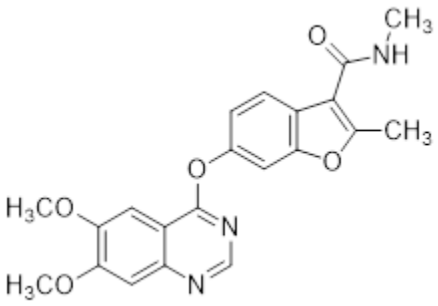
## 1. Name of the Medicinal Product

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** | **Severity[1]** | **Dose modification** |
|---|---|---|
| Hypertension | Grade 3 | • Withhold if Grade 3 hypertension persists despite initiation or modification of antihypertensive treatment.<br>• If hypertension recovers to Grade 1 or baseline, resume at a reduced dose as per Table 1.<br>If the patient still experiences Grade 3 hypertension after taking 3 mg daily, permanently discontinue. |
| | Grade 4 | Permanently discontinue. |

| | | |
|---|---|---|
| Hemorrhagic Events | Grade 2 | • Withhold until bleeding fully resolves or recovers to Grade 1.<br>• Resume at a reduced dose as per Table 1.<br><br>If the patient still experiences Grade 2 hemorrhagic events after taking 3 mg daily, permanently discontinue. |
| | Grade ≥3 | Permanently discontinue. |
| Proteinuria | ≥ 2 g / 24 hours | • Withhold until proteinuria fully resolves or is < 1 g / 24 hours (Grade 1).<br>• Resume at a reduced dose as per Table 1.<br><br>If the patient still experiences ≥ 2 g / 24 hours proteinuria after taking 3 mg daily, permanently discontinue.<br><br>Permanently discontinue for nephrotic syndrome. |
| 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 | • Withhold until liver function test abnormality recovers to Grade 1 or baseline.<br>• Resume at a reduced dose as per Table 1.<br><br>If the patient still experiences Grade 2 or Grade 3 liver function test abnormalities after taking 3 mg daily, permanently discontinue. |
| | ALT or AST greater than 3 times ULN with concurrent total | Permanently discontinue. |

| | | |
|---|---|---|
| | bilirubin greater than 2 times ULN (in the absence of alternative etiologies) | |
| | 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 | Permanently discontinue. |
| Palmar-plantar Erythrodysesthesia Syndrome (PPES) | Grade 2 | • Administer supportive treatment.<br>• Withhold until PPES recovers to Grade 1 or baseline.<br>• Resume at the same dose level. |
| | Grade 3 | • Administer supportive treatment.<br>• Withhold until PPES recovers to Grade 1 or baseline.<br>• Resume at a reduced dose as per Table 1.<br><br>If the patient still experiences Grade 3 PPES after taking 3 mg daily, permanently discontinue. |
| Other Adverse Reactions | Grade 3 | • Withhold until the reaction recovers to Grade 1or baseline.<br>• Resume at a reduced dose as per Table 1.<br><br>If the patient still experiences Grade 3 other adverse reactions after taking 3 mg daily, permanently discontinue. |

| | | |
|---|---|---|
| | Grade 4 | Discontinue.<br><br>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. |

ULN = upper limit of normal
[1]Graded 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 erythrodysaesthesia 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 Cmax 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 ≥ 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 ≥ 5%) were hypertension (19.1%) and PPES (8.3%). The most common serious adverse reactions (incidence ≥ 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 (≥

1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 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<br>Upper respiratory tract infection[1] | Pneumonia |
| | Uncommon | | Upper respiratory tract infection[1] |
| **Blood and lymphatic system disorders** | Very Common | Thrombocytopenia[2] | |
| | Common | Leukopenia[3]<br>Neutropenia[4] | Thrombocytopenia[2] |
| | Uncommon | | Leukopenia[3]<br>Neutropenia[4] |
| **Endocrine disorders** | Very Common | Hypothyroidism[5] | |
| | Uncommon | | Hypothyroidism[5] |
| **Metabolism and Nutrition disorders** | Very Common | Anorexia[6] | |
| | Common | Hypokalemia | Anorexia[6]<br>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<br>Throat pain[9] | |

| | | | |
|---|---|---|---|
| **Gastrointestinal disorders** | Very Common | Diarrhoea<br>Stomatitis[10] | |
| | Common | Gastrointestinal hemorrhage[11]<br>Gastrointestinal perforation[12]<br>Pancreatic enzymes increased[13]<br>Oral pain[14] | Diarrhoea<br>Stomatitis[10]<br>Gastrointestinal hemorrhage[11]<br>Pancreatic enzymes increased[12]<br>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]<br>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<br>Fatigue | |
| | Common | Mucosal inflammation | Asthenia<br>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:

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

[2]Thrombocytopenia includes platelet count decreased and thrombocytopenia

[3]Leukopenia includes leukopenia and white blood cell count decreased

[4]Neutropenia includes neutropenia and neutrophil count decreased

[5]Hypothyroidism includes blood thyroid stimulating hormone increased, hypothyroidism

[6]Anorexia includes appetite decreased and weight loss

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

[8]Dysphonia includes aphonia and dysphonia

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

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

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

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

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

[14]Oral pain includes gingival pain, oral pain, toothache

[15]Pancreatitis includes pancreatitis, pancreatitis acute

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

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

[18]Proteinuria 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 ≤ 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 ≤ 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.

[1]The 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.

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

[3]Assessed by the investigator using RECIST, version 1.1

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

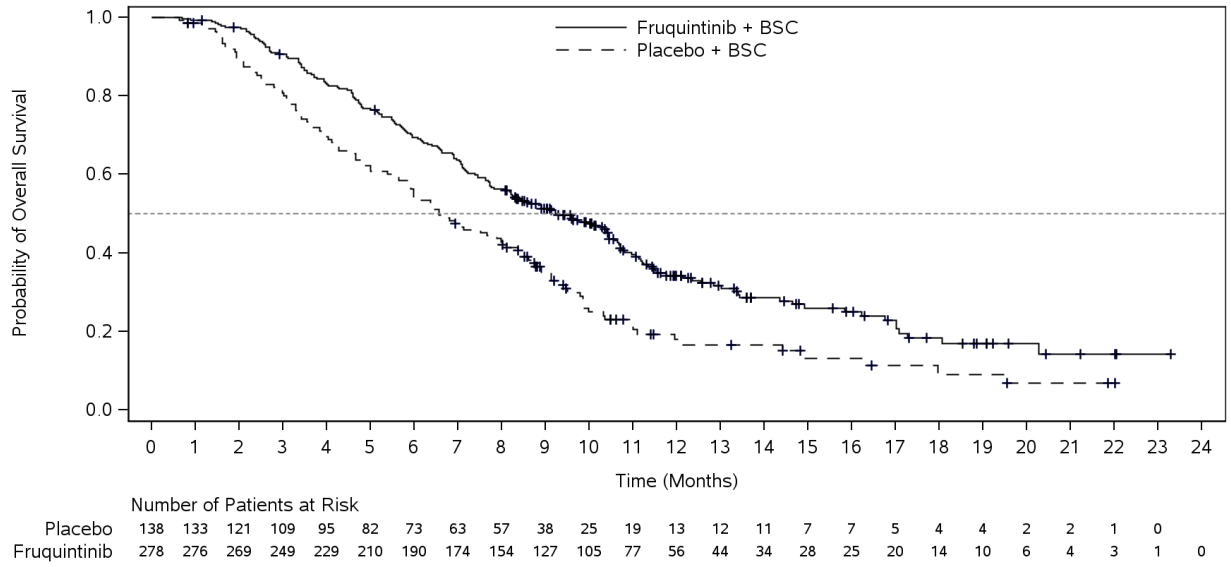
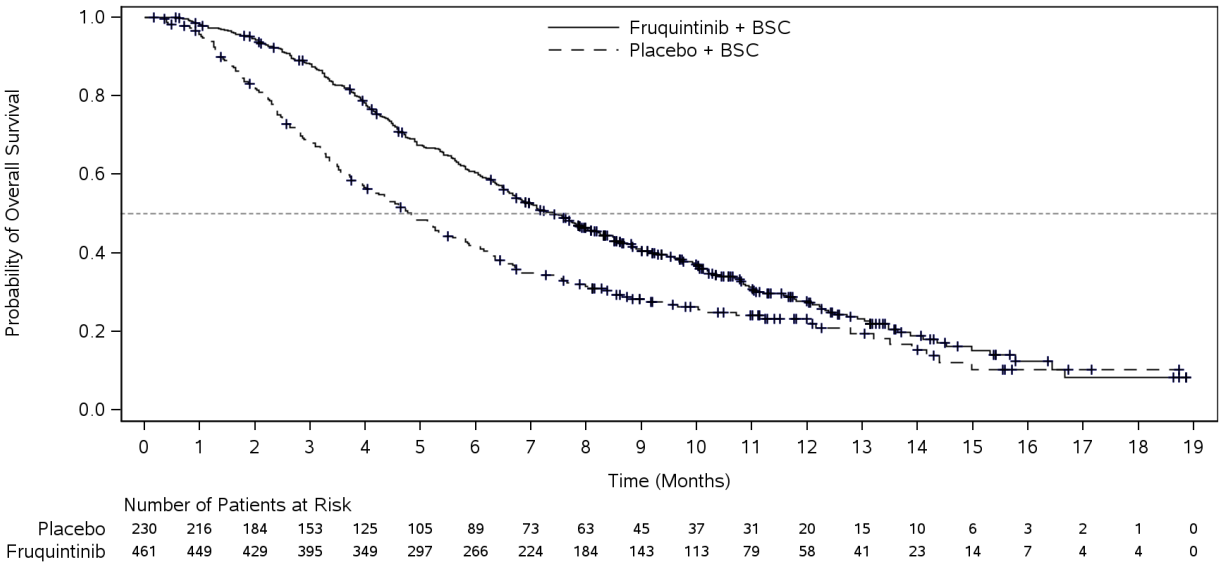



**Figure 2 Kaplan-Meier curve for Overall Survival in FRESCO-2 study**




## 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 $AUC_{024h}$) 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 $AUC_{024h}$ was 4fold relative to a single dose. At the recommended dose of 5 mg of fruquintinib, the geometric mean (%CV) $C_{max}$ and $AUC_{024h}$ 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 ≤ 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 Cmax 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 Cmax 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

Takeda Pharmaceuticals (Asia Pacific) Pte Ltd
8 Marina Boulevard, #05-02
Marina Bay Financial Centre
Singapore (018981)

## 8. Date of Revision

Sept 2024.

Reference: CCDSv2.0