



Summary Report of Benefit-Risk Assessment

FRUZAQLA CAPSULE 1MG AND 5MG

NEW DRUG APPLICATION

Active Ingredient(s)	Fruquintinib
Product Registrant	Takeda Pharmaceuticals (Asia Pacific) Pte. Ltd.
Product Registration Number	SIN17113P, SIN17114P
Application Route	Abridged evaluation
Date of Approval	17 October 2024

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A INTRODUCTION

Fruzaqla 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 agent, and, if RAS wild-type, an anti-EGFR agent.

The active ingredient, fruquintinib, is a highly selective small molecule tyrosine kinase inhibitor targeting vascular endothelial growth factor receptors (VEGFR) -1, -2, and -3, resulting in inhibition of tumour angiogenesis, thereby depriving tumours of essential nutrients and oxygen.

Fruzaqla is available in capsule form containing either 1 mg or 5 mg of fruquintinib. The capsule core includes maize starch, microcrystalline cellulose, and talc. The 1 mg capsule shell contains gelatin, titanium dioxide, tartrazine, and sunset yellow, while the 5 mg capsule shell consists of gelatin, titanium dioxide, brilliant blue, and allura red.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, fruquintinib, is manufactured at Tianjin Asymchem Pharmaceuticals Co., Ltd., Tianjin, China. The drug products, Fruzaqla Capsules 5 mg and 1 mg, are manufactured at STA Pharmaceutical Switzerland SA, Couvet, Switzerland.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities has been appropriately performed. Potential and actual impurities are adequately controlled in accordance with ICH Q3A and Q3C guidelines.

The drug substance specifications were established in accordance with ICH Q6A guideline and the impurity limits have been appropriately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guidelines, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data presented was adequate to support the storage of the drug substance at 30°C with a retest period of 60 months. The packaging is a single-layer low-density polyethylene bag, sealed and stored in a triple-layer aluminium foil bag which is then heat-sealed.

Drug product:

The capsule contents are manufactured using dry blending and are subsequently encapsulated. This is considered a standard manufacturing process. The manufacturing site is compliant with Good Manufacturing Practice (GMP) standard. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications have been established in accordance with ICH Q6A guideline and impurity limits were adequately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guidelines, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data submitted was adequate to support the approved shelf-life of 30 months when stored at or below 30°C. The container closure system is a high-density polyethylene bottle with polypropylene child-resistant lid and an induction-sealed aluminium liner. Each bottle contains 21 capsules and is supplied with a desiccant cartridge.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of fruquintinib for the treatment of metastatic colorectal cancer (mCRC) was assessed in two pivotal Phase III trials: FRESCO and FRESCO-2.

FRESCO Study

The FRESCO trial was a multicentre, randomised, double-blind, placebo-controlled, Phase III study conducted in China. It included mCRC patients who had failed at least two chemotherapy regimens. Participants were randomised in a 2:1 ratio to receive either fruquintinib 5 mg orally daily for 3 weeks followed by 1 week off plus best supportive care (BSC), or placebo plus BSC. Randomisation was stratified by prior VEGF inhibitor use (yes vs no) and K-RAS gene status (wild-type vs mutant).

The primary efficacy endpoint was overall survival (OS), while secondary endpoints included progression-free survival (PFS), objective response rate (ORR), and disease control rate (DCR). Appropriate statistical methods were used for analysing these outcomes.

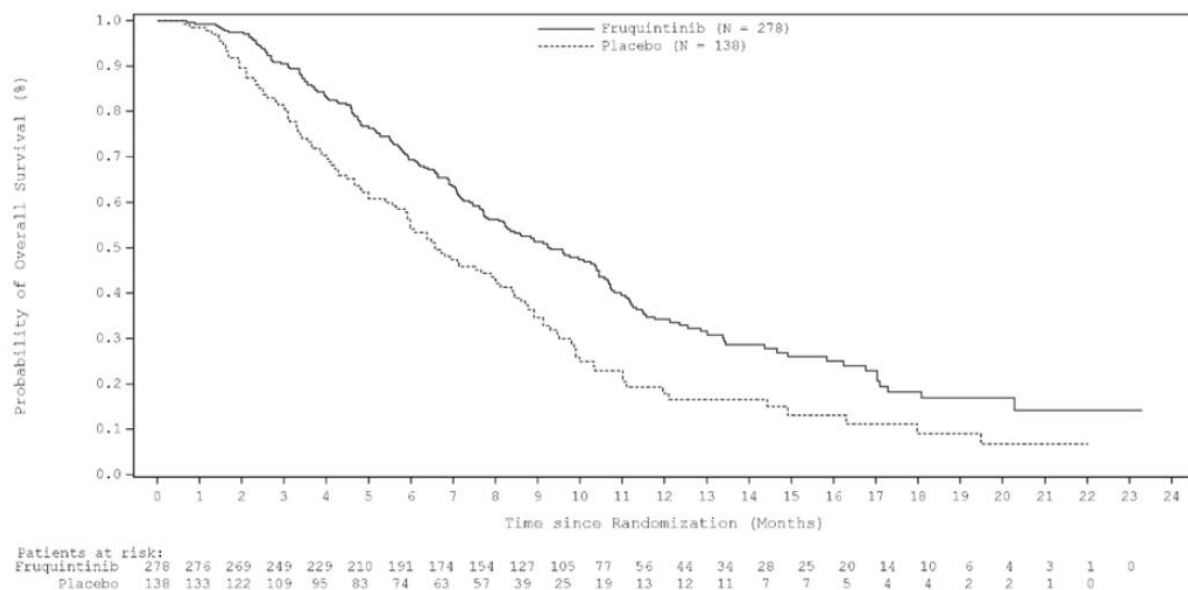
A total of 416 patients were randomised either to the fruquintinib group (n=278) or the placebo group (n=138). The median age was 56 years (range 23 to 75), with 19% aged 65 or older. Of the total participants, 61.3% were male, all were Asian, and their Eastern Cooperative Oncology Group Performance Status (ECOG PS) was either 0 (27%) or 1 (73%). Tumour K-RAS wild type was identified in 55.5% of patients at study entry. The median number of previous treatments for metastatic disease was 2 (range 2 to 3). All participants had received prior treatment with fluorouracil, oxaliplatin and irinotecan. Similar percentages of participants in both groups had previously been treated with VEGF inhibitors (30.2% vs 29.7%) and EGFR inhibitors (14.4% vs 13.8%).

The final analysis showed that the median OS significantly improved for those in the fruquintinib group compared to the placebo group (9.3 vs 6.6 months; HR 0.65; 95% CI 0.51-0.83; p<0.001). The Kaplan-Meier (KM) analysis for OS (Figure 1) showed an early separation of curves in favour of the fruquintinib arm and was maintained over the duration of the study.

Results from subgroup analyses (for prior VEGF (yes vs no) (HR 0.68 vs 0.60) and K-RAS gene status (wild-type vs mutant) (HR 0.56 vs 0.75) for OS were consistent with those observed in the primary analysis.

PFS also showed statistically significant improvement with fruquintinib (3.7 vs 1.8 months; HR 0.26; 95% CI 0.21-0.34; $p < 0.001$). The ORR and DCR for fruquintinib compared to the placebo group were 4.7% vs 0% and 62.2% vs 12.2%, respectively.

Figure 1: KM curves for OS in FRESCO study



FRESCO-2 Study

The FRESCO-2 trial was a global, randomised, double-blind, multicentre, placebo-controlled, Phase III study comprising 691 patients with refractory mCRC. Patients were randomised in a 2:1 ratio to receive either fruquintinib 5 mg orally daily for 3 weeks followed by 1 week off plus BSC, or placebo plus BSC. Randomisation was stratified according to prior therapy (trifluridine/tipiracil vs regorafenib vs both), RAS status (wild-type vs mutant), and duration of metastatic disease (≤ 18 months vs > 18 months). The primary and secondary endpoints (OS, PFS, ORR, DCR) were the same as those investigated in the FRESCO study.

A total of 691 subjects were randomised, with 461 in the fruquintinib group and 230 in the placebo group. The median age was 64 years (ranging from 25 to 86), with 47% aged 65 or older. Among the participants, 55.7% were male, 80.9% White, 8.8% Asian, and their ECOG PS was 0 (43.1%) or 1 (56.9%). Tumour RAS wild type was identified in 36.9% of patients at study entry. The median duration of metastatic disease was 39 months (range 6 months to 16.1 years). The median number of previous metastatic therapy lines was 4 (range 2 to 16).

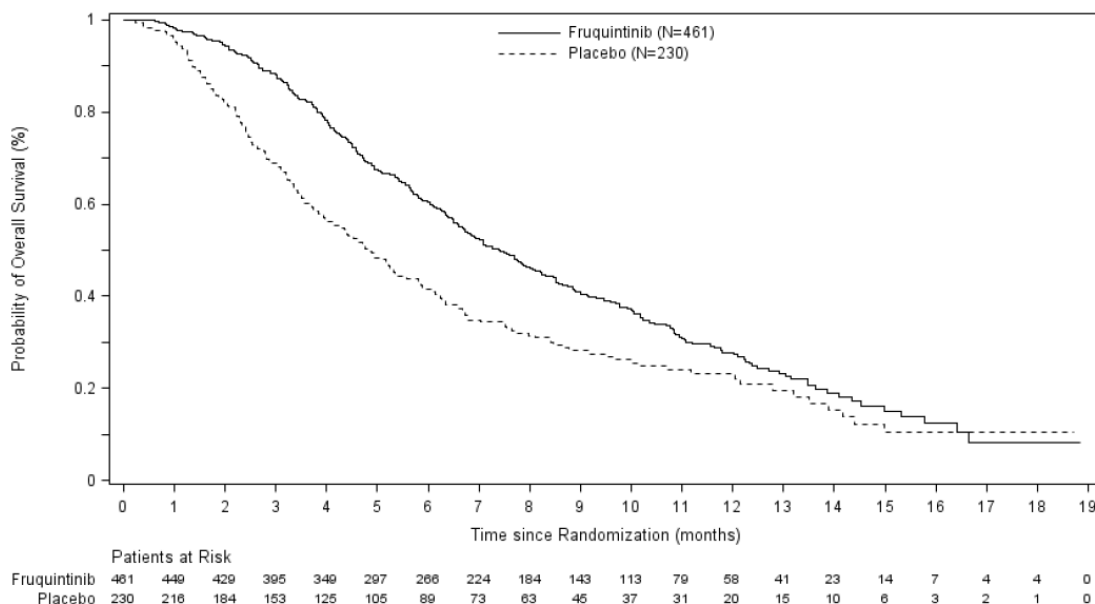
Compared to the FRESCO study population, patients in FRESCO-2 had more extensive treatment histories. Participants were required to have previously received an anti-VEGF biological therapy, an anti-EGFR therapy (if RAS wild type), and to have progressed on or shown intolerance to trifluridine/tipiracil and/or regorafenib, besides standard chemotherapies. Along with fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy, 96.4% of patients underwent prior anti-VEGF therapy, 38.8% received prior anti-EGFR therapy, 52.2% received trifluridine/tipiracil, 8.4% received regorafenib, 39.4% received both trifluridine/tipiracil and regorafenib, 4.6% received immunotherapy, and 2.3% received a BRAF inhibitor.

The final analysis showed that the median OS was 7.4 months in the fruquintinib group compared to 4.8 months in the placebo group (HR 0.66; 95% CI 0.55-0.80; $p < 0.001$). The KM analysis for OS (Figure 3) showed an early separation of curves in favour of the fruquintinib arm.

Results from subgroup analyses for prior therapy (trifluridine/tipiracil vs regorafenib vs both) (HR 0.72 vs 0.77 vs 0.60), K-RAS status (wild-type vs mutant) (HR 0.67 vs 0.68), and duration of metastatic disease (≤ 18 months vs > 18 months) (HR 0.61 vs 0.64) for OS were consistent with those observed in the primary analysis.

PFS also showed significant improvement with fruquintinib (3.7 vs 1.8 months; HR 0.32; 95% CI 0.27-0.39; $p < 0.001$). The ORR and DCR in the fruquintinib group compared to the placebo group were 1.5% vs 0% and 55.5% vs 16.1%, respectively.

Figure 3: KM curves for OS in FRESCO-2 study



Summary of efficacy results for Studies FRESCO and FRESCO-2

	FRESCO		FRESCO-2	
	Fruquintinib + BSC (N = 278)	Placebo + BSC (N = 138)	Fruquintinib + BSC (N = 461)	Placebo + BSC (N = 230)
Primary endpoint				
Median OS (months) (95% CI)	9.3 (8.2, 10.5)	6.6 (5.9, 8.1)	7.4 (6.7, 8.2)	4.8 (4.0, 5.8)
HR (95% CI)	0.65 (0.51, 0.83)		0.66 (0.55, 0.80)	
p-value	<0.001		<0.001	
Secondary endpoints				
Median PFS (months) (95% CI)	3.7 (3.7, 4.6)	1.8 (1.8, 1.8)	3.7 (3.5, 3.8)	1.8 (1.8, 1.9)
HR (95% CI)	0.26 (0.21, 0.34)		0.32 (0.27, 0.39)	
p-value	<0.001		<0.001	
ORR, n (%)	13 (4.7)	0	7 (1.5)	0
DCR, n (%)	173 (62.2)	17 (12.3)	256 (55.5)	37 (16.1)

Based on the above results, fruquintinib showed statistically significant improvements in OS and PFS compared to BSC across the two studies FRESCO and FRESCO-2. Further evidence supporting efficacy was provided by subgroup analyses, including K-RAS type and prior treatment, which demonstrated results consistent with the primary analysis in both studies.

Overall, the efficacy of fruquintinib in the treatment of adult patients with mCRC who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF agent, and, if RAS wild-type, an anti-EGFR agent, has been demonstrated.

D ASSESSMENT OF CLINICAL SAFETY

The safety profile of fruquintinib was evaluated based on data from the FRESCO and FRESCO-2 studies, as well as pooled data from three placebo-controlled studies (FRESCO, FRESCO-2 and Phase II Study 2012-013-00CH1) in 1,172 mCRC patients. In the pooled safety dataset, the median duration of exposure in the fruquintinib and placebo arms was 3.65 and 1.84 months, respectively.

Overview of treatment-emergent adverse events (TEAEs)

Adverse Event Category	FRESCO		FRESCO-2		Pooled safety dataset	
	Fruquintinib 5 mg (N = 278) n (%)	Placebo (N = 137) n (%)	Fruquintinib 5 mg (N = 456) n (%)	Placebo (N = 230) n (%)	Fruquintinib 5 mg (N = 781) n (%)	Placebo (N = 391) n (%)
Any TEAE	274 (98.6)	121 (88.3)	451 (98.9)	213 (92.6)	770 (98.6)	355 (90.8)
Treatment-related TEAE	266 (95.7)	97 (70.8)	395 (86.6)	130 (56.5)	705 (90.3)	243 (62.1)
Grade ≥ 3 TEAE	170 (61.2)	27 (19.7)	286 (62.7)	116 (50.4)	489 (62.6)	151 (38.6)
Treatment-related Grade ≥ 3 TEAE	128 (46.0)	10 (7.3)	164 (36.0)	26 (11.3)	318 (40.7)	41 (10.5)
Serious TEAE	43 (15.5)	8 (5.8)	171 (37.5)	88 (38.3)	228 (29.2)	101 (25.8)

Treatment-related serious TEAE	17 (6.1)	2 (1.5)	43 (9.4)	8 (3.5)	67 (8.6)	13 (3.3)
TEAE leading to treatment discontinuation	42 (15.1)	8 (5.8)	93 (20.4)	49 (21.3)	142 (18.2)	59 (15.1)
TEAE leading to death	9 (3.2)	2 (1.5)	48 (10.5)	45 (19.6)	61 (7.8)	49 (12.5)

In the pooled safety dataset, TEAEs with incidences $\geq 10\%$ and over twice that of the placebo group included hypertension (44.7% vs 11.3%), palmar-plantar erythrodysesthesia (PPE) (32.7% vs 3.1%), proteinuria (28.4% vs 13.3%), dysphonia (26.1% vs 4.1%), diarrhoea (24.8% vs 9.0%), hypothyroidism (18.3% vs 1.0%), stomatitis (16.1% vs 2.3%), increased alanine aminotransferase (ALT) (15.5% vs 6.4%), increased thyroid stimulating hormone (TSH) (14.6% vs 1.8%), and arthralgia (12.2% vs 3.6%). The majority of these events were low grade (Grade 1 or 2) and non-serious.

The incidence of serious TEAEs was similar between the fruquintinib and placebo groups (29.2% vs 25.8%). Serious TEAEs with incidences $\geq 1\%$ and ≥ 2 -fold in the fruquintinib group were abdominal pain (1.0% vs 0.5%), pneumonia (1.4% vs 0.3%), and hypertension (1.3% vs 0%).

There was a slightly higher incidence of TEAEs that led to treatment discontinuation in the fruquintinib arm compared to placebo (18.2% vs 15.1%). The reported adverse events included proteinuria (1.4% vs 0.3%), asthenia (1.0% vs 0.5%), and abnormal hepatic function (0.8% vs 0.3%). The proportion of patients who discontinued treatment due to Grade ≥ 3 TEAEs was similar between groups (14.2% vs 13.3%). Reasons for discontinuation included disease progression (0.8% vs 2.0%), intestinal obstruction (0.6% vs 0.5%), abnormal hepatic function (0.6% vs 0.3%), and proteinuria (0.6% vs 0%).

AEs leading to death were less frequent in the fruquintinib group than in the placebo group (7.7% vs 12.5%). Eight deaths related to fruquintinib included two cases of haemoptysis and one case each of elevated bilirubin, unknown cause, pneumonia, fungal lower respiratory infection, gastrointestinal bleeding, and intestinal perforation, all complicated by underlying conditions.

The most frequently reported AEs of special interest (AESIs) in the fruquintinib group compared to placebo were hypertension (47.5% vs 11.8%), hepatic function abnormal (36.4% vs 23.5%), thyroid dysfunction (33.3% vs 4.3%), proteinuria (32.9% vs 15.1%), PPE (32.7% vs 3.1%), haemorrhagic events (26.5% vs 14.6%), and infections (23.4% vs 13.3%). Appropriate warnings and precautions have been included in the package insert.

Overall, the safety profile of fruquintinib in patients with mCRC was consistent with the known AEs of anti-VEGF therapy. The AESIs which were reported at a higher incidence in the fruquintinib arm compared to placebo included hypertension, hepatic function abnormalities, thyroid dysfunction, haemorrhagic events and PPE. These AESIs would require appropriate management through dose reduction/interruptions, with appropriate warnings and dose modification recommendations included in the product labelling to mitigate the known risks.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Colorectal cancer is the most common cancer in Singapore. For men, it is the second most common type of cancer and for women it comes second after breast cancer. Despite advances

in treatment and screening, metastatic colorectal cancer remains associated with high mortality rates and demonstrates poor 5-year survival outcomes.

Current therapies for mCRC include standard chemotherapy regimens with 5-fluorouracil, capecitabine, irinotecan, and oxaliplatin, as well as targeted therapies including anti-VEGF or anti-EGFR inhibitors for patients harbouring specific genetic mutations. At present, there is no established standard of care for patients who have exhausted standard therapies, and there remains a clinical need for new treatment options.

The efficacy of fruquintinib in mCRC patients who did not respond to available therapies was demonstrated in two Phase III pivotal studies, FRESCO and FRESCO-2. Both studies achieved the primary endpoint of OS. In the FRESCO study, the primary analysis of median OS showed a statistically significant improvement for patients in the fruquintinib group compared to the placebo group (9.3 vs 6.6 months; HR 0.65; 95% CI 0.51-0.83; $p < 0.001$). The efficacy results were consistent with those in FRESCO-2, which involved a more heavily treated population; median OS was 7.4 months in the fruquintinib group versus 4.8 months in the placebo group (HR 0.66; 95% CI 0.55-0.80; $p < 0.001$). The primary endpoint was supported by the key secondary endpoint of PFS, as well as other secondary endpoints such as ORR and DCR.

The safety profile of fruquintinib was generally consistent with its mechanism of action and other anti-VEGF treatments. The key toxicities associated with the treatment compared to placebo were hypertension (47.5% vs 11.8%), hepatic function abnormalities (36.4% vs 23.5%), thyroid dysfunction (33.3% vs 4.3%), proteinuria (32.9% vs 15.1%), PPE (32.7% vs 3.1%), haemorrhagic events (26.5% vs 14.6%), and infections (23.4% vs 13.3%). Risk mitigation strategies including dose modifications and supportive care have been included in the package insert, together with appropriate warnings, monitoring and dose adjustment recommendations to enable clinicians to manage the safety risks.

Overall, the benefit-risk profile of fruquintinib for treating adult patients with mCRC who had previously been treated with chemotherapy, an anti-VEGF agent, and, if RAS wild-type, an anti-EGFR agent, was favourable as both efficacy and safety had been satisfactorily demonstrated.

F CONCLUSION

Based on the review of quality, safety, and efficacy data, the benefit-risk profile of fruquintinib for the treatment of mCRC was deemed favourable and approval of the product registration was granted on 17 October 2024.

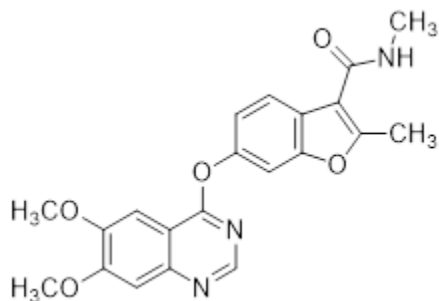
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1. Name of the Medicinal Product

FRUZAQLA (fruquintinib)

2. Qualitative and Quantitative Composition

Each capsule contains 1 or 5 mg of fruquintinib. Fruquintinib is a highly selective tyrosine kinase inhibitor. The chemical name for fruquintinib is 6-[(6,7-dimethoxyquinazolin-4-yl) oxy]-*N*,2-dimethyl-1-benzofuran-3-carboxamide. The molecular formula is $C_{21}H_{19}N_3O_5$, which corresponds to a molecular weight of 393.39 g/mol. The chemical structure is shown below:



Fruquintinib is a white to off-white powder with a dissociation constant (pKa) of 2.78. The aqueous solubility of fruquintinib is pH-dependent, with a solubility of 0.9 µg/mL at pH 6.8 that increases under acidic conditions to 129.9 µg/mL at pH 1.

Fruquintinib capsules for oral administration contain 1 mg or 5 mg of fruquintinib. The inactive ingredients are corn starch, microcrystalline cellulose, and talc. The 1 mg capsule shell contains gelatin, titanium dioxide, FD&C Yellow No. 5 (tartrazine), and FD&C Yellow No. 6 (sunset yellow FCF). The 5 mg capsule shell contains gelatin, titanium dioxide, FD&C Blue No. 1 (brilliant blue FCF), and FD&C Red No. 40 (allura red AC). The printing ink for 1 mg and 5 mg capsules contains shellac, propylene glycol, purified water, potassium hydroxide, and black iron oxide.

For excipients, see section 6.1.

3. Pharmaceutical Form

Dosage Form: Capsules

Available Pharmaceutical Forms	Strength	Color	Size	Markings
Hard capsules	1 mg	White opaque body with yellow opaque cap	3	Imprinted with “HM013” over “1mg” on the body in black ink
	5 mg	White opaque body with Red opaque cap	1	Imprinted with “HM013” over “5mg” on the body in black ink

4. Clinical Particulars

4.1 Therapeutic Indications

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 agent, and, if RAS wild-type, an anti-EGFR agent.

4.2 Posology and Method of Administration

Posology

Fruquintinib should be initiated by a physician experienced in the administration of anticancer therapy.

The recommended dose of fruquintinib is 5 mg (one 5 mg capsule) once daily at approximately the same time each day for 21 consecutive days, followed by a 7-day rest period to comprise a complete cycle of 28 days.

Duration of treatment

Treatment with fruquintinib should be continued until disease progression or unacceptable toxicity occurs.

Missed doses or vomiting.

If a dose is missed by less than 12 hours, it should be taken, and the next dose should be taken as scheduled.

If a dose is missed by more than 12 hours, it should be skipped, and the next dose should be taken as scheduled.

If a patient vomits after taking a dose, the patient should not repeat the dose on the same day, but resume the usual dosing as scheduled on the following day.

Dose Adjustments for Adverse Reactions

The dose should be modified based on safety and tolerability. Fruquintinib should be permanently discontinued in patients unable to tolerate a dose of 3 mg once daily. The recommended dose reduction schedule for adverse reactions is provided in Table 1.

Table 1: Recommended Fruquintinib dose reduction schedule

Dose Reduction Schedule	Dose and schedule	Number and strength of capsules
First dose reduction	4 mg once daily	Four 1 mg capsules once daily
Second dose reduction	3 mg once daily	Three 1 mg capsules once daily

The recommended dose modifications for adverse reactions are provided in Table 2.

Table 2: Recommended dose modifications for Fruquintinib for adverse reactions

Adverse Reaction	Severity¹	Dose modification
Hypertension	Grade 3	<ul style="list-style-type: none"> Withhold if Grade 3 hypertension persists despite initiation or modification of antihypertensive treatment. If hypertension recovers to Grade 1 or baseline, resume at a reduced dose as per Table 1. <p>If the patient still experiences Grade 3 hypertension after taking 3 mg daily, permanently discontinue.</p>
	Grade 4	Permanently discontinue.

Hemorrhagic Events	Grade 2	<ul style="list-style-type: none"> Withhold until bleeding fully resolves or recovers to Grade 1. Resume at a reduced dose as per Table 1. <p>If the patient still experiences Grade 2 hemorrhagic events after taking 3 mg daily, permanently discontinue.</p>
	Grade ≥ 3	Permanently discontinue.
Proteinuria	≥ 2 g / 24 hours	<ul style="list-style-type: none"> Withhold until proteinuria fully resolves or is < 1 g / 24 hours (Grade 1). Resume at a reduced dose as per Table 1. <p>If the patient still experiences ≥ 2 g / 24 hours proteinuria after taking 3 mg daily, permanently discontinue.</p> <p>Permanently discontinue for nephrotic syndrome.</p>
Liver Function Test Abnormalities	Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 3 times upper limit of normal (ULN) if baseline was normal, or greater than 3.0 times baseline if baseline was abnormal; or bilirubin greater than 1.5 times ULN if baseline was normal, or greater than 1.5 times baseline if baseline was abnormal	<ul style="list-style-type: none"> Withhold until liver function test abnormality recovers to Grade 1 or baseline. Resume at a reduced dose as per Table 1. <p>If the patient still experiences Grade 2 or Grade 3 liver function test abnormalities after taking 3 mg daily, permanently discontinue.</p>
	ALT or AST greater than 3 times ULN with concurrent total	Permanently discontinue.

	<p>bilirubin greater than 2 times ULN (in the absence of alternative etiologies)</p>	
	<p>AST or ALT greater than 20 times ULN if baseline was normal, or greater than 20 times baseline if baseline was abnormal; or bilirubin greater than 10 times ULN if baseline was normal, or greater than 10 times baseline if baseline was abnormal</p>	<p>Permanently discontinue.</p>
Palmar-plantar Erythrodysesthesia Syndrome (PPES)	Grade 2	<ul style="list-style-type: none"> • Administer supportive treatment. • Withhold until PPES recovers to Grade 1 or baseline. • Resume at the same dose level.
	Grade 3	<ul style="list-style-type: none"> • Administer supportive treatment. • Withhold until PPES recovers to Grade 1 or baseline. • Resume at a reduced dose as per Table 1. <p>If the patient still experiences Grade 3 PPES after taking 3 mg daily, permanently discontinue.</p>
Other Adverse Reactions	Grade 3	<ul style="list-style-type: none"> • Withhold until the reaction recovers to Grade 1 or baseline. • Resume at a reduced dose as per Table 1. <p>If the patient still experiences Grade 3 other adverse reactions after taking 3 mg daily, permanently discontinue.</p>

	Grade 4	<p>Discontinue.</p> <p>Consider resuming at a reduced dose as per Table 1 if the toxicity recovers to Grade 1 or baseline and the potential benefit outweighs the risks.</p>
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ULN = upper limit of normal

iGraded per national cancer institute common terminology criteria for adverse events. Version 5.0 (NCI CTCAE v5).

Special Patient Populations

Elderly Patients

No dose adjustment is required in patients aged 65 years or above.

Pediatric Patients

The safety and efficacy of fruquintinib in children aged 0 to <18 years have not been established. No data are available.

Impaired Renal Function

No dose adjustment is required for patients with mild, moderate, or severe renal impairment (*see Pharmacokinetic Properties, 5.2*).

Impaired Hepatic Function

No dose adjustment is required for patients with mild hepatic impairment (total bilirubin less than or equal to the ULN with AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN with any AST). A dedicated PK study in a limited sample size showed no clinically meaningful differences in the dose-normalised AUC of fruquintinib between patients with moderate hepatic impairment (total bilirubin greater than 1.5 times and less than 3 times ULN and any AST) and those with normal hepatic function (*see Pharmacokinetic Properties, 5.2*). However, patients with moderate hepatic impairment were excluded from clinical studies. . Fruquintinib is not recommended for use in patients with severe hepatic impairment (total bilirubin greater than 3 times ULN and any AST) as fruquintinib has not been studied in this population.

Method of Administration

Fruquintinib is for oral use.

Fruquintinib capsules can be taken with or without food and should be swallowed whole.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients in the section 6.1.

4.4 Special Warnings and Special Precautions for Use

Hypertension

Hypertension, including hypertensive crisis, has been reported in patients treated with fruquintinib. (*see Undesirable Effects, 4.8*). Pre-existing hypertension should be adequately controlled before starting fruquintinib treatment.

Hypertension should be medically managed with antihypertensive medicinal products and adjustment of the fruquintinib dose, if necessary (*see Posology and Method of Administration, 4.2*). Fruquintinib should be permanently discontinued for hypertension that cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis.

Hemorrhagic events

Hemorrhagic events have been reported in patients treated with fruquintinib, including gastrointestinal (GI) tract events (*see Undesirable Effects, 4.8*). Serious and sometimes fatal bleeding events have been reported in patients after treatment with fruquintinib.

Monitor hematologic and coagulation profiles more frequently in patients at risk for bleeding, including those treated with anticoagulants or other concomitant medicinal products that increase the risk of bleeding.

In the event of severe bleeding requiring immediate medical intervention, fruquintinib should be permanently discontinued (*see Posology and Method of Administration, 4.2*).

Gastrointestinal (GI) perforation

GI perforation events, including fatal events, have been reported in patients treated with fruquintinib (*see Undesirable Effects, 4.8*).

Symptoms of GI perforation should be periodically monitored during treatment with fruquintinib. Fruquintinib should be permanently discontinued in patients developing GI perforation.

Hepatotoxicity

Liver function test abnormalities have been reported in patients treated with fruquintinib, including fatal events in clinical studies (see Undesirable effects).

The liver function test abnormalities should be monitored before initiation and throughout the treatment with fruquintinib. Based on the severity and persistence of liver function abnormalities as manifested by elevated liver function tests, treatment should be withheld, and then reduced or permanently discontinued.

Proteinuria

Proteinuria events have occurred in patients treated with fruquintinib.

Urine protein should be monitored regularly. If urine dipstick proteinuria ≥ 2 g / 24 hours is detected, dose interruptions, adjustments, or discontinuation may be necessary. Fruquintinib should be permanently discontinued in patients developing nephrotic syndrome (*see Posology and Method of Administration, 4.2*).

Palmar-plantar erythrodysesthesia syndrome (PPES)

PPES is the most frequently reported dermatological adverse reactions (*see Undesirable Effects, 4.8*).

If Grade ≥ 2 skin reactions are detected, dose interruptions, adjustments, or discontinuation may be necessary (*see Posology and Method of Administration, 4.2*).

Posterior reversible encephalopathy syndrome (PRES)

PRES has been reported with the use of fruquintinib (0.1%) (*see Undesirable Effects, 4.8*). PRES is a rare neurologic disorder that can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). In patients developing PRES, discontinuation of fruquintinib, along with control of hypertension and supportive medical management of other symptoms, are recommended.

Impaired wound healing

No formal studies of the effect of fruquintinib on wound healing have been conducted.

Impaired wound healing has been reported in 1 patient (0.1%) treated with fruquintinib.

Patients are recommended to withhold fruquintinib for at least 2 weeks prior to surgery. Fruquintinib should not be resumed for at least 2 weeks after surgery, as clinically indicated when there is evidence of adequate wound healing.

Arterial thromboembolic events

It is recommended to avoid starting treatment with fruquintinib in patients with a history of thromboembolic events (including deep vein thrombosis and pulmonary embolism) within the past 6 months or if they have a history of stroke and/or transient ischemic attack within the last 12 months. If arterial thrombosis is suspected, fruquintinib should be discontinued immediately.

Aneurysms and arterial dissections

The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before starting treatment with fruquintinib, this risk should be carefully considered in patients with a history of risk factors such as hypertension or aneurysm.

4.5 Interaction with Other Medications and Other Forms of Interaction

Effect of Other Drugs on Fruquintinib

In vitro results indicated that fruquintinib was metabolized by CYP and non-CYP enzymes. CYP3A4 was the main enzyme among the CYP isoforms involved in the metabolism of fruquintinib, with minor contributions from CYP2C8, CYP2C9 and CYP2C19.

CYP3A Inducers

The concomitant use of fruquintinib with strong and moderate CYP3A inducers should be avoided (*see Pharmacokinetic Properties, 5.2*).

CYP3A Inhibitors

Co-administration of fruquintinib with itraconazole (a strong CYP3A inhibitor) 200 mg twice daily did not result in clinically meaningful changes in the area under the concentration time curve (AUC) and C_{max} of fruquintinib (*see Pharmacokinetic Properties, 5.2*).

Gastric Acid Reducing Agents

Fruquintinib demonstrated pH-dependent aqueous solubility. Co-administration of fruquintinib with rabeprazole (a proton pump inhibitor) 40 mg once daily did not result in clinically meaningful changes in the AUC of fruquintinib (*see Pharmacokinetic Properties, 5.2*).

Effect of Fruquintinib on Other Drugs

P-gp or BCRP Substrates.

Fruquintinib inhibited P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP) in a dose-dependent manner *in vitro*. Based on clinical assessment and physiologically-based pharmacokinetic analysis, no dose adjustment is recommended for P-gp and BCRP substrates during coadministration with fruquintinib (*see Pharmacokinetic Properties, 5.2*).

4.6 Pregnancy, Lactation and Fertility

Women of childbearing potential/Contraception in males and females

Women of childbearing potential and male patients with female partners of childbearing potential should be advised to use effective contraception during treatment and for at least 2 weeks following the last dose of fruquintinib.

Pregnancy

There are no clinical data available on the use of fruquintinib in pregnant women.

Based on its mechanism of action, fruquintinib has the potential to cause fetal harm. Studies in animals have shown reproductive toxicity, including fetal malformations (*see Nonclinical Safety Data 5.3*).

Fruquintinib should not be used during pregnancy unless the woman's clinical condition requires treatment with fruquintinib and after careful consideration of the benefits for the mother and the risk to the fetus.

If fruquintinib is used during pregnancy or if the patient becomes pregnant while on treatment, the patient must be informed of the potential hazard to the fetus.

Lactation

It is unknown whether fruquintinib or its metabolites are excreted in human milk. A risk to new borns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with fruquintinib and for at least 2 weeks after the last dose.

Fertility

There are no data on the effects of fruquintinib on human fertility. Results from animal studies indicate that fruquintinib may impair male and female fertility (*see Nonclinical Safety Data 5.3*).

4.7 Effects on Ability to Drive and Use Machines

Studies to evaluate the effects of fruquintinib on the ability to drive or operate machinery have not been conducted. Fruquintinib may have a minor influence on the ability to drive and use machines. Fatigue may occur following administration of fruquintinib (*see Undesirable Effects, 4.8*).

4.8 Undesirable Effects

Clinical Trials

The overall safety profile of fruquintinib is based on pooled data from clinical studies with 911 patients with mCRC. Patients were exposed to at least one dose (5mg) of fruquintinib (5 mg once daily 3 weeks on/1 week off) during a median of 3.68 months.

In this patient population, the most common adverse reactions of any grade (incidence $\geq 20\%$) were hypertension (49.3%), anorexia (35.6%), proteinuria (35.5%), PPES (34.6%), hypothyroidism (32.4%), dysphonia (28.6%), diarrhoea (26.3%), and asthenia (24.5%), the majority of which were of Grades 1 or 2 severity. The most common adverse reactions of Grade 3/4 (incidence $\geq 5\%$) were hypertension (19.1%) and PPES (8.3%). The most common serious adverse reactions (incidence $\geq 1\%$) were gastrointestinal hemorrhage (1.5%), pneumonia (1.5%), hypertension (1.5%), and gastrointestinal perforation (1.3%).

The frequency of treatment discontinuation due to adverse reactions was 7.6%. The most common adverse reaction leading to treatment discontinuation was proteinuria (1.6%). The frequency of dose reduction due to adverse reactions was 20.5%. The most common adverse reactions leading to dose reduction were PPES (6.4%), hypertension (3.7%), and proteinuria (3.4%).

Adverse reactions reported in clinical studies of fruquintinib are listed in Table 3. These reactions are presented by system organ class and by frequency. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. The following convention is used for the classification of the frequency of an adverse drug reaction (ADR) and is based on the Council for International Organizations of Medical Sciences (CIOMS) guidelines: very common (\geq

1/10); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3: Adverse Reactions Reported in Patients with mCRC Treated with Fruquintinib (N=911)

System Organ Class	Frequency Category	Adverse Reactions All Grades	Adverse Reactions Grade 3/4
Infections and infestations	Common	Pneumonia Upper respiratory tract infection ¹	Pneumonia
	Uncommon		Upper respiratory tract infection ¹
Blood and lymphatic system disorders	Very Common	Thrombocytopenia ²	
	Common	Leukopenia ³ Neutropenia ⁴	Thrombocytopenia ²
	Uncommon		Leukopenia ³ Neutropenia ⁴
Endocrine disorders	Very Common	Hypothyroidism ⁵	
	Uncommon		Hypothyroidism ⁵
Metabolism and Nutrition disorders	Very Common	Anorexia ⁶	
	Common	Hypokalemia	Anorexia ⁶ Hypokalemia
Nervous system disorders	Uncommon	Posterior reversible encephalopathy syndrome	Posterior reversible encephalopathy syndrome
Vascular disorders	Very Common	Hypertension ⁷	Hypertension ⁷
Respiratory, thoracic and mediastinal disorders	Very Common	Dysphonia ⁸	
	Common	Epistaxis Throat pain ⁹	

Gastrointestinal disorders	Very Common	Diarrhoea Stomatitis ¹⁰	
	Common	Gastrointestinal hemorrhage ¹¹ Gastrointestinal perforation ¹² Pancreatic enzymes increased ¹³ Oral pain ¹⁴	Diarrhoea Stomatitis ¹⁰ Gastrointestinal hemorrhage ¹¹ Pancreatic enzymes increased ¹² Gastrointestinal perforation ¹³
	Uncommon	Pancreatitis ¹⁵	Pancreatitis ¹⁵
Hepatobiliary disorders	Very Common	Alanine aminotransferase increased	
	Common		Alanine aminotransferase increased
Skin and subcutaneous tissue disorders	Very Common	Palmar-plantar erythrodysesthesia syndrome	
	Common	Rash ¹⁶	Palmar-plantar erythrodysesthesia syndrome
Musculoskeletal and connective tissue disorders	Very Common	Musculoskeletal discomfort ¹⁷ Arthralgia	
	Common		Musculoskeletal discomfort ¹⁷
	Uncommon		Arthralgia
Renal and urinary disorders	Very Common	Proteinuria ¹⁸	
	Common		Proteinuria ¹⁸

General disorders and administrative site conditions	Very Common	Asthenia Fatigue	
	Common	Mucosal inflammation	Asthenia Fatigue
	Uncommon		Mucosal inflammation

The safety data based on all patients with mCRC who received at least 1 dose (5mg) of fruquintinib (5mg once daily 3 weeks on/1 week off) in the following pooled studies: 2012-013-00CH1; 2013-013-00CH1/ FRESCO; 2019-013-GLOB1/FRESCO-2 including the open-label Japanese safety lead-in cohort; 2009-013-00CH1; 2012 013-00CH3; 2015-013-00US1. MedDRA 25.0.

The following terms represent a group of related events that describe a medical condition rather than a single event:

¹Upper respiratory tract infection includes nasopharyngitis, pharyngitis, upper respiratory tract infection

²Thrombocytopenia includes platelet count decreased and thrombocytopenia

³Leukopenia includes leukopenia and white blood cell count decreased

⁴Neutropenia includes neutropenia and neutrophil count decreased

⁵Hypothyroidism includes blood thyroid stimulating hormone increased, hypothyroidism

⁶Anorexia includes appetite decreased and weight loss

⁷Hypertension includes blood pressure diastolic increased, blood pressure increased, diastolic hypertension, hypertension, hypertensive crisis

⁸Dysphonia includes aphonia and dysphonia

⁹Throat pain includes laryngeal discomfort, laryngeal pain, oropharyngeal discomfort, oropharyngeal pain

¹⁰Stomatitis includes aphthous ulcer, gingival ulceration, mouth ulceration, stomatitis, tongue ulceration

¹¹Gastrointestinal hemorrhage includes anal hemorrhage, anastomotic hemorrhage, gastric hemorrhage, gastrointestinal hemorrhage, hematochezia, hemorrhoidal hemorrhage, intestinal hemorrhage, lower gastrointestinal hemorrhage, rectal hemorrhage, upper gastrointestinal hemorrhage

¹²Gastrointestinal perforation includes gastric perforation, gastric ulcer perforation, gastrointestinal perforation, intestinal perforation, large intestine perforation, rectal perforation, small intestinal perforation

¹³Pancreatic enzymes increased includes amylase increased, hyperamylasemia, hyperlipasemia, lipase increased

¹⁴Oral pain includes gingival pain, oral pain, toothache

¹⁵Pancreatitis includes pancreatitis, pancreatitis acute

¹⁶Rash includes rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic

¹⁷Musculoskeletal discomfort includes bone pain, muscle spasms, musculoskeletal chest pain, musculoskeletal pain, neck pain, pain in extremity

¹⁸Proteinuria includes albuminuria, protein urine present, proteinuria

Description of selected adverse reactions

Data for the following selected adverse reactions are based on patients who received at least 1 dose (5mg) of fruquintinib (5mg once daily 3 weeks on/1 week off) across three randomized placebo-controlled studies (2012-013-00CH1; 2013-013-00CH1/ FRESCO; 2019-013-GLOB1/FRESCO-2). The management guidelines for these adverse reactions are described in *Special Warnings and Special Precautions for Use*, 4.4.

Hypertension

Hypertension was reported in 47.4% of patients in the fruquintinib arm and 11.8% in the placebo arm. Approximately half of these events occurred during the first 2 weeks after initiating treatment with fruquintinib. The incidence of Grade ≥ 3 hypertension events were 18.4% in the fruquintinib arm and 1.3% in the placebo arm. Median time to onset in fruquintinib-treated was 15 days (range: 1 day to 7.6 months). Two patients (0.3%) treated with fruquintinib experienced life-threatening hypertension. The majority of the events recovered or resolved following dose interruption or reduction, which occurred in 3.1% and 3.7% of patients, respectively. In 0.5% of patients treated with fruquintinib, hypertension led to permanent treatment discontinuation.

Hemorrhagic events

Hemorrhagic events were reported in 26.5% of patients in the fruquintinib arm and 14.6% in the placebo arm. Most hemorrhagic events in patients treated with fruquintinib were mild to moderate in severity; the incidence of Grade ≥ 3 hemorrhagic events were 2.0% in the fruquintinib arm and 1.0% in the placebo arm. Median time to onset in fruquintinib-treated patients was 23 days (range: 1 day to 9.8 months). Fatal hemorrhagic events were reported in 0.5% of patients in the fruquintinib arm. In 1.2% of patients treated with fruquintinib, hemorrhagic events led to dose discontinuation. The most common hemorrhagic reactions were gastrointestinal hemorrhage (7%) and epistaxis (5.6%). The most frequently reported serious hemorrhagic event was gastrointestinal hemorrhage, which was reported in 1.5% of patients in the fruquintinib arm compared with 0.5% in the placebo arm.

Gastrointestinal (GI) perforation

GI perforation events were reported in 1.5% of patients in the fruquintinib arm, and no events were reported in the placebo arm. Fatal GI perforation was reported in 0.1% of patients treated with

fruquintinib. The most common GI perforation event was intestinal perforation (0.8%). In 1.0% of patients treated with fruquintinib, GI perforation events led to dose discontinuation.

Proteinuria

Proteinuria was reported in 32.9% of the patients in the fruquintinib arm and 15.1% in the placebo arm. Most of the events in patients treated with fruquintinib were mild to moderate in severity; the incidence of Grade ≥ 3 proteinuria events were 2.8% in the fruquintinib arm and 0.5% in the placebo arm. Median time to onset in fruquintinib treated patients was 28 days (range: 6 days to 1.3 years). The majority of the events recovered or resolved following dose interruption or reduction. In 1.8% of patients treated with fruquintinib, proteinuria led to permanent treatment discontinuation.

Palmar-plantar erythrodysaesthesia syndrome (PPES)

Palmar-plantar erythrodysesthesia syndrome was reported in 32.7% of patients in the fruquintinib arm and 3.1% in the placebo arm. The incidence of Grade ≥ 3 PPES events were 8.5% in the fruquintinib arm and 0.3% in the placebo arm. Median time to onset in fruquintinib-treated patients was 20 days (range: 1 day to 7.4 months). The majority of the events recovered or resolved following dose interruption or reduction, which occurred 6.4% and 6.3%, respectively. In 0.5% of patients treated with fruquintinib, PPES led to permanent treatment discontinuation.

Hypothyroidism

Hypothyroidism was reported in 31.5% of the patients in the fruquintinib arm and 2.8% in the placebo arm. Most of the events in patients treated with fruquintinib were mild to moderate in severity; the incidence of Grade ≥ 3 hypothyroidism in the fruquintinib arm was low (0.3%). Median time to onset in fruquintinib-treated patients was 56 days (range: 18 days to 1.4 years). No events led to dose reduction or discontinuation.

4.9 Overdose

The highest dose of fruquintinib studied in clinical studies was 6 mg per day.

The effects of fruquintinib overdose are unknown, and there is no known antidote for fruquintinib overdose. In the event of an overdose, interrupt fruquintinib, general supportive measures should be undertaken and observe until clinical stabilisation.

4.10 Drug Abuse and Dependence

Fruquintinib has no known potential for abuse or dependence.

5.0 Pharmacological Properties

5.1 Pharmacodynamic Properties

Mechanism of Action

Fruquintinib is a highly selective small molecule tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFR) -1, -2, and -3 with antitumor effects resulting from suppression of tumor angiogenesis and tumor deprivation of nutrients and oxygen.

These receptors are implicated in pathologic angiogenesis, tumor growth, and cancer progression. VEGF mediated endothelial cell proliferation and survival were inhibited by fruquintinib *in vitro* and in mouse models. Fruquintinib was shown to inhibit tumor growth and phosphorylation of VEGFR-2 in tumor xenograft mouse models.

Cardiac electrophysiology

No prolongation of heart rate-corrected QT (QTc) interval (> 10 milliseconds) was observed at the recommended dosage of fruquintinib. A concentration-QT analysis (N=205) showed no evidence of an association between fruquintinib plasma concentrations and changes in QTc interval from baseline.

Clinical Studies

The safety and efficacy of fruquintinib plus best supportive care (BSC) was evaluated in two randomized, placebo controlled, double blind, phase III studies (FRESCO and FRESCO2) in patients with mCRC previously treated with but not limited to oxaliplatin- and- irinotecan-based chemotherapies. The clinical efficacy of fruquintinib in the FRESCO and FRESCO2 studies are described below.

FRESCO Study

The clinical safety and efficacy of fruquintinib were evaluated in a randomized, double blind, placebo controlled, multicentre phase III study (FRESCO) conducted in China in 416 patients with previously treated mCRC. Randomisation was stratified by prior use of VEGF inhibitor (yes vs. no) and K RAS gene status (wild type vs. mutant).

Patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≥ 2 , left ventricular fraction $\leq 50\%$, systolic blood pressure > 140 mm Hg or diastolic blood pressure > 90 mm Hg, urine protein ≥ 1 g/24h, and body weight < 40 kg were excluded. The primary efficacy endpoint was overall survival (OS). Secondary efficacy endpoints included progression-free survival (PFS) as assessed by the investigator using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, tumor objective response rate (ORR), disease control rate (DCR; including complete response, partial response and stable disease), duration of response (DoR), and safety.

In total, 416 patients were randomized (2:1) to receive fruquintinib 5 mg orally once daily (N=278) plus BSC or placebo orally once daily (N=138) plus BSC (hereafter denoted as fruquintinib and placebo, respectively), for 21 days on therapy followed by 7 days off therapy in a 28day treatment cycle. Among the 416 randomized patients, the median age was 56 years (range: 23 to 75), with 19% ≥ 65 years of age. 61.3% of patients were male, all were Asian (100%), and had an (ECOG) PS of 0 (27%) or 1 (73%). The median number of prior lines of therapy for metastatic disease was 2 (range: 2 to 3). Tumor *K-Ras* mutation was reported in 44% of patients at study entry.

In addition to treatment with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, 30% of patients received prior antiVEGF therapy, and 14% received prior antiEGFR therapy.

The addition of fruquintinib to BSC resulted in a statistically significant improvement in OS and PFS compared to placebo plus BSC (see Table 4, Figure 1).

FRESCO-2 Study

The clinical safety and efficacy of fruquintinib were evaluated in a global, randomized, double blind, placebo controlled, multicentre, phase III study (FRESCO-2) in 691 patients with mCRC who had been previously treated with standard approved therapies including fluoropyrimidine-, oxaliplatin-, and irinotecan based chemotherapy; an anti- VEGF biological therapy; an anti- EGFR therapy if RAS wild type, and have progressed on or had intolerance to trifluridine/tipiracil and/or regorafenib. Patients were considered intolerant to trifluridine/tipiracil or regorafenib if they received at least 1 dose of either agent and were discontinued from therapy for reasons other than progressive disease. Patients with MSI-H or dMMR tumors were previously treated with immune checkpoint inhibitors, and patients with BRAF

V600E mutant tumors were previously treated with a BRAF inhibitor, if approved and available in the patients' respective country or region.

Randomization was stratified by prior therapy (trifluridine/tipiracil vs. regorafenib vs. both trifluridine/tipiracil and regorafenib), RAS status (wild-type vs. mutant), and duration of metastatic disease (≤ 18 months vs. > 18 months).

Patients with an ECOG PS ≥ 2 , left ventricular fraction $\leq 50\%$, systolic blood pressure > 140 mm Hg or diastolic blood pressure > 90 mm Hg, urine protein ≥ 1 g/24h, or body weight < 40 kg were excluded. The primary efficacy endpoint was OS. The key secondary efficacy endpoint was PFS as assessed by the investigator using RECIST, version 1.1. Other supportive secondary endpoints included tumor objective response rate (ORR), disease control rate (DCR; including complete response, partial response, and stable disease), duration of response (DoR), and safety.

In total, 691 patients were randomized (2:1) to receive fruquintinib 5 mg orally once daily (N=461) plus BSC or placebo orally once daily (N=230) plus BSC (hereafter denoted as fruquintinib and placebo, respectively), for 21 days on therapy followed by 7 days off therapy in a 28day treatment cycle. Among the 691 randomized patients, the median age was 64 years (range: 25 to 86), with 47% ≥ 65 years of age. 55.7% of patients were male, 80.9% were White, 8.8% Asian, 2.9% Black or African American, and had an ECOG PS of 0 (43.1%) or 1 (56.9%). Tumor *RAS* wild type was reported in 36.9% of patients at study entry. The median duration of metastatic disease of 39 months (range: 6 months to 16.1 years). The median number of prior lines of therapy for metastatic disease was 4 (range: 2 to 16).

In addition to treatment with fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy, 96.4% of patients received prior anti-VEGF therapy, 38.8% received prior anti-EGFR therapy, 52.2 % received trifluridine/tipiracil, 8.4% received regorafenib, 39.4% received both trifluridine/tipiracil and regorafenib, 4.6% received immunotherapy, and 2.3% received BRAF inhibitor.

The addition of fruquintinib to BSC resulted in a statistically significant improvement in OS and PFS compared to placebo plus BSC (see Table 4 and Figure 2).

Table 4: Efficacy Results From FRESCO and FRESCO-2 Studies

	FRESCO		FRESCO-2	
Endpoint	Fruquintinib + BSC N=278	Placebo + BSC N=138	Fruquintinib+ BSC N=461	Placebo + BSC N=230
OS				
Median in months (95% CI)	9.3 (8.2, 10.5)	6.6 (5.9, 8.1)	7.4 (6.7, 8.2)	4.8 (4.0, 5.8)
Hazard ratio ¹ (95% CI)	0.65 (0.51, 0.83)		0.66 (0.55, 0.80)	
p-value ²	< 0.001		< 0.001	
PFS ³				
Median in months (95% CI)	3.7 (3.7, 4.6)	1.8 (1.8, 1.8)	3.7 (3.5, 3.8)	1.8 (1.8, 1.9)
Hazard ratio ¹ (95% CI)	0.26 (0.21 - 0.34)		0.32 (0.27 - 0.39)	
p-value ²	< 0.001		< 0.001	
ORR				
Confirmed ORR (CR + PR) (%)	13 (4.7)	0	7 (1.5)	0
DCR				
DCR (CR + PR + SD), n (%)	173 (62.2)	17 (12.3)	256 (55.5)	37 (16.1)

Abbreviations: CI=confidence interval; HR=hazard ratio; N=number of patients; OS=overall survival; PFS=progression-free survival; ORR = objective response rate; DCR = disease control rate; CR = complete response; PR = partial response; SD = stable disease

The median OS and PFS were calculated using the Kaplan-Meier method.

¹The HR and its 95% CI were estimated using stratified Cox's proportional hazards model (accounting for the stratification factors), in which the treatment arm is the only covariate in the model.

²p-value (2-sided) was calculated using the stratified log-rank test to account for the stratification factors.

³Assessed by the investigator using RECIST, version 1.1

Figure 1. Kaplan-Meier curve for Overall Survival in FRESCO study

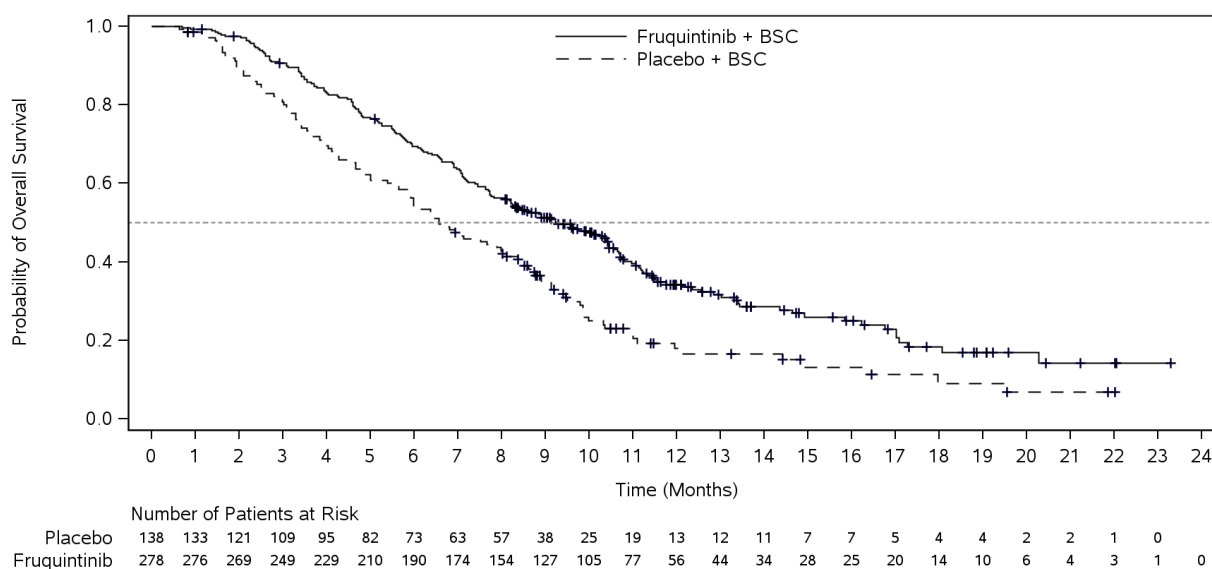
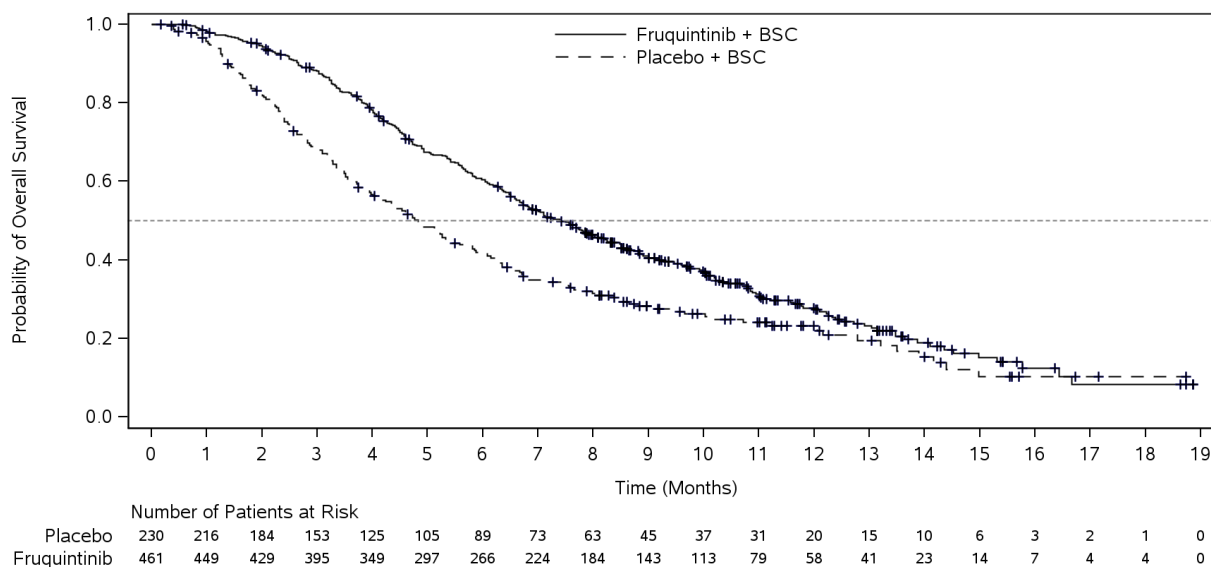


Figure 2 Kaplan-Meier curve for Overall Survival in FRESCO-2 study



5.2 Pharmacokinetic Properties

Absorption

After oral administration of fruquintinib, the median time to achieve peak plasma fruquintinib concentration (T_{max}) was approximately 2 hours. Following repeat once daily dosing, fruquintinib

exposure (C_{\max} and AUC_{0-24h}) increased in a dose proportional manner across the dose range of 1 to 6 mg (0.2 to 1.2 times the recommended dosage).

Following administration of fruquintinib 5 mg once daily for 21 days with 7 days off of each 28day cycle in patients with advanced solid tumors, steady state of fruquintinib was achieved after 14 days, and the mean accumulation based on AUC_{0-24h} was 4fold relative to a single dose. At the recommended dose of 5 mg of fruquintinib, the geometric mean (%CV) C_{\max} and AUC_{0-24h} for fruquintinib at steady-state were 300 ng/mL (28%) and 5880 ng*h/mL (29%), respectively.

Effect of Food

Compared to the fasting state, a high fat meal had no clinically meaningful effect on fruquintinib pharmacokinetics in healthy subjects. Fruquintinib can be administered with or without food.

Distribution

The apparent volume of distribution of fruquintinib is approximately 48.5 L. Plasma protein binding of fruquintinib is approximately 95% *in vitro*.

Metabolism

Fruquintinib is metabolized by multiple enzymes, including CYP450 (CYP3A and CYP2C subfamilies) and nonCYP450 enzyme systems. The *in vivo* metabolism and mass balance study of [14C] labeled fruquintinib showed that fruquintinib mainly exists in human plasma in its unchanged form, accounting for approximately 72% of total exposure in the plasma, and the CYP3A4-mediated N-demethyl metabolite of fruquintinib account for approximately 17% of total exposure in plasma. Other metabolic pathways include multisite mono-oxidation, O-demethylation, N-demethylation, O-dequinazoline ring, and amide hydrolysis. The phase II metabolites are mainly glucuronic acid and sulphuric acid conjugates of phase I products.

Excretion and Elimination

The apparent clearance (CL/F) of fruquintinib is 14.8 mL/min at steady state after once daily dosing in patients with advanced solid tumors. The mean elimination half-life of fruquintinib is approximately 42 hours.

Following administration of a single 5 mg radiolabelled fruquintinib in healthy subjects, approximately 60% of the dose was recovered in urine (0.5% of the dose as unchanged fruquintinib), and 30% of the dose was recovered in feces (5% of the dose as unchanged fruquintinib).

Special Populations

Impaired Renal Function

Based on the population pharmacokinetic analyses, mild to moderate renal impairment (CrCL 30 to 89 mL/min) had no clinically meaningful impact on fruquintinib pharmacokinetics. Based on a dedicated pharmacokinetic study, moderate (CrCL 30 to 59 mL/min, N=8) or severe renal impairment (CrCL 15 to 29 mL/min, N=8) had no clinically meaningful impact on fruquintinib pharmacokinetics.

Impaired Hepatic Function

No clinically meaningful differences in the pharmacokinetics of fruquintinib were observed between patients with normal hepatic function and patients with mild (total bilirubin \leq ULN with AST greater than ULN or total bilirubin > 1 to 1.5 times ULN with any AST) hepatic impairment based on population pharmacokinetic analyses. Based on a dedicated hepatic impairment pharmacokinetic study, moderate (Child Pugh B) hepatic impairment had no clinically meaningful impact on fruquintinib pharmacokinetics.

Age, Body weight, Gender, Race

Population pharmacokinetic analyses showed that age (18 to 82 years), body weight (48 to 108 kg), gender or race had no clinically relevant impact on the pharmacokinetics of fruquintinib.

Drug Interactions

Effect of Other Drugs on Fruquintinib

Strong CYP3A Inducers

Co-administration of fruquintinib with rifampin (a strong CYP3A inducer) 600 mg once daily decreased fruquintinib AUC by 65% and decreased C_{max} by 12%.

Moderate CYP3A Inducers

Co-administration of fruquintinib with efavirenz (a moderate CYP3A inducer) 600 mg once

daily is predicted to decrease fruquintinib AUC by 32% and fruquintinib C_{max} by 4%.

Weak CYP3A Inducers

No clinically meaningful differences in the AUC of fruquintinib are predicted when fruquintinib is co administered with dexamethasone (a weak CYP3A inducer) 8 mg twice daily.

Strong CYP3A Inhibitors

No clinically significant differences in fruquintinib pharmacokinetics were observed when used concomitantly with itraconazole (strong CYP3A inhibitor).

Gastric Acid Reducing Agents

No clinically significant differences in fruquintinib pharmacokinetics were observed when used concomitantly with rabeprazole (proton pump inhibitor; gastric acid reducing agent).

Effect of Fruquintinib on Other Drugs

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

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 transport protein (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 MATE2K .

5.3 Nonclinical Safety Data

In repeat-dose and reproductive animal studies, toxicity was observed at fruquintinib average plasma concentrations below the expected human therapeutic concentrations.

Carcinogenesis, Mutagenesis, Impairment of Fertility, Reproductive Toxicology

Carcinogenicity studies have not been conducted with fruquintinib.

Fruquintinib was not mutagenic in the *in vitro* bacterial reverse mutation (Ames) assay or clastogenic in the *in vitro* Chinese hamster ovary chromosome aberration assay. Fruquintinib was not genotoxic in the *in vivo* rat micronucleus or alkaline comet assays.

In a fertility and early embryonic development study in rats, male and female reproductive indices were decreased at exposures approximately 3.2 and 0.8-fold the human AUC, respectively. Dose dependent increases in pre implantation loss were observed in the same study.

In an embryo-fetal developmental study in rats, embryotoxic and teratogenic effects were observed, consisting of fetal external, visceral, and skeletal malformations.

Animal Toxicology and/or Pharmacology

In repeat dose animal toxicity studies, the main target organ effects were identified in the gastrointestinal tract, hepatobiliary system, immune system, skeletal system (femur and teeth), kidneys, hematopoietic system, and adrenal gland. All findings were reversible after 4 weeks without treatment, apart from the skeletal system (broken/lost teeth).

6. Pharmaceutical Particulars

6.1 List of Excipients

Corn starch

Microcrystalline cellulose

Talc

Capsule shell (1 mg hard capsules only)

Gelatin

Titanium dioxide

Tartrazine (FD&C Yellow No. 5)

Sunset yellow FCF (FD&C Yellow No. 6)

Capsule shell (5 mg hard capsules only)

Gelatin

Titanium dioxide

Brilliant blue FCF (FD&C Blue No. 1)

Allura red AC (FD&C Red No. 40)

Printing ink

Dewaxed shellac

Ethanol anhydrous

Butanol

Ammonia solution, concentrated

Isopropyl alcohol

Propylene glycol

Purified water

Potassium hydroxide

Iron oxide black

6.2 Incompatibilities

Not applicable

6.3 Special Precautions for Storage

Do not store above 30°C (86°F). Protect from moisture. Keep bottle tightly closed. Do not remove desiccant cartridge from the bottle.

6.4 Nature and Contents of Container

Child-resistant bottle.

High-density polyethylene (HDPE) bottle (45 mL) with polypropylene (PP) child-resistant closure and a silica gel desiccant cartridge.

Each bottle contains 21 capsules. Each bottle is packaged in a carton with an insert and sealed with tamper-evident seal.

6.5 Instructions for Use/Handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Product Registrant

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8. Date of Revision

Sept 2024.

Reference: CCDSv2.0