EU RISK MANAGEMENT PLAN (RMP)

for

FRUZAQLA® (FRUQUINTINIB)

RMP Version number: 1.0

Date: 07-May-2024

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EU Risk Management Plan for FRUZAQLA® (FRUQUINTINIB)

RMP version to be assessed as part of this application:

RMP version number: 1.0

Data lock point for this RMP: 24-June-2022

Date of final sign-off: 07-May-2024

Rationale for submitting an updated RMP: Updated the version of Risk Management Plan (RMP) from 0.3 to 1.0 and the indication wordings.

Summary of significant changes in this RMP:

RMP Module:	Significant Changes:
Part I Product Overview	Updated indication wordings
Part II Safety Specification	
• **Module SI Epidemiology of the indication(s) and target population(s)**	Updated indication wordings
• **Module SII Non-clinical part of the safety specification**	Not applicable
• **Module SIII Clinical trial exposure**	Not applicable
• **Module SIV Populations not studied in clinical trials**	Not applicable
• **Module SV Post-authorisation experience**	Not applicable
• **Module SVI Additional EU requirements for the safety specification**	Not applicable
• **Module SVII Identified and potential risks**	Not applicable
• **Module SVIII Summary of the safety concerns**	Not applicable
Part III Pharmacovigilance plan	Not applicable
Part IV Plans for post-authorisation efficacy studies	Not applicable
Part V Risk minimisation measures	Not applicable
Part VI Summary of the risk management plan	Updated indication wordings.
Part VII Annexes	Not applicable

Other RMP versions under evaluation:

Not applicable

Details of the currently approved RMP:

Not applicable

QPPV name: **Jean-Marie Heim, MD**

Please note that e-signature may also be performed by Deputy EU QPPV, on behalf of the EU QPPV (i.e., 'per procurationem').

QPPV signature: Signatures are available on file.

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List of Abbreviations

Abbreviation	Definition/Description
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC code	Anatomical Therapeutic Chemical classification system
CNS	Central nervous system
CRC	Colorectal cancer
CV	Cardiovascular
ECG	Electrocardiogram
EGFR	Epidermal growth factor receptor
eCTD	electronic Common Technical Document
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
GI	Gastrointestinal
INN	International Non-proprietary Names
ISAS	Integrated safety analyses set
MA	Marketing Authorisation
mCRC	Metastatic colorectal cancer
PK	Pharmacokinetic
QT	The length of time between the start of the Q-wave and the end of the T-wave
QTc	Corrected QT interval
QPPV	Qualified Person Responsible for Pharmacovigilance (in the European Union)
RMP	Risk Management Plan
SOC	Standard of Care

Abbreviation	Definition/Description
SmPC	Summary of Product Characteristics
TKI	Tyrosine Kinase Inhibitor
ULN	Upper Limit of Normal
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor

PART I: PRODUCT(S) OVERVIEW

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	Fruquintinib (6-[(6,7-dimethoxyquinazolin-4-yl)oxy]-N,2-dimethyl-1-benzofuran-3-carboxamide)
Pharmacotherapeutic group(s) (ATC Code)	L01EK04
Marketing authorisation holder	Takeda Pharmaceuticals International AG, Ireland Branch
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	FRUZAQLA®
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Tyrosine kinase inhibitor (TKI)
	Summary of mode of action: Fruquintinib, a small molecule anti-tumour quinazoline class TKI, is a highly selective and potent inhibitor of VEGF receptors-1, -2, and -3. Signalling by VEGF via the VEGF receptor (VEGFR) plays a key role in tumour angiogenesis and tumour growth.
	Important information about its composition: Not applicable.
Hyperlink to the Product Information (PI)	Refer to eCTD Module 1.3.1 for proposed PI or latest approved PI.
Indication(s) in the EEA	Current: FRUZAQLA as monotherapy is indicated for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti VEGF agents, and anti EGFR agents, and who have progressed on or are intolerant to treatment with either trifluridine tipiracil or regorafenib.
	Proposed: Not applicable.
Dosage in the EEA	Current: The recommended dose of fruquintinib is 5 mg (one 5 mg capsule) taken orally once daily for 3 weeks followed by 1 week off therapy. This 4-week period is considered a treatment cycle.
	Proposed: Not applicable.

Pharmaceutical form(s) and strengths	Current: 1 mg hard capsule contains 1 mg of fruquintinib. 5 mg hard capsule contains 5 mg of fruquintinib.
	Proposed: Not applicable.
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti VEGF agents, and anti EGFR agents, and who have progressed on or are intolerant to treatment with either trifluridine tipiracil or regorafenib.	
Incidence:	Colorectal cancer (CRC), also known as the cancer of the large bowel, is a cancer located between the colon and rectum. CRC most commonly starts in the glandular tissues as an adenocarcinoma. Sub-types of adenocarcinomas such as signet ring and mucinous typically have a worse prognosis. Colorectal cancer is a major global health issue, with an estimated 1.9 million new cases and 935,000 deaths in 2020 worldwide. CRC is the third most common cause of cancer incidence worldwide. Approximately 22% of patients with CRC in Europe had Stage IV disease at the time of initial diagnosis in those countries with established screening programmes, and ~35% of those individuals in countries which do not have established screening programmes as reported in cancer registries for 2016. In the United States, 33% of CRC was localised, while 38% of cases spread locally and 22% of cases spread to distant parts of the body. The remaining proportion of cases had unknown stage information. The worldwide age-standardised incidence of CRC is estimated to be 19.5/100,000 (both sexes), 23.4/100,000 in males and 16.2/100,000 in females. Incidence rates vary across countries due to differences in risk factors, detection and diagnostic practices, and availability of treatments. The incidence rates per 100,000 inhabitants in 2020 were 33.6 in Northern Europe, 31.9 in Southern Europe, 29.3 in Central and Eastern Europe, and 28.7 in Western Europe. Hungary had the highest CRC incidence in Europe with an incidence rate of 45.3 per 100,000 inhabitants regardless of gender. Hungary also had the highest incidence rate of CRC among males (62 per 100,000) and Norway had the highest incidence rate of CRC among females (38.7 per 100,000). The age-standardised incidence of CRC is 29.8 per 100,000 in Oceania, 8.4 per 100,000 in Africa, 16.6 in Latin America and the Caribbean, 26.2 per 100,000 in Northern America, and 17.6 in Asia. In the US, the incidence is 25.6 per 100,000 overall, while 28.7 per 100,000 for males and 22.9 per 100,000 for females. In Canada the incidence is 31.2 per 100,000 overall, while 34.7 per 100,000 for males and 27.9 per 100,000 for females.

Treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti VEGF agents, and anti EGFR agents, and who have progressed on or are intolerant to treatment with either trifluridine tipiracil or regorafenib.	
Prevalence:	CRC is the third most common malignancy globally diagnosed in both men and women, representing 10% of all cancer diagnoses. In 2020, the 1-year prevalence for CRC in Europe was 55.9/100,000 inhabitants and 5-year prevalence was 205.1/100,000 inhabitants. Denmark, The Netherlands, and Portugal are the countries with the highest 5-year prevalence (proportions per 100,000 inhabitants) of CRC (312.2, 310.7, and 297.4 per 100,000, respectively). In Western Europe, Austria, Luxembourg and Switzerland have the lowest 5-year prevalence rates (153.4, 160.9 and 168.2 per 100,000, respectively). In 2020, the 5-year prevalence was 148.9 per 100,000 in Oceania, 9.7 per 100,000 in Africa, 52.9 per 100,000 in Latin America and the Caribbean, 150.4 per 100,000 in Northern America, and 56.5 per 100,000 in Asia. In the US, the 5-year prevalence is 143.6 per 100,000 overall, while 150.0 per 100,000 for males and 137.3 per 100,000 for females. In Canada, the incidence is 210.2 per 100,000 overall, while 220.6 per 100,000 for males and 200.0 per 100,000 for females.
Demographics of the authorised target population in the indication:	In Europe, the proportion of CRC patients by age (5-year prevalence) is: 19.3% <60 years of age, 25.6% between 60 and 69 years of age, 31.1% between 70 to 79 years of age, and 24.0% for >79 years of age. However, the incidence of CRC is increasing for adults <50 years and decreasing for adults 50 years and older. This trend is observed globally, including in the US, Europe, and Australia and New Zealand. In some Asian countries, including India, Korea, and Thailand, as well as a few European countries including Norway and Finland, the incidence of CRC is increasing across all age groups. Globally, the sex distribution of CRC prevalence is higher in males, with males making up 54% of 1-year prevalent cases for 2020. However, in a study of 26 European cancer registries, there was no statistical difference by age or sex in the proportion of prevalence cases with mCRC (26%). Similar to age, incidence of CRC is increasing among females in some countries, including Ecuador and Thailand, while in some countries the incidence is decreasing, including Slovenia and Japan.
The main existing treatment options:	Metastatic colorectal cancer cannot be cured by surgery in most cases. Therefore, treatment principles are primarily aimed at controlling disease progression and prolonging survival, while maintaining quality of life. Patients with mCRC are treated with established first and second-line systemic treatments. These systemic treatments usually consist of a

Treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti VEGF agents, and anti EGFR agents, and who have progressed on or are intolerant to treatment with either trifluridine tipiracil or regorafenib.	
	fluoropyrimidine-, oxaliplatin-, and irinotecan-based regimen. Depending on the line of therapy, these can be administered either with or without anti-angiogenesis biological therapy (anti-VEGF or anti-VEGFR2 such as bevacizumab, aflibercept or ramucirumab), or with an anti-EGFR therapy such as cetuximab or panitumumab for patients with RAS wild type disease. A small proportion (3% to 5%) of patients with advanced CRC have deficient MisMatch repair or microsatellite instability high and are eligible for approved immunotherapy with either nivolumab, pembrolizumab, or envafolimab in the first-line setting. Likewise, encorafenib, in combination with cetuximab, has been approved for patients BRAF (V600E) mutated tumours, which accounts for 8% to 12% of mCRC patients. When tumours progress after patients have received at least two lines of chemotherapy, the approved options include: trifluridine/tipiracil (TAS-102) or regorafenib - a multi-TKI with numerous in vitro targets at therapeutic concentrations.
Natural history of the indicated condition in the untreated population, including mortality and morbidity:	Globally, there were an estimated 935,000 deaths in 2020 due to CRC, accounting for 9.4% of cancer deaths. While CRC is the third most common cancer, it ranks second in cancer mortality. CRC accounts for the second highest number of deaths from cancers in the EU, with 138,000 deaths in the 28 member states in 2017, equivalent to 11.8% of all deaths from cancer and 3.0% of the total number of deaths from any cause. This is predicted to have risen to 177,400 in 2018. In 2016, the standardised death rates for CRC in the EU for men was 78% higher than for women. The standardised death rate for CRC was 18 times higher for persons aged 65 years and over than younger persons. The age-standardised mortality rate due to CRC is 9.3 per 100,000 in Oceania, 5.6 per 100,000 in Africa, 8.2 in Latin America and the Caribbean, 8.2 per 100,000 in Northern America, and 8.6 in Asia. In the US, the mortality rate is 8.0 per 100,000 overall, while 9.4 per 100,000 for males and 6.7 per 100,000 for females. In Canada the incidence is 31.2 per 100,000 overall, while 9.9 per 100,000 for males and 12.0 per 100,000 for females. Despite advances in treatment, the 5-year survival rate CRC is approximately 60% in Northern and Central Europe, and approximately 50% in Eastern and Southern Europe, 56.9% in China and 64% in the US. In Canada, the 5-year survival rate was 70.8% for colon cancer and 70.9% for rectal cancer. The survival rate is lower with respect to mCRC. One study utilising a French cancer registry examined net survival of liver metastasised CRC. Net survival was 42% at 1 year, 13% at 3 years, and 6% at 5 years for synchronous liver

Treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti VEGF agents, and anti EGFR agents, and who have progressed on or are intolerant to treatment with either trifluridine tipiracil or regorafenib.	
	metastasised CRC and 50% at 1 year, 22% at 3 years, and 13% at 5 years for metachronous liver metastasised CRC. Bouvier et al calculated net survival rate for mCRC using cancer registries from 10 European countries. The 3-year net survival rate was 16% in Bulgaria, 20% in Poland, 21% in Estonia, 26% in Italy, 28% in Portugal, 29% each in Germany and Spain, 33% in Switzerland, 37% in Belgium, and 38% in France. In the US, the 5-year survival rate for distant CRC (cancer that has spread to distant parts of the body) is 16%. Since treatment options for mCRC remain limited, especially following progression on standard therapies, there is a need for new treatments that can prolong survival while maintaining good quality of life. The recurrence after surgical resection was reported to occur for 80% of the patients within 2 years with no differences between hepatic and extrahepatic sites. The estimated median overall survival of untreated recurrent mCRC was 8 to 10 months. Since there is no standard of care (SOC) treatment in patients with refractory mCRC who have progressed on current standard therapies, there is a high unmet medical need for new medications that are safe and effective in patients with refractory mCRC who have progressed on, or were intolerant to, available standard systemic therapies, and for whom no effective therapy or SOC exists given the poor prognosis.
Important co-morbidities:	Co-morbidities are common in mCRC patients. In Europe, the largest comorbidity study was performed in the UK in 2014 including 1,330 patients diagnosed with CRC. The five most prevalent co-morbidities associated with CRC are: cardiovascular (CV) issues (excluding hypertension, 33.5%), hypertension (32.7%), gastrointestinal (GI) system issues (27.6%), diabetes mellitus (17.4%), and osteoarthritis (14.7%). A 2011 study of 12,648 US patients diagnosed with mCRC between January 2005 and June 2008 and in which patient data were analysed for comorbid conditions and medication use in the year prior to diagnosis of mCRC, showed that the most prevalent comorbidity with mCRC was CV disease (55.7% of patients) including hypertension (40.8%), cardiac dysrhythmia (14.2%), coronary artery disease (13.5%), congestive heart failure (7.2%), and arterial and venous thromboembolism (6.2% and 4.6%, respectively).

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage:

Key Safety Findings	Relevance to human usage
Gastrointestinal Gastrointestinal toxicity was observed in single- and repeat-dose studies in rats and dogs and included diarrhoea, cholangiectasis (rat only), gastric and duodenal haemorrhage, hemafecia (dog only), degeneration, necrosis, and inflammation in the Brunner's gland (rats only), reduced food consumption, and/or decreased mean body weight and/or body weight gain. All GI effects were resolved or partially resolved following a recovery period.	Fruquintinib may affect the gastrointestinal system. Some effects observed in animals are likely pharmacologically-mediated effects; therefore, these findings are considered relevant for patients treated with fruquintinib. Gastrointestinal-related effects such as GI haemorrhage, intestinal perforation, diarrhoea, stomatitis, and oral pain have been noted in fruquintinib-treated patients in the clinical studies.
Hepatobiliary In repeat-dose studies, findings occurred primarily in rats and included elevated alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total bilirubin, cholesterol (both species), and triglycerides, hepatocyte necrosis/degeneration (both species) and/or bile duct hyperplasia. All hepatobiliary effects were resolved or partially resolved following a recovery period.	Fruquintinib may affect the hepatobiliary system. Effects observed in animals are likely pharmacologically-mediated effects; therefore, these findings are considered relevant for patients treated with fruquintinib. While liver function test abnormalities, including hepatic enzyme elevation and bilirubin elevation, have been very commonly observed in fruquintinib-treated patients in the clinical studies, most of the abnormalities were mild or moderate and generally tolerable and manageable with dose modification in most patients. Potential Hy's law and fatal events were reported with low incidence and were confounded with other risk factors.
Renal In repeat-dose studies, findings occurred primarily in rats and included elevated blood urea nitrogen, degeneration of renal glomerulus, and/or hyaline casts (both species). All renal effects were resolved or partially resolved following a recovery period.	Fruquintinib may affect the renal system. Effects observed in animals are likely pharmacologically-mediated effects; therefore, these findings are considered relevant for patients treated with fruquintinib. Proteinuria is a known/identified risk with fruquintinib as well as with drugs in the same class of agents with similar mechanisms of action. The risk was generally manageable by dose modification.
Skeletal system Skeletal system effects included increased thickness of the physis in the femur in rats and dogs and broken/lost teeth in rats only. Findings were resolved following a recovery period, except for those in the teeth.	Fruquintinib may affect the skeletal system. Effects observed in animals are likely pharmacologically-mediated effects; however, these findings are considered more relevant to children and adolescents. Skeletal system effects including musculoskeletal discomfort, arthralgia and back pain have been

Key Safety Findings	Relevance to human usage
	noted in fruquintinib-treated patients in clinical studies.
Immune system In repeat-dose studies, effects on the immune system included decreased lymphocytes and atrophy of thymus, atrophy of spleen, and/or mast cell infiltration in the mesenteric lymph nodes (rats only). All effects were resolved or partially resolved following a recovery period.	Fruquintinib may affect the immune system. Effects observed in animals are likely pharmacologically-mediated effects; therefore, these effects are considered relevant for patients treated with fruquintinib. In clinical studies, potentially immune system-related effects (i.e., neutropenia and leukopenia) have been observed.
Adrenal gland Congestion and haemorrhage were noted in repeat-dose studies in rats and dogs.	Fruquintinib may affect the adrenal gland. Effects observed in animals are likely pharmacologically-mediated effects; therefore, these findings are considered relevant for patients treated with fruquintinib. No relevant/significant clinical findings were noted in the clinical studies.
Haematopoietic system Decreased haematopoietic cells in the bone marrow was observed in both rats and dogs.	Fruquintinib may affect the haematopoietic system. Effects observed in animals are likely pharmacologically-mediated effects; therefore, these findings are considered relevant for patients treated with fruquintinib. Thrombocytopenia and neutropenia have been commonly reported in fruquintinib-treated patients.
Reproductive and developmental toxicity In the embryo-foetal developmental toxicity study in rats, fruquintinib-related reductions in number of live foetuses were noted. Developmental toxicity was observed as external, visceral, and skeletal anomalies in foetuses. In the fertility and early embryonic developmental toxicity study in rats, male and female reproduction indices were decreased, there were dose-dependent increases in pre-implantation loss, increases in the number and percent of resorption and post-implantation loss and a decrease in the number and percent of viable foetuses were observed.	There are no data from the use of fruquintinib in pregnant women. Based on its mechanism of action, fruquintinib has the potential to cause foetal harm. Studies in animals have shown reproductive toxicity. Fruquintinib should not be used during pregnancy unless the benefit to the mother outweighs the potential risks to the foetus. If a pregnant woman needs to be treated, she should be clearly advised on the potential risk to the foetus. Women of childbearing potential should use effective contraception during and up to 2 weeks after completion of treatment.
Genotoxicity Fruquintinib was not genotoxic based on the results of in vitro and in vivo genotoxicity studies comprising of an in vitro bacterial reverse mutation assay in Salmonella	No anticipated safety concerns in humans.

Key Safety Findings	Relevance to human usage
typhimurium, an in vitro chromosome aberration assay in Chinese hamster ovary cells, and an in vivo rat micronucleus test with inclusion of an alkaline comet assay.	
Safety pharmacology: Non-clinical safety pharmacology studies and assessments both in vitro [on the human ether-à-go-go related gene] and in vivo indicated that there is a low likelihood for effects of fruquintinib or the main human metabolite (M11) on the CV, respiratory, and/or central nervous (CNS) systems.	Concentration QT analyses showed no major association between plasma concentrations of fruquintinib or metabolite M11 and ΔΔQTcP. The by-time point analysis performed on ΔΔQTcP found no clinically significant QT prolongation following fruquintinib administration in 2019-013-GLOB1 (FRESCO-2). There were no clinically relevant changes in other electrocardiogram (ECG) parameters or abnormal ECG findings attributable to the administration of fruquintinib. Increased incidence of hypertension has been noted in the fruquintinib-treated patients. No major CNS findings were observed.
Other toxicity-related information or data:	Not applicable.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Safety data from 8 clinical monotherapy studies (2012-013-00CH1; 2013-013-00CH1/FRESCO; 2019-013-GLOB1/FRESCO-2; 2009-013-00CH1; 2012-013-00CH3; 2015-013-00US1; 2014-013-00CH1; and 2015-013-00CH1/FALUCA) was pooled into 3 Integrated Safety Analysis Set (ISAS) to increase the sensitivity to detect adverse events (AEs) and to better assess as well as understand the safety profile of fruquintinib using the dosing schedule of 5 mg once daily (QD) 3 weeks on/1 week off of each 28-day cycle in different clinical settings (further also abbreviated as "fruquintinib 5 mg 3/1").

These 3 ISAS for pooled patient populations treated under the monotherapy setting are as described below:

- Integrated Safety Analysis Set—Metastatic Colorectal Cancer (ISAS—mCRC): All patients from the 3 randomised, placebo-controlled, double-blinded mCRC studies (i.e., 2012-013-00CH1; 2013-013-00CH1/FRESCO; 2019-013-GLOB1/FRESCO-2 excluding patients from the open-label Japanese safety lead-in) who received at least 1 dose of study drug (fruquintinib or placebo) were included in this analysis set. This dataset was split into 2 groups, the fruquintinib 5 mg 3/1 group and the placebo group.
- Integrated Safety Analysis Set—Expanded Metastatic Colorectal Cancer (ISAS—Expanded mCRC): All patients with mCRC who received at least 1 dose of fruquintinib monotherapy at the dosing schedule used in FRESCO-2 (fruquintinib 5 mg 3/1) were included in this analysis set. Thus, in addition to the patients in the ISAS—mCRC (placebo-controlled group), those patients from the 3 open-label studies (i.e., 2009-013-00CH1; 2012-013-00CH3; and 2015-013-00US1), and the Japanese safety lead-in portion of study 2019-013-GLOB1/FRESCO-2were included. In these 3 open-label studies, only mCRC patients who received the dosing schedule of fruquintinib 5 mg 3/1 were added to this analysis set.
- Integrated Safety Analysis Set—Fruquintinib Overall (ISAS—Fruquintinib Overall): All patients from the 8 monotherapy studies detailed above, regardless of indication, who received at least 1 dose of fruquintinib monotherapy at the dosing schedule used in FRESCO-2 (fruquintinib 5 mg 3/1) were included in this analysis set.

Table SIII.1: Duration of exposure

Cumulative for all indications (ISAS-Fruquintinib Overall)		
Duration of exposure	**Patients number (%)**	**Person-year**
<1 m	175 (12.8)	11.7
1 to <3 m	439 (32.0)	74.2
3 to <6 m	426 (31.1)	158.2
≥6 m	331 (24.1)	277.2
Total	**1,371 (100)**	**521.4**
ISAS-Expanded mCRC		
Duration of exposure	**Patients number (%)**	**Person-year**
<1 m	106 (11.6)	7.0
1 to <3 m	306 (33.6)	52.0

Cumulative for all indications (ISAS-Fruquintinib Overall)		
Duration of exposure	**Patients number (%)**	**Person-year**
3 to <6 m	277 (30.4)	103.9
≥6 m	222 (24.4)	179.4
Total	**911 (100)**	**342.2**

Table SIII.2: Age group and gender

Cumulative for all age/gender groups (ISAS-Fruquintinib Overall)				
Age group	**Patients number (%)**		**Person-year**	
	Male	**Female**	**Male**	**Female**
Adults (18 to 64 years)	524 (38.2)	450 (32.8)	208.4	171.2
Elderly people	237 (17.3)	160 (11.7)	87.3	54.6
• 65-74 years	188 (13.7)	129 (9.4)	70.2	44.1
• 75+ years	49 (3.6)	31 (2.3)	17.1	10.5
Total	**761 (55.5)**	**610 (44.5)**	**295.6**	**225.8**
ISAS-Expanded mCRC				
Age group	**Patients number (%)**		**Person-year**	
	Male	**Female**	**Male**	**Female**
Adults (18 to 64 years)	327 (35.9)	276 (30.3)	133.9	98.1
Elderly people	180 (19.8)	128 (14.1)	64.1	46.1
• 65-74 years	137 (15.0)	100 (11.0)	48.7	36.7
• 75+ years	43 (4.7)	28 (3.1)	15.4	9.4
Total	**507 (55.7)**	**404 (44.3)**	**198.0**	**144.2**

Note: No paediatric age groups were enrolled into the studies.

Table SIII.3: Dose

Cumulative for all doses of exposure (ISAS-Fruquintinib Overall)		
Dose of exposure	**Patients number (%)**	**Person-year**
Fruquintinib 1 mg continuous dosing	1 (0.1)	0.2

Cumulative for all doses of exposure (ISAS-Fruquintinib Overall)		
Dose of exposure	**Patients number (%)**	**Person-year**
Fruquintinib 2 mg continuous dosing	3 (0.2)	0.4
Fruquintinib 3 mg 3/1	7 (0.5)	5.1
Fruquintinib 4 mg continuous dosing	36 (2.5)	10.4
Fruquintinib 5 mg continuous dosing	3 (0.2)	0.5
Fruquintinib 5 mg 3/1	1,371 (95.9)	521.4
Fruquintinib 6 mg continuous dosing	3 (0.2)	0.3
Fruquintinib 6 mg 3/1	6 (0.4)	0.9
ISAS-Expanded mCRC		
Dose of exposure	**Patients number (%)**	**Person-year**
Fruquintinib 1 mg continuous dosing	1 (0.1)	0.2
Fruquintinib 2 mg continuous dosing	2 (0.2)	0.3
Fruquintinib 3 mg 3/1	2 (0.2)	2.6
Fruquintinib 4 mg continuous dosing	26 (2.8)	8.8
Fruquintinib 5 mg continuous dosing	1 (0.1)	0.2
Fruquintinib 5 mg 3/1	911 (96.4)	342.2
Fruquintinib 6 mg continuous dosing	2 (0.2)	0.2
Fruquintinib 6 mg 3/1	0	0

Table SIII.4: Ethnic origin

Cumulative for all ethnic origin (ISAS-Fruquintinib Overall)		
Ethnic origin	**Patients number (%)**	**Person-year**
Asian	842 (61.4)	340.2
Caucasian/White	463 (33.8)	158.9
Black or African American	25 (1.8)	8.1
Other	41 (3.0)	14.2

Cumulative for all ethnic origin (ISAS-Fruquintinib Overall)		
Ethnic origin	**Patients number (%)**	**Person-year**
Total	**1,371 (100)**	**521.4**
ISAS-Expanded mCRC		
Ethnic origin	**Patients number (%)**	**Person-year**
Asian	419 (46.0)	170.1
Caucasian/White	431 (47.3)	151.8
Black or African American	21 (2.3)	6.4
Other	40 (4.4)	13.9
Total	**911 (100)**	**342.2**

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1. EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

Patients who were pregnant or breast feeding	
Reason for exclusion:	Based on its mechanism of action, fruquintinib has the potential to cause foetal harm. Studies in animals have shown reproductive toxicity, including foetal malformations.
Is it considered to be included as missing information?	No
Rationale:	Fruquintinib may affect foetal development in humans. Women of childbearing potential are advised to use effective contraception during and for at least 2 weeks following the last dose of fruquintinib.

Patients with history of, or active gastric/duodenal ulcer or ulcerative colitis, active haemorrhage of an unresected GI tumour, history of perforation or fistulas; or any other condition that could, in the investigator's judgement, result in GI haemorrhage or perforation; within the 6 months prior to screening were excluded.	
Reason for exclusion:	Gastrointestinal perforations have been identified as a class effect with other drugs having a similar mechanism of action. This exclusion criterion minimised the risk of treating patients who are prone to develop GI perforation.
Is it considered to be included as missing information?	No
Rationale:	GI perforation is a known risk associated with VEGF inhibitors. Fruquintinib has been associated with increased risk of GI perforation.

Patients with a history or presence of haemorrhage from any other site within 2 months prior to screening	
Reason for exclusion:	Haemorrhages are known risks of other medicinal products with a similar mechanism of action and therefore this criterion was added to

Patients with a history or presence of haemorrhage from any other site within 2 months prior to screening	
	minimise the risk of treating patients prone to develop these events.
Is it considered to be included as missing information?	No
Rationale:	Haemorrhage was observed in clinical trials with fruquintinib. Fruquintinib has been associated with increased risk of haemorrhagic events, mainly of the GI tract.

History of a thromboembolic event, including deep vein thrombosis, pulmonary embolism, or arterial embolism within 6 months prior to screening	
Reason for exclusion:	Serious and sometimes fatal arterial thromboembolic events including transient ischaemic attack, myocardial infarction, cerebrovascular accident, and retinal artery occlusion have been reported in patients receiving other VEGF pathway inhibitors.
Is it considered to be included as missing information?	No
Rationale:	Arterial thrombosis is a known risk for other VEGF inhibitors.

Patients with urine dipstick or urinalysis with protein ≥2+ or 24-hour urine protein ≥1.0 g/24-h were excluded	
Reason for exclusion:	Proteinuria and the potential for acute renal failure are known risks associated with medicines targeting the VEGF pathway. This criterion minimises the risk of treating patients prone to developing these events.
Is it considered to be included as missing information?	No
Rationale:	Proteinuria is a known risk for other VEGF inhibitors. Fruquintinib has been associated with increased risk of proteinuria.

Patients with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 × upper limit of normal (ULN) for those without hepatic metastases; ALT or AST > 5 × ULN for those with hepatic metastases were excluded	
Reason for exclusion:	Hepatotoxicity is a known adverse effect of other drugs with a similar mechanism of action and effects on the hepatobiliary system were observed in non-clinical studies with fruquintinib. This exclusion criterion minimises the risk of treating these types of patients who even prior to receipt of fruquintinib may already be prone to developing these events.
Is it considered to be included as missing information?	No
Rationale:	Fruquintinib use is associated with increased incidence of ALT; however, most of the events reported were assessed as Grade 1 or 2. Additionally, there was no increase in incidence for severe or serious liver test abnormalities with fruquintinib use compared to placebo. In case of Grade 2 or higher events of liver test abnormalities, the dose should be modified as recommended in the label. Taking together the safety evidence and dose modification recommendation, the safety profile in these excluded patients is unlikely to be different from the known safety profile of fruquintinib.

Patients with uncontrolled hypertension, defined as: systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mm Hg despite optimal medical management were excluded.	
Reason for exclusion:	Hypertension is a known class effect of agents with similar mechanism of action.
Is it considered to be included as missing information?	No
Rationale:	Hypertension is a known risk for other VEGF inhibitors. Fruquintinib has been associated with increased risk of hypertension.

Patients with clinically uncontrolled active infection requiring IV antibiotics were excluded	
Reason for exclusion:	The use of VEGFR-TKIs could be associated with increased risk of severe infections in cancer patients.

Patients with clinically uncontrolled active infection requiring IV antibiotics were excluded	
Is it considered to be included as missing information?	No
Rationale:	Fruquintinib use is associated with increased incidence of upper respiratory tract infection and pneumonia; however, most of the events reported were assessed as Grade 1 or 2. Additionally, there was no increase in incidence for serious infections with fruquintinib use compared to placebo. In case of Grade 3 or higher events of infections, the dose should be modified as recommended in the label. Taking together the safety evidence and dose modification recommendation, the safety profile in these excluded patients is unlikely to be different from the known safety profile of fruquintinib.

SIV.2. LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged exposure.

SIV.3. LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme.
Breastfeeding women	
Patients with relevant co-morbidities: - Patients with hepatic impairment	Pharmacokinetic(s) data from 133 patients with mild hepatic impairment were available from fruquintinib clinical trials. Eight subjects with moderate hepatic impairment without cancer were included in the Phase 1 hepatic impairment pharmacokinetic (PK) study 2021-013-00US1. Fruquintinib has not been studied in patients with severe hepatic impairment.

Type of special population	**Exposure**
- Patients with renal impairment	PK data from 219 patients with mild to moderate renal impairment were available from fruquintinib clinical trials. Three subjects with severe renal impairment and 8 subjects with moderate renal impairment without cancer were included in the Phase 1 renal impairment PK study 2021-013-00US2.
- Patients with cardiovascular impairment	In the ISAS-Expanded mCRC population (n=911), a total 396 patients (43.5%) reported at least 1 event of hypertension in their medical history, with 284 patients (31.2) reporting at least 1 concomitant antihypertensive medication.
- Immunocompromised patients	Patients with absolute neutrophil count (ANC) $<1.5\times10^9$/L and known human immunodeficiency virus (HIV) infection were not included in the clinical development program.
- Patients with a disease severity different from inclusion criteria in clinical trials	A total 323 patients (35.5%) were ECOG 0 and 588 (64.5%) patients were ECOG 1. All patients met the inclusion criteria.
Population with relevant different ethnic origin	Data below for the 911 patients of the ISAS-Expanded mCRC: • 431 patients (47.3%) were White. • 419 patients (46.0%) were Asian. • 21 patients (2.3%) were Black or African American. • 8 patients (0.9%) were Other (non-White or non-Asian). • 3 patients (0.3%) were Native Hawaiian or Other Pacific Islander. • 2 patients (0.2%) were Multiple Races. • 27 patients (3.0%) were missing data collection.
Sub-populations carrying relevant genetic polymorphisms	Not applicable.
Other	Not applicable.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1. POST-AUTHORISATION EXPOSURE

SV.1.1. Method used to calculate exposure

The cumulative number of patients exposed to fruquintinib from post-approval or post marketing experience was estimated from the amount of the product distributed. The 5 mg capsule was usually administered to patients when prescribed according to the approved dosage regimen cycle as 5 mg daily, 3 weeks on/1 week off, and the 1 mg capsule was usually administered when the dose was reduced to 4 mg daily or below 4 mg daily (3 mg orally daily is the lowest recommended dose), 3 weeks on /1 week off. Therefore, the patient days were estimated by 5 mg capsule as "5 mg daily" and by 1 mg capsule as "4 mg daily", respectively.

SV.1.2. Exposure

As of 03-September-2022, the cumulative post-authorisation exposure is approximately 52,462 patients.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

Given the pharmacological class of fruquintinib and the absence of psychotropic effects, there is no expected potential for drug abuse and the potential for misuse for illegal purposes is low.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1. IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

- **Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):**
  - Liver function test abnormalities
  - Infections
  - Thyroid Dysfunction (Hypothyroidism)
- **Known risks for products involving VEGF pathway inhibition that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the PI are adhered to by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorised):**
  - Haemorrhage
  - Hypertension
  - Posterior reversible encephalopathy syndrome (PRES)
  - Gastrointestinal perforation
  - Dermatologic toxicity
  - Proteinuria
  - Arterial thromboembolic events
  - Delayed wound healing
  - Aneurysms and artery dissections

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

None.

SVII.2. NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Not applicable.

SVII.3. DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

SVII.3.1. Presentation of important identified risks and important potential risks

None.

SVII.3.2. Presentation of the missing information

None.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1: Summary of safety concerns

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1. ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

None.

Specific adverse reaction follow-up questionnaires:

None.

Other forms of routine pharmacovigilance activities:

None.

III.2. ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

None.

III.3. SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table Part III.1: On-going and planned additional pharmacovigilance activities

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

None.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Not applicable.

V.2. Additional Risk Minimisation Measures

Not applicable.

V.3. Summary of risk minimisation measures

Not applicable.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for FRUZAQLA® (FRUQUINTINIB)

This is a summary of the RMP for FRUZAQLA. The RMP details important risks of FRUZAQLA's and how more information will be obtained about FRUZAQLA's risks and uncertainties (missing information).

FRUZAQLA's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how FRUZAQLA should be used.

This summary of the RMP for FRUZAQLA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of FRUZAQLA's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

FRUZAQLA as monotherapy is indicated for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan based chemotherapies, anti VEGF agents, and anti EGFR agents, and who have progressed on or are intolerant to treatment with either trifluridine tipiracil or regorafenib (see SmPC for the full indication). It contains fruquintinib as the active substance and it is given orally as 1 mg or 5 mg hard capsule.

Fruzaqla's benefits can be found in Fruzaqla's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks, together with measures to minimise such risks and the proposed studies for learning more about risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of FRUZAQLA are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of FRUZAQLA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety

of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Currently, no important risks are associated with this product for inclusion in this EU RMP.

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of important risks

Not applicable.

II.C. Post-authorisation development plan

II.C.1. Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of FRUZAQLA.

II.C.2. Other studies in post-authorisation development plan

There are no studies required for FRUZAQLA.

PART VII: ANNEXES

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Annex 4: Specific adverse drug reaction follow-up forms

Not applicable.

Annex 6: Details of proposed additional risk minimisation activities

Not applicable.