endpoint	Exposure Measure	AIC	LRT p-Value
Dermatological Toxicity Any Grade	Fruquintinib AUC_{ave}	704.58	0.0103
	Fruquintinib C_{maxSS} + regimen	677.33	< 0.0001
Gr3+ Dermatological Toxicity	Fruquintinib AUC_{ave}	289.10	0.0010
	Fruquintinib C_{maxSS} + regimen	281.72	< 0.0001
Hemorrhage Any Grade	Fruquintinib AUC_{ave}	507.03	0.0466
	Fruquintinib C_{maxSS} + regimen	498.12	0.0006
Gr3+ Hepatic Function Abnormal	M11 AUC_{ave}	252.69	0.0352
Proteinuria Any Grade	Fruquintinib C_{maxSS} + regimen	629.10	0.0135
Gr3+ Proteinuria	Fruquintinib C_{maxSS} + regimen	126.41	0.0170

Source: \Analysis\Development\ER\safety\ER_safety_binary20230126_v2.html
AIC = Akaike information criterion; AUC_{ave} = average daily area under the plasma concentration-time curve over the4-week cycle at steady state; C_{maxSS} = steady-state maximum plasma concentration; Gr3+ = Grade 3 or higher; LRT = likelihood ratio test

Source: population-pk-and-exposure-response-final-analysis-report, Page 109 (link).

Safety final E-R models

Based on basic models, covariates were investigated, including age, sex, body weight, race, and baseline ECOG performance status score. The final model for any grade dermatological toxicity included fruquintinib C_{maxSS} + regimen, race, and ECOG performance status score. Parameter estimates for the final model are presented in Table 62. The selected race/country categorization were as follows: China, Japan, other Asian, White/other/missing (reference), and Black. Neither the C_{maxSS} term nor the regimen term was (nominally) statistically significant (slope p-values = 0.265 and 0.192, respectively).

Table 61. Final Model Parameter Estimates for Any Grade Dermatological Toxicity

Parameter	Units	Estimate	%RSE	p-Value	Odds Ratio (95% CI)
Intercept		-1.35	29.8%	0.0008	
Fruquintinib C_{maxSS}	1/(ng/mL)	0.00134	89.4%	0.265	1.00 (0.999, 1.00)
Regimen = QD Continuous		-1.09	76.3%	0.192	0.338 (0.0483, 1.48)
Race/Country = Black		0.119	404.5%	0.804	1.13 (0.414, 2.82)
Race/Country = Other Asian		0.947	82.2%	0.224	2.58 (0.554, 13.4)
Race/Country = China		3.54	20.9%	< 0.0001	34.6 (10.2, 216)
Race/Country = Japan		1.04	32.2%	0.0019	2.83 (1.48, 5.54)
ECOG Performance Status Score = 0		0.539	38%	0.0085	1.72 (1.15, 2.56)

Source: \Analysis\Development\ER\safety\ER_safety_binary20230126_v2.html
%RSE = percent relative standard error; CI = confidence interval; C_{maxSS} = steady-state maximum plasma concentration; ECOG = Eastern Cooperative Oncology Group; QD = once daily

Source: population-pk-and-exposure-response-final-analysis-report, Page 113 (link).

The final model for Grade ≥ 3 dermatological toxicity included only C_{maxSS} and regimen, shown in Table 63. Higher fruquintinib exposure was associated with a higher probability of Grade ≥ 3 dermatological toxicity. The QD continuous regimen was associated with a markedly higher AE probability.

Table 62. Final Model Parameter Estimates for Gr3+ Dermatological Toxicity

Parameter	Units	Estimate	%RSE	p-Value	Odds Ratio (95% CI)
Intercept		-3.98	15.2%	< 0.0001	
Fruquintinib C_{maxSS}	1/(ng/mL)	0.00411	41.5%	0.0159	1.00 (1.00, 1.01)
Regimen = QD Continuous		1.75	22.5%	< 0.0001	5.73 (2.58, 12.3)

Source: \Analysis\Development\ER\safety\ER_safety_binary20230126_v2.html
%RSE = percent relative standard error; CI = confidence interval; C_{maxSS} = steady-state maximum plasma concentration; Gr3+ = Grade 3 or higher; QD = once daily

Source: population-pk-and-exposure-response-final-analysis-report, Page 118 (link).

The final model for Gr3+ hepatic function abnormal included M11 AUC^{ave} and baseline AST. Parameter estimates are presented in Table 64. The AUC_{ave} of M11 was not (nominally) statistically significant (p = 0.07) indicating no E-R relationship for Grade ≥ 3 hepatic function abnormal.

Table 63. Final Model Parameter Estimates for Gr3+ Hepatic Function Abnormal

Parameter	Units	Estimate	%RSE	p-Value	Odds Ratio (95% CI)
Intercept		-3.53	10.7%	< 0.0001	
M11 AUC_{ave}	1/(ng•h/mL)	0.000216	55.2%	0.07	1.00 (1.00, 1.00)
AST	1/(IU/L)	0.0176	29.9%	0.0008	1.02 (1.01, 1.03)

Source: \Analysis\Development\ER\safety\ER_safety_binary20230126_v2.html
%RSE = percent relative standard error; AUC_{ave} = average daily area under the plasma concentration-time curve over the 4-week cycle at steady state; AST = aspartate aminotransferase; CI = confidence interval; Gr3+ = Grade 3 or higher

Source: population-pk-and-exposure-response-final-analysis-report, Page 128 (link).

The final model for any grade proteinuria included sex, race, body weight, C_{maxSS}, and regimen, shown in Table 65. The selected race/country categorization were as follows: China, Japan, other Asian, White/other/missing (reference), and Black. The C_{maxSS} and QD continuous regimen terms were not statistically significant, indicating that there is no (nominally) statistically significant E-R relationship for any grade proteinuria.

Table 64. Final Model Parameter Estimates for Any Grade Proteinuria

Parameter	Units	Estimate	%RSE	p-Value	Odds Ratio (95% CI)
Intercept		-2.58	30.9%	0.0012	N/A
Fruquintinib C_{maxSS}	1/(ng/mL)	-0.00101	142.0%	0.484	0.999 (0.996, 1.02)
Regimen = QD Continuous		-0.553	86.2%	0.246	0.575 (0.223, 1.45)
Sex = Female		0.659	34.3%	0.004	1.93 (1.24, 3.02)
Race/Country = Black		0.342	144.0%	0.488	1.41 (0.507, 3.59)
Race/Country = Asian		-0.568	193.0%	0.604	0.567 (0.0295, 3.47)
Race/Country = China		2.05	19.3%	< 0.0001	7.74 (3.62, 17.2)
Race/Country = Japan		1.38	25.2%	< 0.0001	3.99 (2.02, 7.92)
Body Weight	1/kg	0.0172	38.2%	0.009	1.02 (1.00, 1.03)

Source: \Analysis\Development\ER\safety\ER_safety_binary20230126_v2.html
%RSE = percent relative standard error; CI = confidence interval; C_{maxSS} = steady-state maximum plasma concentration; N/A = not applicable; QD = once daily

Source: population-pk-and-exposure-response-final-analysis-report, Page 131 (link).

The final model for Gr3+ proteinuria included only C_{maxSS}, and regimen shown in Table 66. Fruquintinib C_{maxSS} was not (nominally) statistically significant (p = 0.642).

Table 65. Final Model Parameter Estimates for Grade 3+ Proteinuria

Parameter	Units	Estimate	%RSE	p-Value	Odds Ratio (95% CI)
Intercept		-4.38	23.7%	<0.0001	
Fruquintinib C_{maxSS}	1/(ng/mL)	0.00143	214.6%	0.642	1.00 (0.995, 1.01)
Regimen = QD Continuous		1.87	31.5%	0.0015	6.50 (1.90, 20.1)

Source: \Analysis\Development\ER\safety\ER_safety_binary20230126_v2.html
%RSE = percent relative standard error; CI = confidence interval; C_{maxSS} = steady-state maximum plasma concentration; N/A = not applicable; QD = once daily

Source: population-pk-and-exposure-response-final-analysis-report, Page 134 (link).

The final model of any grade hemorrhage included only C_{maxSS} and regimen, shown in Table 67. The fruquintinib C_{maxSS} term was not (nominally) statistically significant (p = 0.166).

Table 66. Final Model Parameter Estimates for Any Grade Hemorrhage

Parameter	Units	Estimate	%RSE	p-Value	Odds Ratio (95% CI)
Intercept		-2.13	20.3%	< 0.0001	
Fruquintinib C_{maxSS}	1/(ng/mL)	0.00180	72.3%	0.166	1.00 (0.999, 1.00)
Regimen = QD Continuous		1.27	25.8%	0.0001	3.57 (1.86, 6.75)

Source: \Analysis\Development\ER\safety\ER_safety_binary20230126_v2.html
%RSE = percent relative standard error; CI = confidence interval; C_{maxSS} = steady-state maximum plasma concentration; QD = once daily

Source: population-pk-and-exposure-response-final-analysis-report, Page 138 (link).

Based on the basic and final logistic model assessment, the E-R of safety is as following:

- Higher model-predicted fruquintinib C_{maxSS} was associated with a higher probability of Grade ≥ 3 dermatological toxicity.
- Compared to the QD 3/1 regimen, the QD continuous regimen was associated with higher probabilities of Grade ≥ 3 dermatological toxicity, any grade hemorrhage, and Grade ≥ 3 proteinuria.
- There was no trend of positive E-R relationships with fruquintinib or M11 exposure identified for any grade dermatological toxicity, any grade or Grade ≥ 3 hypertension, any grade or Grade ≥ 3 hepatic function abnormal, any grade proteinuria, or Grade ≥ 3 + hemorrhage.

E-R analysis for efficacy

There were 374 patients with mCRC who had fruquintinib exposure data in Study 2019-013-GLOB1 (N = 334) and Cohort B of Study 2015-013-00US1 (N = 40). One patient in Cohort B of Study 2015-013-00US1 who had a primary disease site of stomach was excluded from the analysis. There were 6 patients in the Japanese safety lead-in cohort of Study 2019-013-GLOB1 who were not in the intent-to-treat population and were

therefore excluded from the efficacy E-R analysis. Consequently, 368 patients were included in the E-R analysis (328 in Study 2019-013-GLOB1 and 40 in Cohort B of Study 2015-013-00US1) for each efficacy endpoint, shown in Table 68 with summary statistics of covariates and exposures demography shown in Table 69. The relative dose intensity (RDI) in the analysis dataset was shown in Table 70.

Table 67. Summary of Patients Included in the Efficacy E-R Analyses

Study Subset	Total Number of Patients	Number of Patients With Fruquintinib Exposure Data
2019-013-GLOB1	456	328
2015-013-00US1 Cohort B	40	40
Total	496	368

Source: \Analysis\Development\ER\efficacy\fruq-efficacyER_Final_startingdose_21FEB2023_UpdatedSurvPredictions.html
Note: Only patients with mCRC are included in the summary. This excludes the patient in Study 2015-013-00US1 Cohort B who had a primary disease site of stomach.
E-R = exposure-response; mCRC = metastatic colorectal cancer.

Source: population-pk-and-exposure-response-final-analysis-report, Page 140 (link).

Table 68. Summary Statistics of Covariates and Exposures for Efficacy Exposure-Response Analysis

	2015-013-00US1 Cohort B (N = 40)	2019-013-GLOB1 (N = 328)	Overall (N = 368)
Age (y)			
Mean (SD)	58.3 (10.2)	62.6 (10.1)	62.1 (10.2)
Median (%CV)	57.5 (17.5)	64.0 (16.2)	63.0 (16.4)
[Min, Max]	[34.0, 76.0]	[25.0, 82.0]	[25.0, 82.0]
Sex			
Female	20 (50.0%)	153 (46.6%)	173 (47.0%)
Male	20 (50.0%)	175 (53.4%)	195 (53.0%)
Body Weight (kg)			
Mean (SD)	89.1 (20.8)	73.9 (17.3)	75.5 (18.3)
Median (%CV)	86.3 (23.4)	73.0 (23.5)	74.1 (24.3)
[Min, Max]	[53.1, 127]	[40.1, 158]	[40.1, 158]
Race			
Asian	1 (2.5%)	42 (12.8%)	43 (11.7%)
Black or African American	4 (10.0%)	12 (3.7%)	16 (4.3%)
Other	3 (7.5%)	3 (0.9%)	6 (1.6%)
White	32 (80.0%)	250 (76.2%)	282 (76.6%)
Multiple	0 (0%)	2 (0.6%)	2 (0.5%)
Not reported	0 (0%)	16 (4.9%)	16 (4.3%)
Unknown	0 (0%)	3 (0.9%)	3 (0.8%)
Country			
Rest of the World	40 (100%)	289 (88.1%)	329 (89.4%)
Japan	0 (0%)	39 (11.9%)	39 (10.6%)
ECOG Performance Status Score			
0 - Fully Active	15 (37.5%)	145 (44.2%)	160 (43–5%)
1 - Restricted Activity	25 (62.5%)	183 (55.8%)	208 (56.5%)
Prior Therapy With TAS-102 and/or Regorafenib			
Both	14 (35.0%)	131 (39.9%)	145 (39.4%)
Regorafenib	8 (20.0%)	30 (9.1%)	38 (10.3%)
TAS-102	18 (45.0%)	167 (50.9%)	185 (50.3%)
RAS Status			
Mutant	17 (42.5%)	206 (62.8%)	223 (60.6%)
Missing	14 (35.0%)	0 (0%)	14 (3.8%)
Wild Type	9 (22.5%)	122 (37.2%)	131 (35.6%)

	2015-013-00US1 Cohort B (N = 40)	2019-013-GLOB1 (N = 328)	Overall (N = 368)
Duration of Metastatic Disease			
> 18 Months	36 (90.0%)	303 (92.4%)	339 (92.1%)
≤ 18 Months	4 (10.0%)	25 (7.6%)	29 (7.9%)
Dose Regimen			
5 mg QD 3/1	40 (100%)	328 (100%)	368 (100%)
Fruquintinib Average Daily AUC Based on Starting Dose (ng•h/mL)			
Mean (SD)	4100 (941)	4990 (1360)	4900 (1350)
Median (%CV)	3910 (22.9)	4850 (27.2)	4760 (27.5)
[Min, Max]	[1790, 6520]	[1560, 12700]	[1560, 12700]
Fruquintinib Steady-State C_{min} Based on Starting Dose (ng/mL)			
Mean (SD)	193 (49.4)	233 (70.0)	229 (69.1)
Median (%CV)	183 (25.6)	224 (30.0)	221 (30.2)
[Min, Max]	[70.6, 318]	[58.3, 610]	[58.3, 610]
Fruquintinib Average Daily AUC Adjusted for RDI (ng•h/mL)			
Mean (SD)	3670 (1040)	4240 (1370)	4180 (1350)
Median (%CV)	3410 (28.4)	4150 (32.3)	4080 (32.3)
[Min, Max]	[1750, 6520]	[1500, 12400]	[1500, 12400]
Fruquintinib Steady-State C_{min} Adjusted for RDI (ng/mL)			
Mean (SD)	173 (52.9)	198 (68.1)	195 (67.0)
Median (%CV)	161 (30.6)	194 (34.4)	191 (34.3)
[Min, Max]	[70.9, 318]	[58.3, 573]	[58.3, 573]

%CV = percent coefficient of variation; AUC = area under the plasma concentration-time curve;

Cmin = minimum plasma concentration; ECOG = Eastern Cooperative Oncology Group; Max = maximum;

Min = minimum; N =number of patients; RAS = rat sarcoma virus; RDI = relative dose intensity;

SD = standard deviation

Source: population-pk-and-exposure-response-final-analysis-report, Page 141 (link).

Table 69. Summary Statistics of Relative Dose Intensity in the Efficacy Exposure-Response Analysis Dataset

	2015-013-00US1 (N = 40)	2019-013-GLOB1 (N = 328)	Overall (N = 368)
Relative Dose Intensity (%)			
Mean (SD)	89.3 (14.0)	85.1 (17.5)	85.6 (17.2)
Median (%CV)	95.6 (15.7)	91.1 (20.6)	92.1 (20.1)
[Min, Max]	[50.4, 100]	[24.7, 114]	[24.7, 114]
Missing	1 (2.5%)	13 (4.0%)	14 (3.8%)

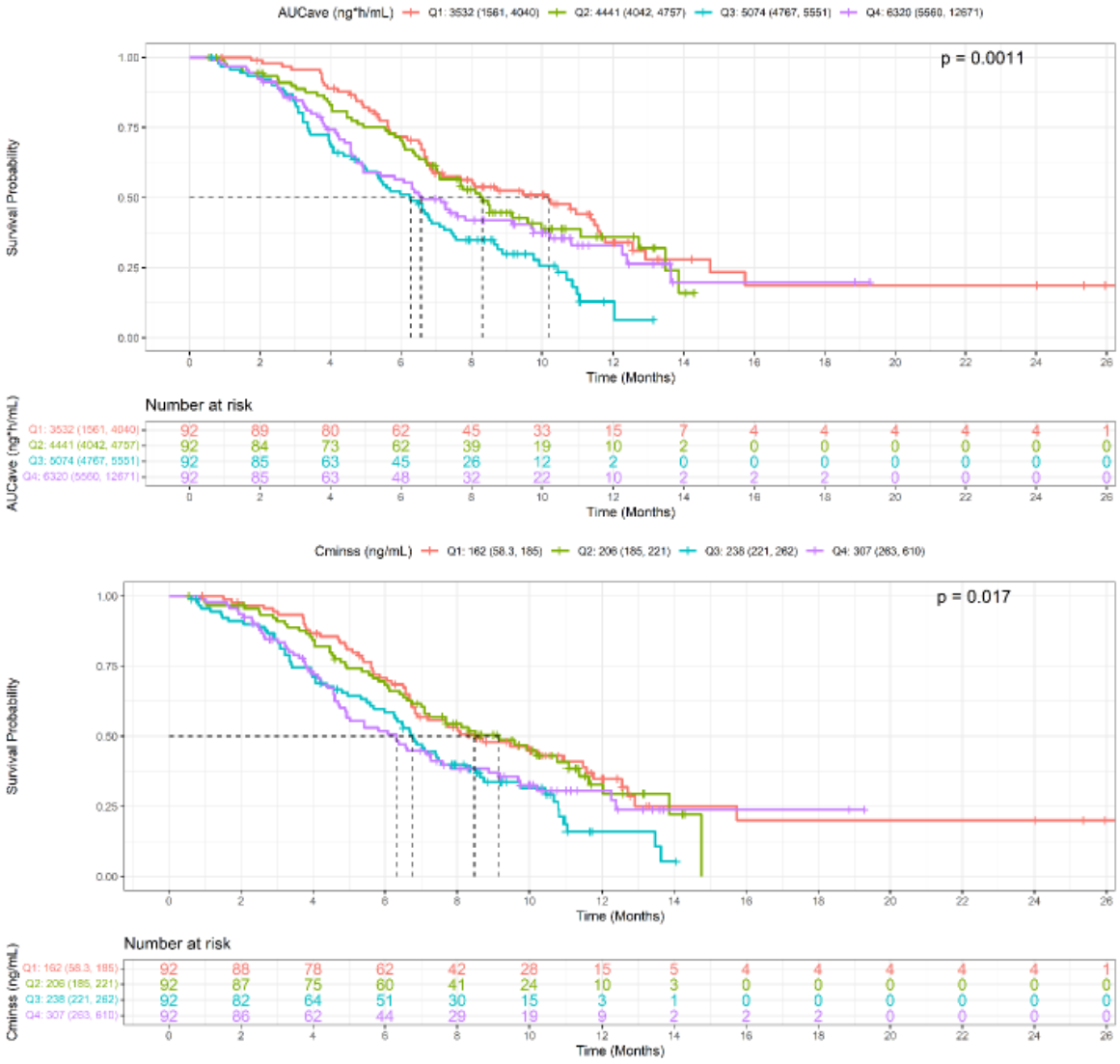
Source: population-pk-and-exposure-response-final-analysis-report, Page 143 (link).

OS E-R Analysis

Of the 368 patients in the analysis dataset, 236 (64.1%) died during the study. The median (95% CI) OS was 7.26 (6.74, 8.51) months. Kaplan-Meier curves for OS stratified by quartiles of fruquintinib AUC_{ave} and C_{minSS} based on the starting dose (5 mg QD 3/1) are presented in Figure 19. The OS for the 2 lowest exposure quartiles was longer for both exposure measures. Kaplan-Meier curves for covariates are presented in Figure 20, respectively. There were apparent trends for longer OS with increasing

body weight and for ECOG performance status score of 0 and shorter OS for duration of metastatic disease ≤ 18 months.

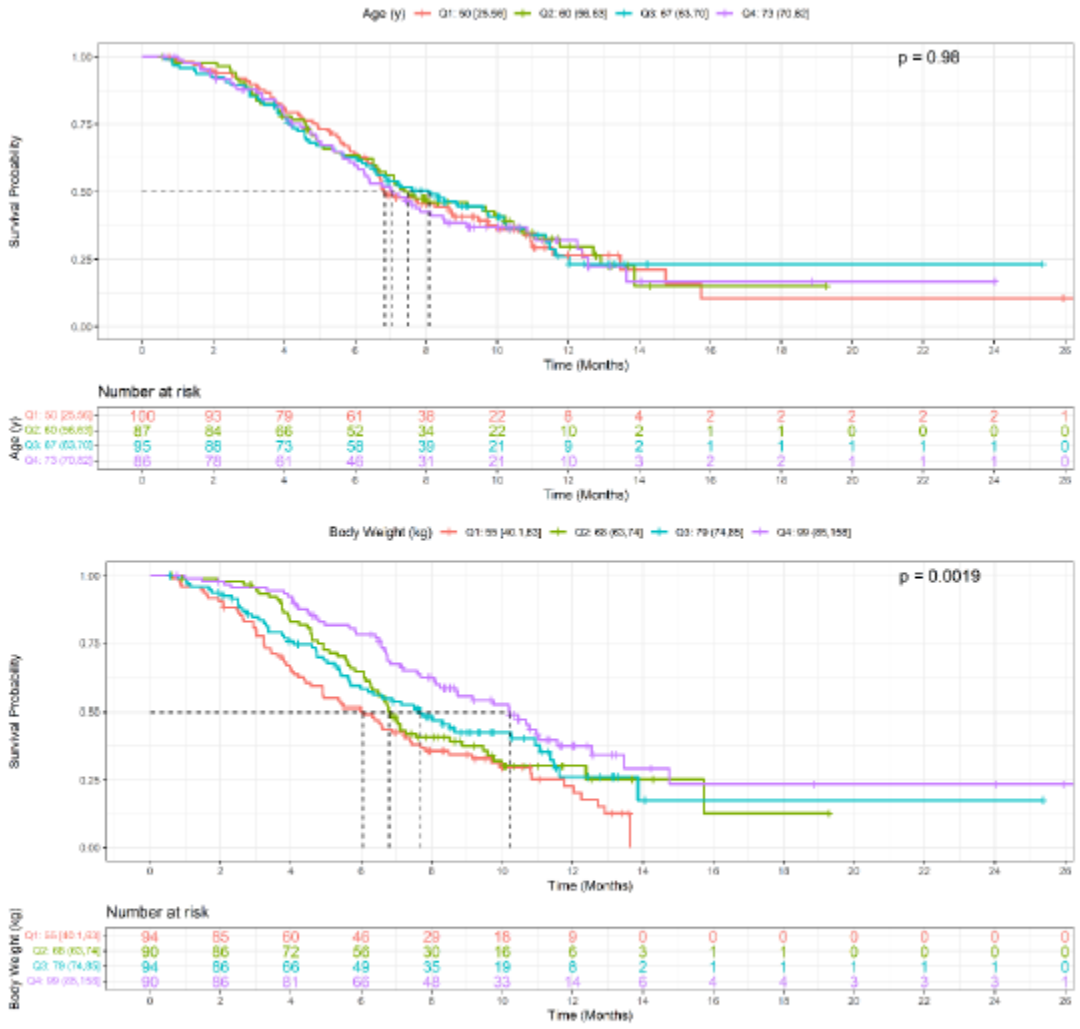
Figure 19. Kaplan-Meier Plots for OS Stratified by Fruquintinib Exposures Based on Starting Dose (Studies 2019-013-GLOB1 and 2015-013-00US1 Cohort B)



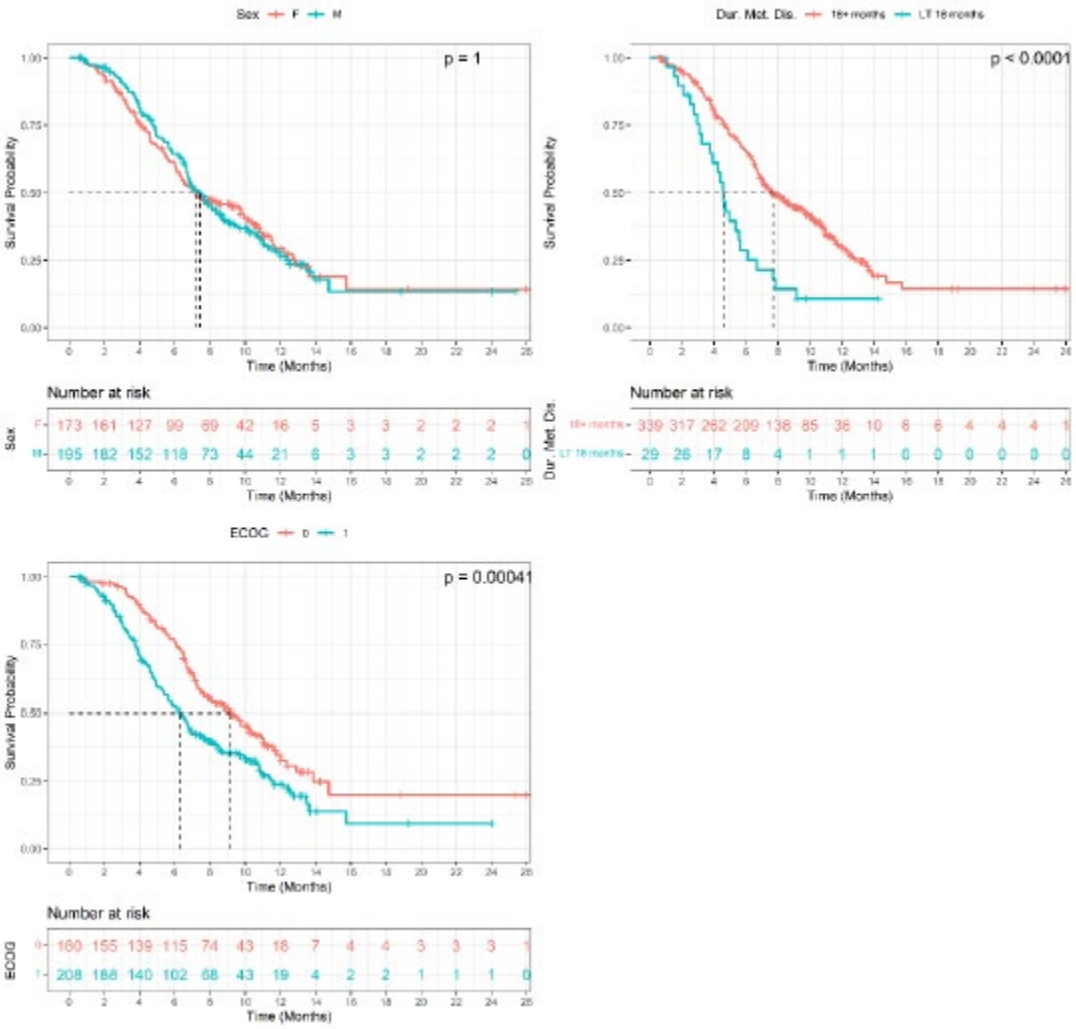
Source: \Analysis\Development\ER\efficacy\fruq-efficacyER_Final_startingdose_21FEB2023_UpdatedSurvPredictions.html
Notes: The legend shows the median (minimum, maximum) for each exposure quartile.
AUCave = average daily area under the plasma concentration-time curve over the 4-week cycle at steady state; Cminss = steady-state minimum plasma concentration; p = p-value from log-rank test; OS = overall survival; Qn = nth quartile

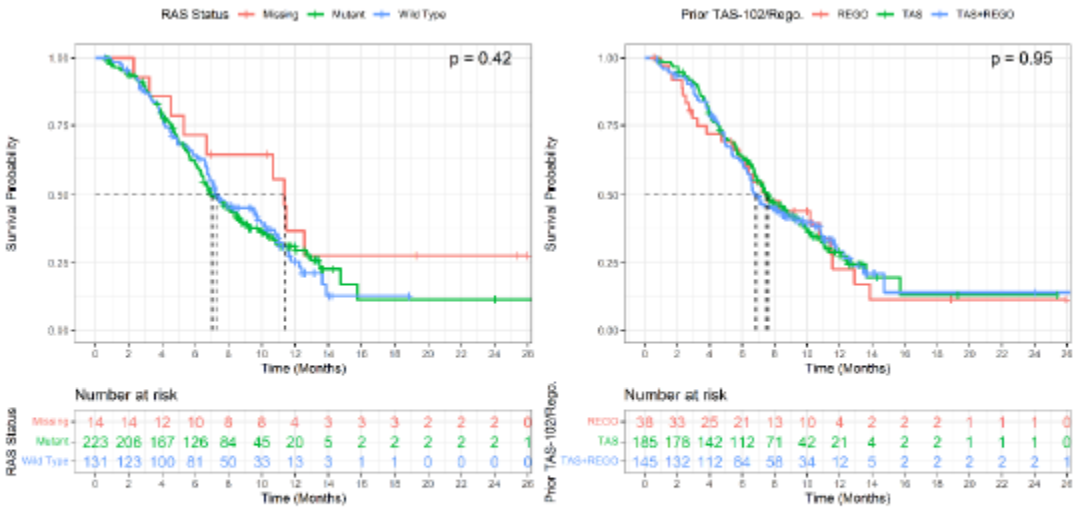
Source: population-pk-and-exposure-response-final-analysis-report, Page 144 (link).

Figure 20. Kaplan-Meier Plots for OS Stratified by Covariates (Studies 2019-013-GLOB1 and 2015-013-00US1 Cohort B)



Source: \Analysis\Development\ER\efficacy\fruq-efficacyER_Final_startingdose_21FEB2023_UpdatedSurvPredictions.html
Notes: The legend shows the median and within the parentheses or square brackets, the minimum and maximum for each covariate quartile. Parentheses indicate an open interval, while square brackets indicate a closed interval.
OS = overall survival; p = p-value from log-rank test; Qn = nth quartile


Sex F M
p = 1
Survival Probability
Time (Months)
Number at risk
Sex
F 173 161 127 99 69 42 16 5 3 3 2 2 2 1
M 195 182 152 118 73 44 21 6 3 3 2 2 2 0
Dur. Mot. Dis. 18+ months LT 18 months
p < 0.0001
Survival Probability
Time (Months)
Number at risk
Dur. Met. Dis.
18+ months 339 317 262 209 138 85 36 10 6 6 4 4 4 1
LT 18 months 29 26 17 8 4 1 1 1 0 0 0 0 0 0
Time (Months)
ECOG 0 1
p = 0.00041
Survival Probability
Time (Months)
Number at risk
ECOG
0 160 155 139 115 74 43 18 7 4 4 3 3 3 1
1 208 188 140 102 68 43 19 4 2 2 1 1 1 0
Time (Months)



Source: \Analysis\Development\ER\efficacy\fruq-efficacyER_Final_startingdose_21FEB2023_UpdatedSurvPredictions.html
Notes: The legend shows the median (minimum, maximum) for each exposure quartile.
Dur. Met. Dis. = duration of metastatic disease; ECOG = Eastern Cooperative Oncology Group; F = female; LT = less than; M = male; OS = overall survival; p = p-value from log-rank test; RAS = rat sarcoma virus; REGO = regorafenib

Source: population-pk-and-exposure-response-final-analysis-report, Page 145-147 (link).

Based on the starting dose, the Cox proportional hazards models for OS with fruquintinib exposure measures were assessed and the final model consisted of terms for C_{minSS}, baseline body weight, ECOG performance status score, and duration of metastatic disease. Parameter estimates for the OS E-R final model that used exposures based on the starting dose of fruquintinib are shown in Table 71, which showed that C_{minSS} is not (nominally) statistically significant.

Table 70. Final E-R Model Parameter Estimates for OS Using Exposures Based on the Starting Dose

Parameter	Units	Estimate	%RSE	p-Value	Hazard Ratio (95% CI)
Fruquintinib C_{minSS}	1/(ng/mL)	0.00193	53.2	0.0600	1.0019 (0.99992, 1.0039)
Body Weight	1/kg	-0.0108	33.9	0.0032	0.98924 (0.98215, 0.99637)
ECOG Performance Status Score = 0	-	-0.477	28.2	0.0004	0.62059 (0.47657, 0.80813)
Dur. of Met. ≤ 18 Months	-	0.931	23.1	< 0.0001	2.5373 (1.666, 3.8643)

Source: population-pk-and-exposure-response-final-analysis-report, Page 148 (link).

Parameter estimates for the OS E-R final model used on exposures adjusted for RDI are shown in Table 72 and are similar to those of the model that used exposures based on the starting doses. After accounting for covariate effects, the association of CminSS with OS was not statistically significant, with a hazard ratio 95% CI that included 1 (hazard ratio [95% CI] = 1.0004 [0.99715, 1.0037]). The positive value of the CminSS:

sex interaction coefficient suggests a less sensitive OS E-R relationship for female patients.

Table 71. Final E-R Model Parameter Estimates for OS Using Exposures Adjusted for Relative Dose Intensity

Parameter	Units	Estimate	%RSE	p-Value	Hazard Ratio (95% CI)
Fruquintinib C_{minSS}	1/(ng/mL)	0.000407	408.3	0.8065	1.0004 (0.99715, 1.0037)
Sex = Female	-	-0.298	48.5	0.0394	0.74201 (0.55863, 0.98559)
Body Weight	1/kg	-0.0141	26.9	0.0002	0.98597 (0.97864, 0.99335)
ECOG = 0	-	-0.478	28.2	0.0004	0.62031 (0.47644, 0.80761)
Dur. of Met. ≤ 18 Months	-	0.869	24.9	0.0001	2.3855 (1.5606, 3.6462)
C_{minSS}:Sex = Female Interaction	1/(ng/mL)	0.00568	37.0	0.0068	N/A

Source: population-pk-and-exposure-response-final-analysis-report, Page 151 (link).

PFS E-R Analysis

There were no clear trends of PFS with exposure as evidenced by the log rank test. Kaplan-Meier curves for the continuous and categorical covariates showed that there was a trend of shorter PFS for duration of metastatic disease ≤ 18 months.

Parameter estimates for the PFS E-R final model that used on exposures based on the starting dose of fruquintinib are shown in Table 73. After accounting for covariate effects, the association of C_{minSS} with PFS was (nominally) statistically significant, with a hazard ratio 95% CI that excluded 1 (hazard ratio [95% CI] = 1.0018 [1.0002, 1.0035]).

Table 72. Final E-R Model Parameter Estimates for PFS Using Exposures Based on the Starting Dose

Parameter	Units	Estimate	%RSE	p-Value	Hazard Ratio (95% CI)
Fruquintinib C_{minSS}	1/(ng/mL)	0.00185	45.6	0.0285	1.0018 (1.0002, 1.0035)
Body Weight	1/kg	-0.00665	45.3	0.0273	0.99338 (0.98753, 0.99926)
Dur. of Met. ≤ 18 Months		0.76100	26.4	0.0001	2.1399 (1.4445, 3.1703)

Source: population-pk-and-exposure-response-final-analysis-report, Page 158 (link).

Parameter estimates for the PFS E-R final model that used on exposures adjusted for RDI are shown in Table 74, which are similar to those of the model that used exposures based on the starting doses. After accounting for covariate effects, the association of

C_{minSS} with PFS was (nominally) statistically significant, with a hazard ratio 95% CI that excluded 1 (hazard ratio [95% CI] = 1.0038 [1.0021, 1.0055]).

Table 73. Final E-R Model Parameter Estimates for PFS Using Exposures Adjusted for Relative Dose Intensity

Parameter	Units	Estimate	RSE%	p-Value	Hazard Ratio (95% CI)
Fruquintinib C_{minSS}	1/(ng/mL)	0.00380	22.9	< 0.0001	1.0038 (1.0021, 1.0055)
Body Weight	1/kg	-0.00714	41.0	0.0146	0.99289 (0.98721, 0.99859)
Dur. of Met. ≤ 18 Months	-	0.70800	28.3	0.0004	2.0305 (1.3704, 3.0086)

Source: population-pk-and-exposure-response-final-analysis-report, Page 161 (link).

Based on final cox model assessments, the E-R of efficacy is as following:

- There was no trend of positive relationships between OS and fruquintinib CminSS derived based on the starting dose or adjusted for RDI following the 5 mg QD 3/1 regimen in Studies 2019-013-GLOB1 and 2015-013-00US1 Cohort B.
- There is a positive trend of ER relationship between exposure (CminSS) and progression-free survival (PFS). But given the context of a lack of an E-R relationship for OS and the PFS treatment effect in Study 2019-013-GLOB1, this observation may not be clinically meaningful.

Physiologically based Pharmacokinetic Modeling Analysis Review

Application Number	NDA 217564
Drug Name (Generic)	Fruquintinib
Proposed Indication	For treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti-VEGF therapy; and, if *RAS* wild-type, an anti-epidermal growth factor receptor (EGFR) therapy.
Clinical Division	CDER/OTS/OCP/DCPI
PBPK Consult request	Wentao Fu, Ph.D.
Primary PBPK Reviewer	Miyoung Yoon, Ph.D.
Secondary PBPK Reviewer	Yuching Yang, Ph.D.
Applicant	HUTCHMED Limited/Takeda Pharmaceuticals International, AG

Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's physiologically based pharmacokinetic (PBPK) modeling and simulation analyses for the purpose of evaluating the drug-drug interaction (DDI) potentials of fruquintinib as victim of CYP3A enzyme modulators to inform the prescribing information.

Based on the review of the Applicant's PBPK report (HUMP-2-B), PBPK report addendum 1, and the responses to the FDA information requests (IRs) submitted on May 4, July 11, and August 2, 2023, as well as the submitted modeling and simulation files, the Division of Pharmacometrics concluded that the Applicant's PBPK model is adequate to predict the effects of CYP3A4 modulators on the PK of fruquintinib as follows:

The Applicant's PBPK analysis captured the clinical DDI study results (Study 2020-013-00US2), which reported about 10% increase in the area under the curve (AUC) of fruquintinib when coadministered with itraconazole, whereas about 65% decrease in AUC with rifampin. They suggested that the expected drug interaction of fruquintinib is not clinically meaningful with strong CYP3A4 inhibitors, while it is expected to be moderate with strong CYP3A4 inducers. The Applicant's PBPK analysis predicted about 32% decrease in the fruquintinib AUC with efavirenz coadministration suggesting that the drug interaction potential of fruquintinib with the moderate CYP3A4 inducer is weak.

In addition, the PBPK analysis was adequate to assess potential risks and provide support in predicting DDI potential of fruquintinib as perpetrator for P-gp and BCRP transporter substrates based on the clinical DDI study conducted with a single dose fruquintinib.

Background

Fruquintinib is proposed for treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti-VEGF therapy; and, if *RAS* wild-type, an anti-epidermal growth factor receptor therapy. The proposed dose regimen is 5 mg QD taken orally with or without food for 3 weeks followed by 1 week off in each 28-day treatment cycle.

Fruquintinib exhibits low solubility that is pH dependent and high permeability. Food did not affect fruquintinib exposure and rabeprazole (a proton pump inhibitor) did not show clinically significant DDI. Fruquintinib Tmax was around 2 h, while half-life was 42 h. Absolute bioavailability was not evaluated. Steady state was achieved after 14 days of repeat QD dosing (Studies 2009-013-00CH1 and 2015-013-00US1) with an accumulation ratio of about 4 and 31 for fruquintinib and its metabolite, M11, respectively (PK Memo for Module 2.7.2).

Fruquintinib and M11 PK are dose proportional and time independent. Fruquintinib exposure increased linearly in patients over 1 to 6 mg (Study 2009-013-00CH1). Fruquintinib CL/F was similar after single vs. multiple dosing in patients (Study 2009-013-00CH1 and PK Memo for Module 2.7.2). Fruquintinib and M11 exposure were similar between healthy and patient populations (PK Memo for Module 2.7.2) and the

effects of health status (i.e., healthy subject vs. patient) on fruquintinib and M11 exposures were negligible in the PopPK analysis (Summary of Clinical Pharmacology Studies).

The human mass balance study (Study 2015-013-00CH2) showed approximately 60% of the administered dose was recovered in urine (0.5% as unchanged) and 30% of the dose was recovered in feces (5% unchanged) after a single oral administration. Oral bioavailability was assumed to be greater than 60% based on the recovery of the dose in urine. M11 was identified as primary metabolite of fruquintinib in plasma, which slowly formed from fruquintinib (Tmax around 48 h) and the half-life was about 65 hr. Of note, M11 contribution to the overall pharmacological activity of fruquintinib is considered not clinically meaningful (<5% of total pharmacological activity of fruquintinib at a therapeutic exposure).

Fruquintinib is metabolized by multiple enzymes including both CYP and non-CYP enzymes. In vitro data suggested that CYP3A4 is the main CYP enzyme with minor contributions from CYP2C8, CYP2C9, and CYP2C19. Also, CYP3A4 is the main CYP involved in M11 formation (DMPKR20190006-E-01). Fruquintinib is not a substrate of CYP1A2, CYP2B6, or CYP2D6; is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 (IC50 values >50 uM); and not an inducer of CYP1A2, CYP2B6, and CYP3A4. In vitro, fruquintinib did not show time-dependent inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5.

Fruquintinib is not a substrate of P-glycoprotein (P-gp), organic anion transport protein (OATP)1B1 or OATP1B3 (Report 400253-2019032601; DMPKR20090007-01). Fruquintinib is an inhibitor of P-gp and BCRP in vitro (DMPKR20090007-01; DMPKR20150080-E-01). M11 is a weak inhibitor of P-gp (IC50 >20uM) and is an inhibitor of BCRP (IC 50 of 1.03 uM) in vitro (DMPKR20150021-E-01; DMPKR20150027-E-01). Fruquintinib is not an inhibitor of OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, and MATE2-K (Report 400253-2019032601). The M11 metabolite was an inhibitor of OATP1B1, OATP1B3, MATE1, and MATE2-K, but not for OAT1, OAT3, and OCT2 (ADME-HJHP-210908-SLC Inhibition).

In the clinical DDI studies, itraconazole did not affect fruquintinib exposure (about 10% increase in AUC), while rifampin showed moderate effects showing about 65% decrease in AUC (Study 2020-013-00US2). A single dose fruquintinib did not show clinically meaningful effects on the PK of P-gp and BCRP substrates, dabigatran etexilate and rosuvastatin, respectively. The observed AUC ratios of dabigatran and rosuvastatin with and without fruquintinib were within 0.8-1.25 (Study 2021-013-00US3).

The Applicant conducted PBPK analysis to assess DDI potentials of fruquintinib as a victim when coadministered with CYP3A4 modulators and as an inhibitor when coadministered with P-gp and BCRP transporter substrates.

Methods

Below is the summary of the applicant's PBPK analysis.

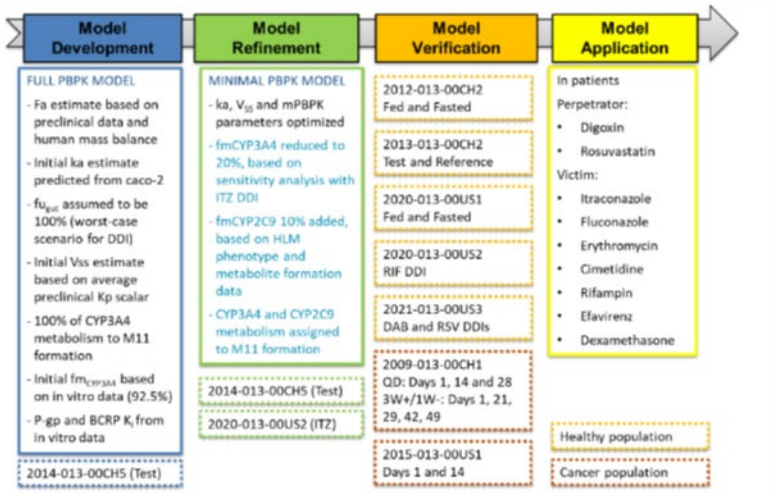
Software:
Simcyp population-based simulator (Version 20) was used for PBPK modeling and simulation.[5]

Modeling Strategy:
The Applicant's modeling strategy is shown below for both fruquintinib and M11 (Figure 21).

[5] Reviewer comments: The FDA reviewer used Simcyp V21 to run the analysis using the applicant developed models.

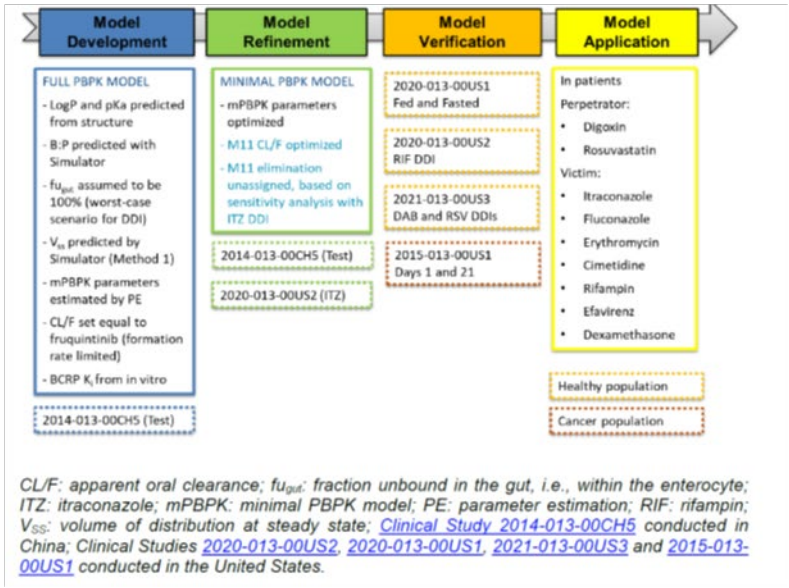
Figure 21. Schematic illustration of the key PBPK modeling steps and components of each clinical study used in model building and verification for fruquintinib (A) and M11 (B)

A. Fruquintinib model:



fa: fraction absorbed; fm: fraction metabolised; fu_{gut}: fraction unbound in the gut, i.e., within the enterocyte; ITZ: itraconazole; ka: first order absorption rate constant; K_p: tissue-plasma partition coefficient; mPBPK: minimal PBPK model ; RIF: rifampin; V_{SS}: volume of distribution at steady state; Clinical Studies 2014-013-00CH5, 2012-013-00CH2, 2013-013-00CH2 and 2009-013-00CH1 conducted in China; Clinical Studies 2020-013-00US2, 2020-013-00US1, 2021-013-00US3 and 2015-013-00US1 conducted in the United States.

B. M11 model:



CL/F: apparent oral clearance; fu_{gut}: fraction unbound in the gut, i.e., within the enterocyte; ITZ: itraconazole; mPBPK: minimal PBPK model; PE: parameter estimation; RIF: rifampin; V_{SS}: volume of distribution at steady state; Clinical Study 2014-013-00CH5 conducted in China; Clinical Studies 2020-013-00US2, 2020-013-00US1, 2021-013-00US3 and 2015-013-00US1 conducted in the United States.

Source: Figures 1 and 2 in the applicant PBPK report humb-2-b.

Model Structure and Parameters:

The minimal model was selected for both fruquintinib and M11 with the first order absorption model. The final model parameters used in the PBPK model and simulations are summarized in Table 75.

Table 74. PBPK model final input parameters for fruquintinib and M11

A. Fruquintinib

PARAMETER	Value	Reference
Physicochemical and Binding Parameters		
Molecular Weight (g/mol)	393.39	2.7.1 Summary
Log P	4.26	
Compound type	Base	Data Checklist
pKa	2.85	2.7.1 Summary
B:P	0.60	Report DMPKR20190004-E-01
fu	0.05	Report DMPKR20150039-E-02
Main binding protein	AAG	Assumed (base)
Absorption Model – First Order Model		
fu_{gut}	1	Assumed
ka (1/h)	1.0	Optimised; Clinical Study 2014-013-00CH5
fa	0.60	Assumed; Clinical Study 2015-013-00CH2
Formulation type	Capsule	Investigator Brochure (v 13.0)
Distribution Model – Minimal PBPK Model		
V_{SS} (L/kg)	0.40	Optimised; Clinical Study 2014-013-00CH5
k_{in} (1/h)	0.004	
k_{out} (1/h)	~0	
V_{SAC} (L/kg)	0.11	
Elimination Parameters – Healthy Western and Cancer Populations		
CL/F (L/h)	0.9	Optimised to reproduce Clinical Study 2020-013-00US2
fm_{CYP3A4}	0.20	Sensitivity analysis; Clinical Study 2020-013-00US2
fm_{CYP2C9}	0.10	Assumed
CYP3A4 CL_{int} (µL/min/pmol)	0.0036819	Retrograde model. CL/F optimised from Clinical Study 2020-013-00US2 (0.62 L/h used for retrograde)
CYP2C9 CL_{int} (µL/min/pmol)	0.0036739	
Additional HLM CL_{int} (µL/min/mg)	1.61884	
CL_R (L/h)	0	Clinical Study 2015-013-00CH2
Elimination Parameters – Chinese Population		
CL/F (L/h)	0.889	Clinical Study 2014-013-00CH5
fm_{CYP3A4}	0.20	Sensitivity analysis; Clinical Study 2020-013-00US2
fm_{CYP2C9}	0.10	Assumed
CYP3A4 CL_{int} (µL/min/pmol)	0.004297	Retrograde model. CL/F optimised from Clinical Study 2014-013-00CH5 (0.55 L/h used for retrograde)
CYP2C9 CL_{int} (µL/min/pmol)	0.004879	
Additional HLM CL_{int} (µL/min/mg)	1.7253	
CL_R (L/h)	0	Clinical Study 2015-013-00CH2
Interaction		
P-gp K_i (µM)	3.1	Report DMPKR20150077-E-01
BCRP K_i (µM)	1.2	Report DMPKR20150080-E-01
fu_{inc}	1	Assumed
Modified input parameters for fruquintinib based on 100 % fa.		
Absorption Model – First Order Model		
fa	1	Assumed
Distribution Model – Minimal PBPK Model		
V_{SS} (L/kg)	0.60	Optimised
Elimination Parameters – Healthy Western and Cancer Populations		
CYP3A4 CL_{int} (µL/min/pmol)	0.0056938	Retrograde model
CYP2C9 CL_{int} (µL/min/pmol)	0.0057196	
Additional HLM CL_{int} (µL/min/mg)	2.55147	

B. M11

PARAMETER	Value	Reference
Physicochemical and Binding Parameters		
Molecular Weight (g/mol)	~380	Clinical Study 2015-013-00CH2
Log P	2.3	ACD Percepta (consensus)
Compound type	Base	
pKa	3.2	
B:P	0.60	Predicted; Simcyp Simulator V20
fu	0.02	Report DMPKR20210018-E-01
Main binding protein	AAG	Assumed (base)
fu_{gut}	1	Assumed
Distribution Model – Minimal PBPK Model		
K_p Scalar	1.9	Optimised; Clinical Study 2014-013-00CH5
V_{SS} (L/kg) (scaled)	0.74	Predicted; Simcyp Simulator V20; Method 1
k_{in} (1/h)	0.30	Optimised; Clinical Study 2014-013-00CH5
k_{out} (1/h)	0.67	
V_{SAC} (L/kg)	0.26	
Elimination Parameters – Healthy Western and Cancer Populations		
CL/F (L/h)	0.40	Optimised to reproduce Clinical Study 2020-013-00US2
fm_{CYP3A4}	0.20	Sensitivity analysis; Clinical Study 2020-013-00US2
fm_{CYP2C9}	0.20	Assumed
CYP3A4 CL_{int} (µL/min/pmol)	0.00857	Retrograde model. CL/F optimised from Clinical Study 2020-013-00US2
CYP2C9 CL_{int} (µL/min/pmol)	0.01707	
Additional HLM CL_{int} (µL/min/mg)	3.23134	
CL_R (L/h)	0	Assumed
Elimination Parameters – Chinese Population		
CL/F (L/h)	0.45	Optimised to reproduce Clinical Study 2014-013-00CH5
fm_{CYP3A4}	0.20	Sensitivity analysis; Clinical Study 2020-013-00US2
fm_{CYP2C9}	0.20	Assumed
CYP3A4 CL_{int} (µL/min/pmol)	0.01139	Retrograde model. CL/F optimised from Clinical Study 2014-013-00CH5
CYP2C9 CL_{int} (µL/min/pmol)	0.02583	
Additional HLM CL_{int} (µL/min/mg)	3.92102	
CL_R (L/h)	0	Assumed
Interaction Parameters		
BCRP K_i (µM)	0.98	Report DMPKR20150080-E-01
fu_{inc}	1	Assumed

Source: Tables 4 and 5 in the applicant PBPK report humb-2-b and Table 54 in the applicant PBPK report humb-2-b-addendum-1. When fa=1 was used, the applicant re-estimated Vss and Clints of CYP3A4, CYP2C9 and additional HLM, while keeping all other input parameters identical to those used with fa =0.6.

Reviewer comments: *The Applicant estimated fa at 60% based on the fraction of the total radioactivity recovered in urine in the human mass balance study (Study 2015-013-00CH2). An IR was issued to justify the fa=0.6 and evaluate the impact of fa on PBPK conclusion considering about 30% of the total radioactivity was recovered in feces. In the response to the IR, the Applicant justified fa =0.6 based on the uncertainty in*

attributing the fecal excreted radioactivity to the extent of absorption/from biliary excretion. The Applicant provided additional simulations using a higher fa of 1 and showed there is no meaningful difference in the PBPK analysis results. The justification was considered reasonable and supported by the additional simulation results. This review presents the updated DDI simulation results using fa = 1 provided by the Applicant in the response to the IR and the PBPK report addendum-1 and/or provided discussions based on the FDA reviewer's additional simulations using fa=1 performed to confirm the applicant's result of no meaningful differences in PBPK analysis conclusion between fa=0.6 and 1.

Model Development, Refinement, and Verification:

Model development and refinement:

As shown in Figure 21 above, the model was developed using the data from in vitro studies and clinical PK studies.

The clinical DDI study data with itraconazole (Study 2020-013-00US2) was used to refine fmCYP3A4 for fruquintinib and M11, the final values of which were selected based on the sensitivity analysis (SA). The fmCYP2C9 for fruquintinib was estimated using in vitro metabolite formation data, whereas the fmCYP2C9 for M11 was estimated based on the human mass balance data (Study 2015-013-00CH2). Based on in vitro metabolite ID data, M11 was assumed to be metabolized equally by CYP3A4 and CYP2C9. The fmCYP3A4 and fmCYP2C9 for M11 were estimated 20% each to M11's metabolism based on the sensitivity analysis using clinical rifampin DDI study data (Study 2020-013-00US2). Fruquintinib oral clearance in Chinese subjects was assumed to be approximately 89% of that of the US subjects in all PBPK simulations to capture the oral clearance in each population calculated from the observed data.

Reviewer comments: *Refer to the discussion in Q1 regarding simulations in Chinese subjects.*

Model verification:

The refined fruquintinib model with fruquintinib fmCYP3A4 and fmCYP2C9 as 20% and 10%, respectively, was verified by comparing the simulated vs. observed DDI effect with rifampin. The fruquintinib model was further verified by comparing the model predicted to the observed fruquintinib PK in healthy subjects and cancer patients after single and repeat oral doses of fruquintinib 4 to 5 mg QD (Clinical studies 2020-013-00US2, 20210013-00US3, 2012-013-00CH2, 2013-013-00CH2, 2020-013-00US1, 2009-013-00CH1 and 2015-013-00US1). The refined M11 model with fmCYP3A4 and fmCYP2C9 for M11 each as 20% of the total M11 metabolism, was verified by comparing the model simulated vs observed M11 DDI effect with itraconazole. The M11 model was further verified by comparing the model predicted to the observed M11 PK after single and repeat oral doses of fruquintinib 5 mg in healthy subjects and cancer patients (Clinical studies 2020-013-00US1, 2020-013-00US2 and 2015-013-00US1).

Reviewer comments: *In vitro Ki values for P-gp and BCRP were used in the PBPK model. Refer to the discussion in the Question 3 below regarding additional sensitivity*

analysis conducted by the FDA reviewer to assess uncertainties regarding DDI simulations for P-gp and BCRP substrates.

Model Applications:
The Applicant used the final PBPK model to predict DDI potentials of fruquintinib as victim of CYP3A4 modulators and as perpetrator for P-gp and BCRP substrates in cancer patients. To simulate DDIs with moderate CYP3A4 inducers, the efavirenz model in the Simcyp compound library (SV-efavirenz, V20) was used without any modification, whereas the rifampin model (SV-rifampin, V20) was used with the IndMax for CYP3A4 increased from 16 to 37. DDIs with weak CYP3A4 inducers were simulated using the dexamethasone model in Simcyp compound library (SV-dexamethasone, V20).

Reviewer's comment: *The Applicant was requested to justify this IndMax modification via the IR sent on 4/26/23. See the discussion in the Question 2 below.*

Results

1. Can the PBPK model adequately describe the PK profiles of fruquintinib and its major metabolite M11 after single dose administration of fruquintinib?

Yes. The fruquintinib PBPK model reasonably well described PK parameters (AUC and Cmax) of fruquintinib and M11 (Table 76) and their concentration-time profiles in plasma (Figure 22) following a single oral administration of fruquintinib**.**

Table 75. Comparison of the Observed and Simulated PK Parameters of Fruquintinib and M11 Following a single dose administration of fruquintinib in healthy subjects

A	4 mg	00CH2	(fed)	4490	108			Observed*
				1.23	**1.20**			**Sim/Obs**
B	4 mg	2012-013-00CH2	HV Chinese (fasted)	5532	130			Simulated*
				4644	129			Observed*
				1.00	**1.00**			**Sim/Obs**
C	5 mg	2020-013-00US1	HV Western (fed)	5463	123	1957	8.00	Simulated
				5287	114	1969	13.00	Observed
				1.03	**1.08**	**0.99**	**0.62**	**Sim/Obs**
D	5 mg	2020-013-00US1	HV Western (fasted)	5541	124	2009	8.07	Simulated
				5058	117	1729	12.20	Observed
				1.10	**1.06**	**1.16**	**0.66**	**Sim/Obs**
E	5 mg	2013-013-00CH2	HV Chinese (Reference)	5574	143			Simulated
				5820	157			Observed
				0.96	**0.91**			**Sim/Obs**
F	5 mg	2013-013-00CH2	HV Chinese (Test)	5574	143			Simulated
				5870	167			Observed
				0.95	**0.86**			**Sim/Obs**

*Source: Applicant's PBPK report humb-2-b. * The arithmetic mean values were compared for A and B. Note that these simulations were conducted using Fa=0.6. HV represents healthy volunteers. The reviewer calculated the ratio of simulated vs. observed (Sim/Obs) for each trial.*

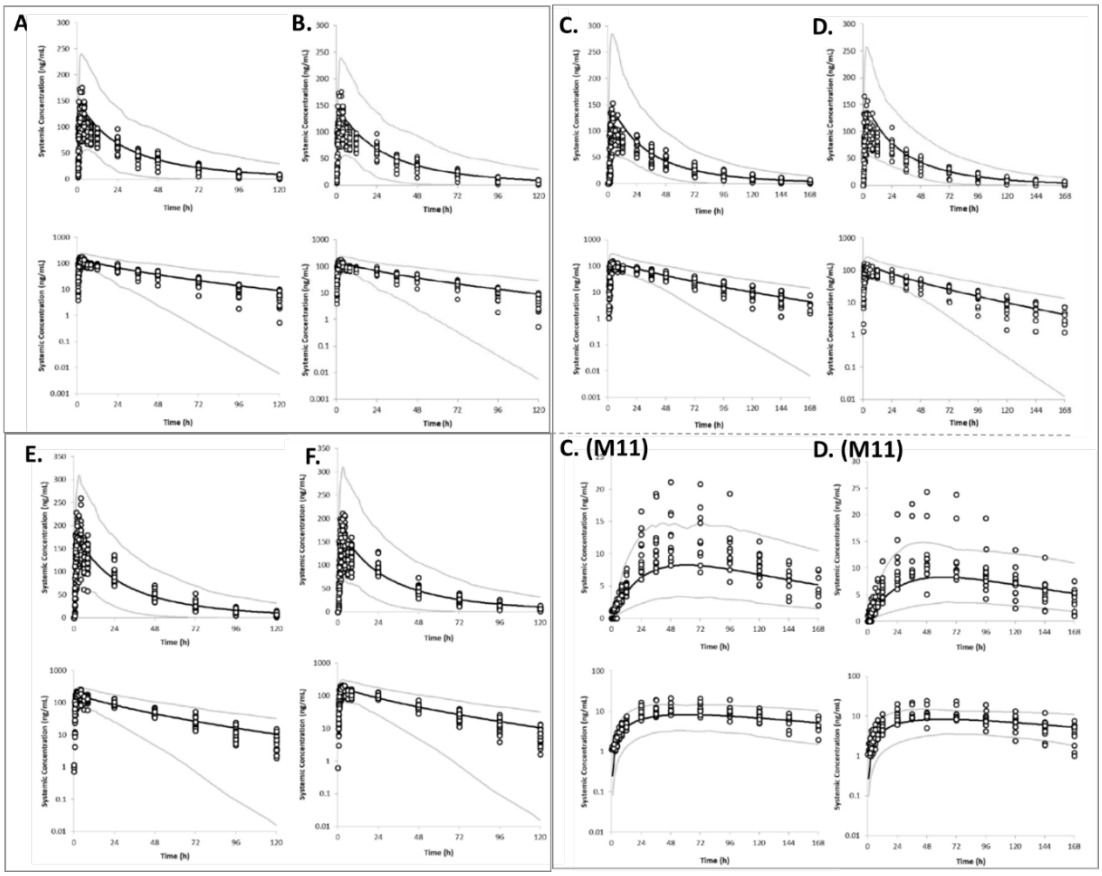
Reviewer's comment: *To simulate fruquintinib PK in Chinese subjects, the Applicant adjusted Clint values for CYP3A4 and CYP2C9 to address the difference in oral clearance calculated from the observed PK data between US (Western) vs. Chinese healthy subjects. These estimated Clint values were used for PBPK analysis along with*

Sim-Chinese or Sim-Cancer populations in Simcyp. The Applicant's approach attributes the observed difference solely to clearance difference, while oral clearance is determined by both clearance and bioavailability. Note that the clinical DDI studies with itraconazole and rifampin, which were used for model development/verification, were conducted in healthy Western subjects. The FDA reviewer conducted simulations for Chinese subjects using CYP3A4 and CYP2C9 Clints in Table 75 (i.e., input parameters for Western healthy volunteers), and the model still reasonably captured well fruquintinib AUC and Cmax. This was reasonable as the observed difference in oral clearance between Chinese and Western subjects is about 10%. It was considered that the Applicant's Chinese population simulations provided support to model performance evaluation.

The FDA reviewer repeated the applicant's simulations in Table 76 using fa=1. Overall, fruquintinib AUC and Cmax were well captured and M11 PK was reasonably well captured using the alternative fa of 1. M11 Cmax, which reflects M11 formation rate by CYP3A4 and CYP 2C9, was better captured with fa=1 simulations compared to those with fa=0.6 (simulated vs. observed ratio with fa=1 were 0.92 and 0.97 for C and D in Table 76 above), while AUCs were somewhat overestimated (still within 2-fold difference). This seems due to that M11 elimination parameters were not updated in the fa sensitivity analysis provided in the Applicant's IR response. Considering the purpose of the PBPK analysis, the impact of this was considered not meaningful as it does not affect victim DDI evaluation of fruquintinib. In addition, overestimation of M11 exposure considered as more conservative scenario (i.e., higher inhibitor exposure) for DDI evaluation with BCRP substrates.

The Applicant conducted multiple dose simulations in cancer populations using Simcyp default cancer population (Sim-Cancer). Western and Chinese cancer patients were simulated by using each population specific CYP3A4 and CYP2C9 Clint values estimated in respective HV populations in Sim-Cancer population. In general, the ratios of fruquintinib AUC simulated in Sim-cancer population and observed in clinical studies with cancer patients ranged from 1.32 to 1.67 and from 1.13 to 1.84 for fruquintinib Cmax. Given the uncertainties associated with using an unselected (all comer) cancer population, cancer population simulations were considered as supportive. Because fruquintinib showed dose proportional PK from 1 mg to 6 mg and did not show time-dependent kinetics, it is reasonable to use single dose administration of fruquintinib in victim DDI simulations.

Figure 22. Comparison of the observed and simulated PK profiles of fruquintinib and M11 following single dose administration of fruquintinib



Source: Applicant's PBPK report humb-2-b. Each plot presents the simulated mean (black line) with the 5th and 95th percentiles (gray lines) and the observed individual data. For clinical study numbers and trial design details, refer to corresponding alphabetical identifiers in the Table 76 above.

2. Are the PBPK analyses adequate to predict the effect of CYP3A modulators on the PK of fruquintinib?

Yes, the PBPK analyses are adequate to predict the effects of CYP3A modulators on the PK of fruquintinib (Table 77). The model captured the observed fruquintinib PK changes when coadministered with itraconazole (AUCR was 1.1) and rifampin (AUCR was 0.35), a strong CYP3A4 inhibitor and a strong CYP3A4 inducer, respectively.

The PBPK analysis predicted the DDI potential of fruquintinib with a moderate CYP3A4 inducer efavirenz would be weak as suggested by the predicted fruquintinib AUC with efavirenz as 68% of that without efavirenz (Table 77).

Table 76. Summary of the clinical and simulated DDI studies in healthy subjects

Modulator	Modulator Type	Dosing regimen		Fruquintinib Ratio		Trial
Healthy subjects		Modulator	Fruquintinib	AUCR	CmaxR	
Rifampin	Strong CYP3A4 inducer	600 mg QD for D1-D28	5 mg on D8	0.34	0.87	Sim
				0.35	0.88	Obs
				0.97	0.99	Sim/Obs
Itraconazole	Strong CYP3A4 inhibitor	200 mg QD for D1-D11	5 mg on D5	1.18	1.02	Sim
				1.1	0.94	Obs
				1.07	1.09	Sim/Obs
Efavirenz	Moderate CYP3A4 inducer	600 mg QD for D1-D28	5 mg on D15	0.68	0.96	Sim*

*Source: Applicant's PBPK report humb-2-b and PBPK report humb-2-b-addendum-1. Sim represents the applicant's simulated data using Fa=0.6, whereas Obs represents the observed data in the applicant's clinical studies. Sim/Obs ratios were calculated by the reviewer. * indicates the applicant's simulation result with fa=1 provided in the PBPK report addendum-1.*

Reviewer comments: *The clinical DDI studies with itraconazole and rifampin were conducted in healthy subjects. The Applicant used cancer population (Sim-Cancer, Simcyp V20) for efavirenz and dexamethasone DDI simulations. The FDA reviewer obtained similar results (less than 15 % difference in the simulated AUCRs) using the healthy volunteer population to those of the Applicant's in a cancer population. In response to FDA's IR, the Applicant provided efavirenz simulation in healthy volunteer population on July 11, 2023, and provided the updated simulation of this using fa=1 in the PBPK report addendum-1 in both healthy (included in Table 77) and cancer populations; the results were similar in healthy vs. cancer populations.*

The FDA reviewer repeated rifampin and itraconazole DDI simulations using fa=1. There was no meaningful difference (less than 1% difference in the simulated AUCR and CmaxR) from the Applicant's results obtained with fa=0.6 (Table 77).

The Applicant's PBPK model estimated CYP3A4 Clint with fruquintinib fmCYP3A4 of 20 % using the itraconazole clinical DDI data. Risk assessment was conducted using an alternative CYP3A4 Clint (0.0072113 was estimated using fmCYP3A4 of 30% and fa=1) that is higher than the current value (0.0056938 estimated with fmCYP3A4 of 20% and fa=1). This fmCYP3A4 of 30% resulted in 27% increase in AUC of fruquintinib with itraconazole, which was considered as the upper bound of fmCYP3A4 for fruquintinib for subsequent sensitivity analyses below.

In the FDA reviewer's sensitivity analysis using fmCyp3A4 of 30%, fruquintinib AUC in the presence of efavirenz was decreased to 68% of that without efavirenz, which was consistent with the Applicant's conclusion that drug interaction potential with moderate CYP3A4 inducers such as efavirenz would be weak.

The Applicant's PBPK report and the addendum-1 included additional PBPK analyses for moderate and weak CYP3A4 inhibitors. Considering that itraconazole did not show clinically meaningful effect on fruquintinib exposure, it is reasonable to expect no

clinically meaningful DDIs with other strong, moderate, and weak CYP3A4 inhibitors and no additional PBPK analysis is necessary for those CYP3A4 inhibitors.

The Applicant also included DDI simulations for weak CYP3A4 inducers. DDI potentials of weak CYP3A4 inducers on the exposure of fruquintinib are expected to be weak based on the efavirenz simulation. The Applicant's DDI simulation for dexamethasone coadministration predicted less than 10% decrease in simulated Cmax and AUC of fruquintinib.

The Applicant increased CYP3A4 IndMax to 37 from the default value of 16 in the Simcyp (V20) rifampin model to better recover the observed rifampin effects on fruquintinib PK. In response to FDA's IR, the Applicant provided three references[6],[7],[8] that used higher CYP3A4 IndMax for rifampin, as justification. The FDA reviewer conducted sensitivity analysis (for both fa=0.6 and fa=1) to evaluate the impact of IndMax on fmCYP3A4 estimation. Using the original IndMax of 16, rifampin DDI effects were underpredicted (the predicted AUCR was 0.52 which did not capture the observed 0.35). As the higher fruquintinib fmCYP3A4 of 30% did not capture the AUCR if IndMax =16 was used (the predicted AUCR was 0.44), and considering that 30% as the upper bound of fmCYP3A4 to be consistent with the observed itraconazole effect on fruquintinib exposure, this sensitivity analysis supports the currently optimized fruquintinib fmCYP3A4 (20%) using IndMax=37. The choice of IndMax value in the rifampin model would not affect the dose recommendations for concomitant use with strong and moderate CYP3A4 inducers in the labeling. The clinical DDI data were used for strong CYP3A4 inducers and for moderate CYP3A4 inducers, the Applicant's analysis and FDA reviewer's risk assessment are consistent regarding the magnitude of the predicted DDI potential as weak.

3. Can PBPK analyses provide support to determination of drug interaction potentials of fruquintinib as perpetrator with P-gp and BCRP substrates using the single dose clinical DDI study?

Yes, PBPK analyses can provide support to the decision based on the single dose clinical DDI study in healthy subjects (Study 2021-013-00US3) where fruquintinib did not show clinically meaningful interaction effects on the PK of dabigatran etexilate, a P-gp substrate, and of rosuvastatin, a BCRP substrate.

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[6] Almond et al., 2016. Prediction of Drug-Drug Interactions Arising from CYP3A induction Using a Physiologically Based Dynamic Model. Drug Metab Dispos 44(6): 821-832.
[7] Fahmi et al., 2016. Evaluation of CYP2B6 Induction and Prediction of Clinical Drug-Drug Interactions: Considerations from the IQ Consortium Induction Working Group-An Industry Perspective. Drug Metab Dispos 44: 1720- 1730.
[8] Yamashita et al., 2013. Modeling of Rifampicin-Induced CYP3A4 Activation Dynamics for the Prediction of Clinical Drug-Drug Interactions from In Vitro Data. PLoS ONE 8(9): 1-11.

The simulated AUCR and CmaxR for dabigatran and rosuvastatin by the applicant's PBPK model were consistent with the observed data that indicate no clinically meaningful inhibition of P-gp and BCRP transporters after single dose administration of fruquintinib (Table 78).

Table 77. Comparison of the simulated and observed fruquintinib DDI potentials as inhibitors of P-gp and BCRP transporters in healthy subjects after single dose administration of fruquintinib

Substrate	Substrate Type	Dosing regimen		Substrate		Substrate + Fruquintinib		Substrate Ratio		Trial
		Substrate	Fruquintinib	AUC	Cmax	AUC	Cmax	AUCR	CmaxR	
Dabigatran	P-gp substrate	150 mg	5 mg	859	79.7	888	82.2	1.03	1.03	Sim
				1014	123	924	111	0.91	0.90	Obs
				0.85	**0.65**	**0.96**	**0.74**	**1.13**	**1.14**	**Sim/Obs**
Rosuvastatin	BCRP substrate	10 mg	5 mg	29.2	2.13	31.0	2.30	1.06	1.08	Sim
				36.1	4.00	29.3	3.38	0.81	0.84	Obs
				0.81	**0.53**	**1.06**	**0.68**	**1.31**	**1.29**	**Sim/Obs**

Source: Applicant's PBPK report humb-2-b. Sim/Obs ratios were calculated by the reviewer. Sim represents the applicant's simulated data, whereas Obs represents the observed data in the applicant's clinical studies.

Reviewer comments: *For both dabigatran and rosuvastatin, Cmax values were underpredicted with and without fruquintinib. The applicant discussed the underprediction of dabigatran Cmax, partly attributable to the difference between the measured (total dabigatran) vs. simulated (free dabigatran only), which was considered reasonable. For rosuvastatin Cmax, no discussion was provided in the PBPK report. Rosuvastatin AUC was reasonably well captured.*

The FDA reviewer repeated dabigatran and rosuvastatin DDI simulations using fa=1, there were no meaningful difference compared to the Applicant's results obtained with fa=0.6 in Table 78 (less than 1% difference in the simulated AUCR and CmaxR).

The FDA reviewer performed additional PBPK analyses using both single dose and multiple dose scenarios of fruquintinib administration in healthy subjects along with the sensitivity analysis for P-gp and BCRP Ki values and hepatic BCRP abundance (Table 79). The FDA reviewer's sensitivity analysis suggested that fruquintinib DDI potentials with P-gp and BCRP substrates under the worst-case scenarios would be 26% and 49 % as indicated by the increase in dabigatran and rosuvastatin exposure (AUC), respectively, when co-administered with fruquintinib (Table 79).

Collectively, PBPK analyses provided support to the use of the single dose clinical study for evaluation of perpetrator DDI potential of fruquintinib when coadministered with P-gp and BCRP substrates.

Table 78. PBPK-simulated fruquintinib DDI potentials as inhibitors of P-gp and BCRP transporters after multiple dose administration of fruquintinib

Substrate	Substrate Type	Inhibitor dosing	Transporter Hepatic Abundance	Transporter Ki in Gut & Liver (uM)	Dosing regimen		Substrate GMR		Trial
HV Subjects					Substrate	Fruquintinib	AUCR	CmaxR	
Dabigatran	P-gp substrate	SD	default	default (3.1)	150 mg	5 mg	1.03	1.03	Sim
		SD	default	lower (0.35)	150 mg	5 mg	1.25	1.23	Sim*
		SD	default	lower (0.35)	75 mg	5 mg	1.26	1.25	Sim*
		MD	default	default (3.1)	150 mg on D14	5 mg QD for D1-D21	1.08	1.08	Sim*
Rosuvastatin	BCRP substrate	SD	default	default: 1.23 (Fru); 0.98 (M11)	10 mg	5 mg	1.06	1.08	Sim
		SD	10 X higher	default: 1.23 (Fru); 0.98 (M11)	10 mg	5 mg	1.07	1.05	Sim*
		SD	10 X higher	lower: 0.18 (Fru); 0.14 (M11)	10 mg	5 mg	1.25	1.37	Sim*
		MD	default	default: 1.23 (Fru); 0.98 (M11)	10 mg on D14	5 mg QD for D1-D21	1.14	1.18	Sim*
		MD	10 X higher	lower: 0.18 (Fru); 0.14 (M11)	10 mg on D14	5 mg QD for D1-D21	1.49	1.69	Sim*

Source: Applicant's PBPK report humb-2-b and the reviewer's analysis. Sim represents the applicant's simulations (also listed in Table 78), whereas Sim represents the reviewer's simulations using the applicant's model with modified parameter values and/or dosing regimen. SD and MD represent single dose and multiple dose, respectively. GMR represents geometric mean ratio. All simulations in Table 79 were conducted with fa=6.*

Reviewer's comments: *The Applicant provided fruquintinib multiple dose DDI simulations with digoxin (as P-gp substrate) and rosuvastatin (as BCRP substrate) in cancer patients, which showed less than 20% difference in each transporter substrate AUCs with and without fruquintinib. Limitations of rosuvastatin model (SV-rosuvastatin V20), such as ability to capture BCRP polymorphism, have been identified. Given the clinical DDI data with rosuvastatin is available for fruquintinib, PBPK analysis was used to evaluate the fruquintinib DDI risk with rosuvastatin in this analysis. The FDA reviewer repeated the simulations in healthy subjects, the conclusion from which was consistent with the Applicant's using the cancer population simulations. No clinically meaningful effect of fruquintinib on P-gp and BCRP substrates' exposure is expected.*

The FDA reviewer's risk assessment evaluated the sensitivity of 1) P-gp or BCRP Ki values and 2) fruquintinib dosing regimen (single vs. multiple dosing) on fruquintinib DDI effect as perpetrator of P-gp and BCRP substrates considering the uncertainties in using in vitro Ki values for transporter DDI evaluation and the observed accumulation ratios of fruquintinib and M11 at about 4 and 31, respectively. In addition, P-gp and BCRP Ki values of fruquintinib and M11 (for BCRP only) were verified using the data shown minimal DDI effects.

Fruquintinib effects on dabigatran PK would mainly be mediated by inhibition of gut P-gp because dabigatran etexilate (prodrug) is a P-gp substrate, which is rapidly hydrolyzed to dabigatran. Dabigatran is not a P-gp substrate. Therefore, accumulation due to multiple dosing of fruquintinib would minimally affect its DDI effect with dabigatran as confirmed by the minimal difference in AUCR between single dose vs. multiple dose simulations (Table 79).

The FDA reviewer's sensitivity analysis showed that fruquintinib P-gp Ki can be lowered to 0.35 uM from the in vitro determined value of 3.1 uM, while still capturing the

*observed no clinically meaningful interaction effect (defined as less than 25% change in AUC). Using this about 9-fold lower Ki value and the lower substrate dose (75 mg) as the worst-case scenario, fruquintinib-dabigatran DDI potential is still expected to be less than 25% (*Table 79*).*

For rosuvastatin DDI evaluation, it should be noted that both fruquintinib and M11 can inhibit BCRP. The FDA reviewer's analysis showed that multiple dosing can increase DDI effects as expected, but the impact was minimal (AUCR increased to 1.14 from 1.06 in Table 79). The FDA reviewer's analysis showed that BCRP Ki values can be lowered up to about 7-fold from the in vitro measured value of 1.23 uM and 0.98 uM for fruquintinib and M11, respectively[9], while still capturing the observed no clinically meaningful interaction effect (less than 25% change in AUC) (Table 79)

*In addition, a potential impact of uncertainty in hepatic BCRP abundance on fruquintinib-rosuvastatin DDI was investigated given that hepatic BCRP contribution to the DDI may increase after multiple dosing due to accumulation. Of note, BCRP-mediated biliary excretion of rosuvastatin in the rosuvastatin model (SV-Rosuvastatin, Simcyp V20) was the value derived from activity abundance relationship in sandwich cultured human hepatocytes and corrected for hepatic BCRP expression. Increasing the hepatic BCRP abundance parameter in the model by 10-fold only minimally affected AUCR in the single dose fruquintinib-rosuvastatin DDI simulation (AUCR to 1.07 vs. 1.06 in Table 79). Under the worst-case scenario simulated using the lowered Ki values of fruquintinib and M11, respectively, together with 10 fold higher liver abundance of BCRP and multiple dosing of fruquintinib, fruquintinib-rosuvastatin DDI potential can be increased to 49 % (*Table 79*). It should be noted that literature search indicated hepatic BCRP expression level appears to be low or below detection limits [10],[11], indicating that 10x higher value can represent the worst-case and not a realistic scenario.*

The FDA reviewer conducted the above discussed dabigatran and rosuvastatin DDI risk assessment scenarios in Table 79 using both fa=0.6 and fa=1 and found no meaningful difference (less than 2% difference in the simulated AUCR and CmaxR).

Conclusions

The Applicant's PBPK analyses are adequate to evaluate the effects of moderate CYP3A4 inducers such as efavirenz on the exposure of fruquintinib and can be used to inform the prescription information. The expected drug interaction potential of fruquintinib with moderate CYP3A4 inducers is expected to be weak.

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[9] This evaluation was conducted using 10-fold higher hepatic BCRP expression level, which minimally affected fruquintinib-rosuvastatin interaction with a single dose fruquintinib.

[10] Burt HJ et al, Abundance of Hepatic Transporters in Caucasians: A Meta-Analysis. Drug Metab Dispos. 2016 Oct;44(10):1550-61. doi: 10.1124/dmd.116.071183.

[11] Drozdzik, M et al., Protein Abundance of Clinically Relevant Drug Transporters in the Human Liver and Intestine: A Comparative Analysis in Paired Tissue Specimens. Clin. Pharmacol. Ther., 2019, 105: 1204-1212. https://doi.org/10.1002/cpt.1301

The risk assessment using PBPK analysis collectively provided support to using the single dose clinical study data to determine fruquintinib interaction potentials with P-gp and BCRP substrates.

Model Performance and Credibility Assessment

1. **Context of use:** The Applicant conducted PBPK analyses to investigate the drug interaction potential of fruquintinib as a victim of moderate and weak CYP3A4 inducers and as an inhibitor to P-gp and BCRP substrates to inform the dose recommendations for concomitant use of other drugs in the prescribing information.

2. **Model influence:** The reviewer considers the model influence is high regarding drug interaction potential with CYP3A perpetrators and low as P-gp or BCRP inhibitors. PBPK model was used to predict drug interaction potentials for moderate CYP3A4 inducers without conducting clinical studies. The PBPK predicted drug interaction potentials were used in conjunction with other information including safety data to inform the dosing recommendation for concomitant use of moderate CYP3A4 inducers and with the single dose clinical drug interaction study for concomitant use of P-gp and BCRP substrates in the prescription information.

3. **Decision consequence:** The reviewer considers the decision consequence is high regarding drug interaction potential with CYP3A perpetrators and low as P-gp or BCRP inhibitors. If the model was incorrect and drug interaction potentials with moderate CYP3A4 inducers were underpredicted, patients will get lower exposure than the recommended dose when coadministered with moderate CYP3A4 inducers, but exposure difference is expected to be less than 65% observed in the clinical drug interaction study with rifampin. If the model was incorrect and drug interaction effects of fruquintinib on P-gp and BCRP substrates were underpredicted, patients will get higher exposure to these drugs than the recommended dose when coadministered with fruquintinib, but this decision was informed by both clinical study and the PBPK analysis.

4. **Model risk:** The reviewer considers the level of model risk high regarding drug interaction potential with CYP3A perpetrators and low as P-gp or BCRP inhibitors.

Signatures NDA 217564

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Brian Christmas, Ph.D.	OOD/DHOT	Section: 5	**Select one:** ☒Authored ☐Approved
	Signature: Brian J. Christmas -S Digitally signed by Brian J. Christmas -S Date: 2023.11.03 09:28:57 -04'00'			
Nonclinical Team Leader	Matthew Thompson, Ph.D., M.P.H.	OOD/DHOT	Section: 5	**Select one:** ☒Authored ☒Approved
	Signature: Matthew D. Thompson -S Digitally signed by Matthew D. Thompson -S Date: 2023.11.03 13:46:08 -04'00'			
Nonclinical Team Division Director	John Leighton, Ph.D.	OOD/DHOT	Section: 5	**Select one:** ☐Authored ☒Approved
	Signature: John K. Leighton -S Digitally signed by John K. Leighton -S Date: 2023.11.03 13:59:50 -04'00'			
Clinical Reviewer	Michael Fusco, Pharm.D.	OOD/DO3	Sections: 1, 2, 3, 7, 8, 9, 10, 13, 19	**Select one:** ☒Authored ☐Approved
	Signature: Michael J. Fusco -S Digitally signed by Michael J. Fusco -S Date: 2023.11.03 09:51:21 -04'00'			
Clinical Team Leader	Sandra Casak, M.D.	OOD/DO3	Sections: All	**Select one:** ☒Authored ☒Approved
	Signature: Refer to final multi-disciplinary review electronic signature.			
Statistics Reviewer	Sirisha Mushti, Ph.D.	OB/DBV	Sections: 1, 8	**Select one:** ☒Authored ☐Approved
	Signature: Sirisha Mushti -S Digitally signed by Sirisha Mushti -S Date: 2023.11.03 10:39:54 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Statistics Team Leader	Joyce Cheng, Ph.D.	OB/DBV	Sections: 1, 8	**Select one:** ☒Authored ☒Approved
	Signature: Joyce Cheng -S Digitally signed by Joyce Cheng -S Date: 2023.10.30 10:24:15 -04'00'			
Division Director (OB)	Shenghui Tang, Ph.D.	OB/DBV	Sections: 1, 8	**Select one:** ☐Authored ☒Approved
	Signature: Shenghui Tang -S Digitally signed by Shenghui Tang -S Date: 2023.11.03 13:54:38 -04'00'			
Clinical Pharmacology Reviewers	Wentao Fu, Ph.D.	OCP/DCPI	Sections: 6, 19.4	**Select one:** ☒Authored ☐Approved
	Signature: Wentao Fu -S Digitally signed by Wentao Fu -S Date: 2023.11.06 08:08:14 -05'00'			
	Hezhen Wang, Ph.D.	OCP/DPM	Sections: 6, 19.4	**Select one:** ☒Authored ☐Approved
	Signature: Hezhen Wang -S Digitally signed by Hezhen Wang -S Date: 2023.11.03 13:10:43 -04'00'			
	Miyoung Yoon, Ph.D.	OCP/DPM	Sections: 6, 19.4	**Select one:** ☒Authored ☐Approved
	Signature: Miyoung Yoon -S Digitally signed by Miyoung Yoon -S Date: 2023.11.03 11:05:29 -04'00'			
Clinical Pharmacology Team Leaders	Jason Moore, Pharm.D.	OCP/DCPII	Sections: 6, 19.4	**Select one:** ☒Authored ☒Approved
	Signature: Jason N. Moore Jr -S Digitally signed by Jason N. Moore Jr -S Date: 2023.11.06 07:41:47 -05'00'			
	Youwei Bi, Ph.D.	OCP/DPM	Sections: 6, 19.4	**Select one:** ☒Authored ☒Approved
	Signature: Youwei Bi -S Digitally signed by Youwei Bi -S Date: 2023.11.06 11:18:10 -05'00'			

	Yuching Yang, Ph.D.	OCP/DPM	Sections: 6, 19.4	**Select one:** ☒Authored ☒Approved
	Signature: Yuching Yang -S Digitally signed by Yuching Yang -S Date: 2023.11.06 08:50:24 -05'00'			
Clinical Pharmacology Division Director	Nam Atiqur (Atik) Rahman, Ph.D.	OCP/DCPII	Sections: 6, 19.4	**Select one:** ☐Authored ☒Approved
	Signature: Nam A. Rahman -S Digitally signed by Nam A. Rahman -S Date: 2023.11.06 07:47:01 -05'00'			
Associate Director for Labeling (ADL)	Doris Auth, Pharm.D.	OCE	Sections: 11	**Select one:** ☒Authored ☒Approved
	Signature: Doris Auth -S Digitally signed by Doris Auth -S Date: 2023.11.06 08:35:42 -05'00'			
Cross-Disciplinary Team Leader (CDTL)	Sandra Casak, M.D.	OOD/DO3	Sections: All	**Select one:** ☒Approved
	Signature: Refer to final multi-disciplinary review electronic signature.			
Division Director	Steven Lemery, M.D., M.H.S.	OOD/DO3	Sections: All	**Select one:** ☒Approved
	Signature: Refer to final multi-disciplinary review electronic signature.			

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SANDRA J CASAK
11/06/2023 12:09:22 PM

STEVEN J LEMERY
11/06/2023 12:38:33 PM

PAUL G KLUETZ
11/07/2023 11:27:31 PM