25 April 2024
EMA/CHMP/462300/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Fruzaqla

International non-proprietary name: fruquintinib

Procedure No. EMEA/H/C/005979/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

5-FU	Fluorouracil
A/G	Albumin To Globulin Ratio
AAS	Atomic Absorption Spectrometry
ADME	Absorption, Distribution, Metabolism, Excretion
AE	Adverse Event
AESI	Adverse Event Of Special Interest
ALB	Albumin
ALK	Anaplastic Lymphoma Kinase
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
Anti-PD-1	Anti-Programmed Death-1
Anti-PD-L1	Anti-Programmed Death-Ligand 1
API	Active Pharmaceutical Ingredient
aPTT	Activated Partial Thromboplastin Time
AR	Accumulation Ratio
AR	Assessment Report
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
AUC	Area Under The Plasma Concentration-Time Curve
AUC_{0-24}	Area Under The Plasma Concentration-Time Curve From Time 0 To 24 Hours Postdose
AUC_{0-inf}	Area Under The Plasma Concentration-Time Curve From Time 0 To Infinity
AUC_{0-t}	Area Under The Plasma Concentration-Time Curve From Time 0 To The Last Measurable Concentration
AV	Acceptance Value
BC	Breast Cancer
BCRP	Breast Cancer Resistance Protein
BCS	Biopharmaceutics Classification System
BMI	Body Mass Index
BOR	Best Overall Response
BRAF	B-Raf Proto-Oncogene
BRAF	Serine/Threonine Protein Kinase B-Raf
BSC	Best Supportive Care
BSE	Bovine Spongiform Encephalopathy
BUN	Blood Urea Nitrogen
C	Cycle
CA-19-9	Carbohydrate Antigen 19-9
Caco-2	Human Colorectal Adenocarcinoma Cell Model
CAM	Chorioallantoic Membrane
CD	Cycle Day
CD	Cluster Of Differentiation
CEA	Carcinoembryonic Antigen
CEP	Certificate Of Suitability Of The European Pharmacopoeia
CFDA	China Food And Drug Administration
CFU	Colony Forming Units

CFU	Colony Forming Units
CHMP	Committee For Medicinal Products For Human Use
CHOL	Cholesterol
ChT	Chemotherapy
CI	Confidence Interval
CL	Apparent Total Clearance
Cmax	Peak (Maximum) Plasma Concentration
CMC	(Sodium) Carboxymethylcellulose
cMET	Mesenchymal Epithelial Transition Factor
CMH	Cochran-Mantel-Haenszel Test
CNS	Central Nervous System
CoA	Certificate Of Analysis
COSY	1H - 1H Correlation Spectroscopy
COVID-19	Coronavirus Disease 2019
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CR	Complete Response
CRC	Colorectal Cancer
CREA	Creatinine
CRF	Case Report Form
CRO	Contract Research Organization
CRS	Chemical Reference Substance (Official Standard)
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria For Adverse Events
ctDNA	Circulating Tumor DNA
CV	Cardiovascular
CYP	Cytochrome P450
DBL	Database Lock
DCO	Data Cutoff
DCR	Disease Control Rate
DEPT	Distortionless Enhancement By Polarization Transfer
DILI	Drug-Induced Liver Injury
dMMR	Deficient Mismatch Repair
DoE	Design Of Experiments
DoR	Duration Of Response
DP	Drug Product
DPD	Dihydropyrimidine Dehydrogenase
DS	Drug Substance
DSC	Differential Scanning Calorimetry
E3S	Estrone-3-Sulfate
EC	Ethical Committee
EC	European Commission
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDQM	European Directorate For The Quality Of Medicines
EFD	Embryo-Foetal Development

EGFR	Epidermal Growth Factor Receptor
EHR	Electronic Health Record
EMA	European Medicines Agency
EORTC	European Organization For Research And Treatment Of Cancer
EOT	End-Of-Treatment
EQ-5D-5L	Euroqol Group 5-Dimension 5-Level
ESMO	European Society Of Medical Oncology
EU	European Union
FISH	Fluorecent In Situ Hybridisation
FMO	Flavin Containing Monooxygenases
FOLFIRI	Folinic Acid, Fluorouracil, And Irinotecan
FT-IR	Fourier Transmission Infra Red (Spectroscopy)
F-U	Follow-Up
f_{ub}	Unbound Fraction In Whole Blood
GC	Gas Chromatography
GCP	Good Clinical Practice
GD	Gestation Day
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HA	Health Authority
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDPE	High-Density Polyethylene
HEK293	Human Embryonic Kidney 293
HER2	Human Epidermal Growth Factor Receptor
hERG	Human *Ether-À-Go-Go*-Related Gene
HMBC	Heteronuclear Multiple Bond Correlation
HNSTD	Highest Non-Severely Toxic Dose
HPLC	High Performance Liquid Chromatography
HR	Hazard Ratio
HR+	Hormone Receptor Positive
HRQoL	Health-Related Quality Of Life
HRU	Health Resource Utilization
HSQC	Heteronuclear Singular Quantum Correlation
HUVEC	Human Umbilical Vein Endothelial Cells
IB	Investigator's Brochure
IC	Inhibitory Concentration
IC50	Half-Maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Council For Harmonisation Of Technical Requirements For Pharmaceuticals For Human Use
ICI	Immune Checkpoint Inhibitor
ICP-MS	Inductively Coupled Plasma Mass Spectrometry
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
ILD	Interstitial Lung Disease
IND	Investigational New Drug

INR	International Normalized Ratio
IP	Investigational Product
IPC	In-Process Control
IR	Infrared
IR	Infrared
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	Intent-To-Treat
IV	Intravenous
IWRS	Interactive Web Response System
KF	Karl Fisher
KF	Karl Fischer Titration
KRAS	Kirsten Rat Sarcoma
LDPE	Low-Density Polyethylene
LOA	Letter Of Access
LOAEL	Lowest-Observed-Adverse-Effect Level
LOD	Loss On Drying
LoD	Limit Of Detection
LoQ	Limit Of Quantification
LSC	Liquid Scintillation Counting
LSM	Least Squares Mean
LYM%	Lymphocyte Percentage
M11	Metabolite Of Fruquintinib, Also Known As HM5025423
MA	Marketing Authorisation
mAb	Monoclonal Antibody
MAH	Marketing Authorisation Holder
MATE	Multidrug And Toxin Extrusion Transporter
mBC	Metastatic Breast Cancer
mCRC	Metastatic Colorectal Cancer
MDT	Multidisciplinary Team
MedDRA	Medical Dictionary For Regulatory Activities
MHRA	Medicines And Healthcare Products Regulatory Agency *(UK)*
MID	Minimally Important Difference
MMR	Mismatch Repair
MMRM	Mixed-Model Repeated Measures
MO	Major Objection
MS	Mass Spectrometry
MS	Mass Spectrometry
MSI	Microsatellite Instability
MSI-H	Microsatellite Instability-High
MTD	Maximum Tolerated Dose
N	Number Of Subjects
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
NAS	New Active Substance
NCI	National Cancer Institute
NE	Not Evaluable
NF	National Formulary
NIR	Near Infra Red

NLT	Not Less Than
NMPA	National Medical Products Administration *(China)*
NMR	Nuclear Magnetic Resonance
NMR	Nuclear Magnetic Resonance
NMT	Not More Than
NOAEL	No-Observed-Adverse-Effect Level
NOR	Normal Operating Range
NRAS	Neuroblastoma Rat Sarcoma
NTRK	Neurotrophic Receptor Tyrosine Kinase
OAT	Organic Anion Transporter
OATP	Organic Anion Transporting Polypeptide
OATr	Other Anticancer Treatment
OCT	Organic Cation Transporter
OECD	Organisation For Economic Co-Operation And Development
ORR	Objective Response Rate
OS	Overall Survival
P	Proton Pump Inhibitor
P_{app}, A→B	Permeability Coefficient
PAR	Proven Acceptable Range
PD	Pharmacodynamic(S)
PD	Progressive Disease
PDE	Permitted Daily Exposure
PE	Polyethylene
PET	Polyethylene Terephthalate
PFS	Progression-Free Survival
P-gp	P-Glycoprotein
Ph. Eur.	European Pharmacopoeia
PI	Principal Investigator
PK	Pharmacokinetic(S)
PL	Package Leaflet
Pl	Placebo
PO	Oral(Ly)
PP	Polypropylene
PP	Per Protocol
PR	Partial Response
PRO	Patient-Reported Outcome
PS	Performance Status
PT	Preferred Term
PVC	Poly Vinyl Chloride
q.d.	Once Daily *(Quaque Die)*
Q1	Lower Quartile/25th Percentile
Q3	Upper Quartile/75th Percentile
QD	Once Daily
QLQ-C30	Quality Of Life Core Questionnaire
QoL	Quality Of Life
QOS	Quality Overall Summary
QTc	Corrected QT Interval
QTcF	Corrected QT Interval Using The Fridericia Method

QTPP	Quality Target Product Profile
RAS	Rat Sarcoma
R_B	Blood-To-Plasma Concentration Ratio
RBC	Red Blood Cell
RCT	Randomised Controlled Trial
RECIST 1.1	Response Evaluation Criteria In Solid Tumors, Version 1.1
RET	Rearranged During Transfection
RH	Relative Humidity
RH	Relative Humidity
RP2D	Recommended Phase 2 Dose
rpm	Rotations Per Minute
RPM	Rotations Per Minute
RRF	Relative Response Factor
RWD	Real World Data
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SD	Stable Disease
SEER	Surveillance, Epidemiology, And End Results
SGF	Simulated Gastric Fluid
SLS	Sodium Lauryl Sulfate
SmPC	Summary Of Product Characteristics
SOC	System Organ Class
Std Dev	Standard Deviation
t1/2	Apparent Terminal Elimination Half-Life
TAS-102	Trifluridine/Tipiracil
TEAE	Treatment-Emergent Adverse Event
TG	Triglycerides
TGA	Thermo-Gravimetric Analysis
TGI	Tumour Growth Inhibition
THF	Tetrahydrofuran
TK	Toxicokinetic(S)
TKI	Tyrosine Kinase Inhibitor
Tmax	Time To Peak (Maximum) Plasma Concentration
TNBC	Triple Negative Breast Cancer
TP	Total Protein
TRKi	Tropomyosine Receptor Kinase Inhibitor
TSE	Transmissible Spongiform Encephalopathy
TTD	Time To Deterioration
ULN	Upper Limit Of Normal
US	United States
US FDA	United States Food And Drug Administration
USP	United States Pharmacopoeia
UV/Vis	Ultraviolet/Visible
VAS	Visual Analog Scale
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor

V_z	Volume Of Distribution
Vz/F	Apparent Volume Of Distribution
WBC	White Blood Cells
Wt	Wild Type
XRPD	X-Ray Powder Diffraction
ΔQTc	Mean Changes From Baseline In Qtc
ΔΔQTc	Difference In Δqtc Between Fruquintinib And Placebo

2. Background information on the procedure

2.1. Submission of the dossier

The applicant Takeda Pharmaceuticals International AG submitted on 25 May 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Fruzaqla, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 July 2021.
The applicant applied for the following indication:

Fruzaqla is indicated for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with or are not considered candidates for available therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and an anti-EGFR therapy.

2.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

2.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0360/2020 on the granting of a (product-specific) waiver.

2.4. Information relating to orphan market exclusivity

2.4.4. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

2.5. Applicant's request(s) for consideration

2.5.4. New active substance status

The applicant requested the active substance fruquintinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

2.6. Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
26 March 2020	EMEA/H/SA/4402/1/2020/III	*Walter Janssens, Kolbeinn Guðmundsson*

The applicant received Scientific Advice on the development of fruquintinib (HMPL-013), for the treatment of metastatic colorectal cancer, from the CHMP on 26 March 2020 (EMEA/H/SA/4402/1/2020/III). The Scientific Advice pertained to the following quality, non-clinical, and clinical aspects:

- Proposed starting materials for the synthetic route to manufacture fruquintinib.
- Adequacy of the non-clinical package, together with the clinical safety data from completed and ongoing clinical trials and the proposed bridging toxicology study, to support a marketing authorization application (MAA).
- Adequacy of the clinical pharmacology studies conducted in China, together with planned additional studies and analyses, to support an MAA.
- Design of a global, multicentre, randomised, double-blind, placebo-controlled Phase 3 trial of fruquintinib plus best supportive care (BSC) versus placebo plus BSC (2019-013-GLOB1) including patient population, use of best supportive care as control, statistical assumptions for sample size calculation, and analysis of primary and key secondary endpoints.
- Adequacy of study 2019-013-GLOB1, supported by data from the FRESCO and 2015-013-00US1 studies to support an MAA for an indication in patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and, if RAS wild-type, an anti-EGFR therapy.
- Adequacy of Phase 3 FRESCO study and the ongoing US Phase 1/1b study to support a regular or conditional MAA for the treatment of metastatic colorectal cancer together with a commitment of the Applicant to conduct the global, multicentre, randomised, double-blind, placebo-controlled Phase 3 trial of fruquintinib plus BSC versus placebo plus BSC (2019-013-GLOB1).

2.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johanna Lähteenvuo Co-Rapporteur: Alexandre Moreau

The application was received by the EMA on	25 May 2023
The procedure started on	15 June 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	4 September 2023
The PRAC Rapporteur's first Assessment Report was circulated to all	19 September 2023

PRAC and CHMP members on	
The CHMP agreed on a List of Questions in writing to be sent to the applicant on	12 October 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	14 December 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	29 January 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	08 February 2024
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	22 February 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	25 February 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	10 April 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Fruzaqla on	25 April 2024
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	25 April 2024

3. Scientific discussion

3.1. Problem statement

3.1.4. Disease or condition

The applied indication is: "Fruzaqla is indicated for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with or are not considered candidates for available therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and an anti-EGFR therapy."

CRC is the third most common cancer worldwide, with 1.1 million new cases per year, and is the 2nd leading cause of cancer death (Sung et al. CA Cancer J Clin 2021[1]). In the EU it is the second most frequently occurring cancer. In Europe in 2018, CRC accounted for the second highest number of cancer deaths.

3.1.5. Epidemiology and risk factors, screening tools/prevention

CRC occurs more frequently in middle- to high-income countries with an eightfold variation in incidence across the world. This may be associated with known risk factors, including alcohol intake, tobacco use, obesity, sedentariness, and dietary patterns (Malvezzi et al. Ann Oncol 2018[2]). Of all CRC, 2-5% are related to an inherited cancer syndrome, e.g., familial adenomatosis polyposis and Lynch syndrome (Argiles et al. Ann Oncol 2020[3]). Other predisposing factors are e.g., inflammatory bowel diseases. Currently CRC screening is recommended in the EU for individuals between 50 and 74 years.

3.1.6. Biologic features

Colon and rectal cancer arise from the mucosa of the bowel, growing both into the lumen and the bowel wall, and/or spreading to adjacent and/or distant organs. CRCs typically originate from adenomas or flat dysplasia, with gradual progression into premalignant and invasive malignant lesions. For molecular biology, see 3.1.7 section. The vast majority of CRCs are carcinomas and more than 90% of them adenocarcinomas. Colon and rectal cancers are grouped together as CRC as they share many identical features. Systemic therapies in late line setting do not differentiate between colon and rectal primaries.

3.1.7. Clinical presentation, diagnosis and stage/prognosis

Approximately 15%-30% of patients present with metastases, and 20%-50% of patients with initially localised disease will develop metastases. The most common locations of metastases are liver, then lung, peritoneum and distant lymph nodes (Cervantes et al Ann Oncol 2022[4]*). The mortality rate in the EU

[1] Sung HS, Ferlay J, Siegel RL et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin; 04 February 2021https://doi.org/10.3322/caac.21660
[2] Malvezzi M, Carioli G, Pertuccio P et al. European cancer mortality predictions for the year 2018 with focus on colorectal cancer. Ann Oncol 2018; Apr 1: 29(4):1016-1022. doi: 10.1093/annonc/mdy033.
[3] Argiles G, Tabernero J, Labiance R et al. Localized colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2020; 31; 10 (1291-1305). DOI: 10.1016/j.annonc.2020.06.022
[4] Cervantes, R. Adam, S. Roselló, et al. Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2023;34(1):10-32. DOI: 10.1016/j.annonc.2022.10.003

is 15–20 out of 100 000 in males and 9–14 out of 100 000 in females and has decreased over time, particularly in females (Argiles et al Ann Oncol 2020).

In an advanced stage CRC without the possibility to curative intent (generally achieved with systemic therapy and surgery and/or ablative techniques), the goal of the treatment is to improve tumour-related symptoms, delay progression and prolong survival, while maintaining a good quality of life (Cervantes et al Ann of Oncol 2022). According to SEER data from 1986-2015 in patients with mCRC receiving chemotherapy as 1st line therapy, median survival has improved (Figure 1 below). According to Gbolahan et al[5], using Flatiron Health RWD from 2013-2020, the median OS in mCRC was 24 months in patients who received at least one line of systemic therapy. In an RWD study mCRC patients without the possibility to metastasectomy treated in 2012-2018 with systemic therapy alone had a median OS of 20.8 months and patients treated with BSC of 2.9 months (Österlund et al. Lancet Reg Health Eur 2021[6]). OS times in clinical trials have been approximately 30 months and longer[7]. Furthermore, according to Zeineddine et al.[8] the median OS in de novo mCRC was 32.4 months treated in MD Anderson Cancer Center during 2016-2019.

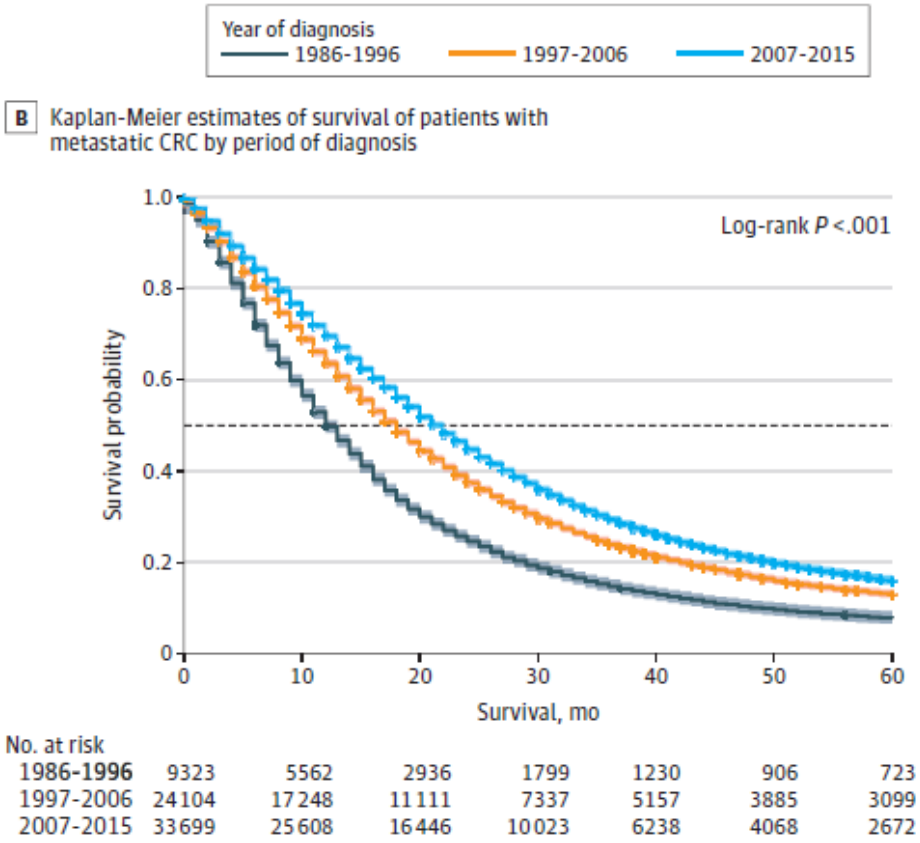


Figure 1: Kaplan-Meier estimates of survival in mCRC according to SEER data 1986-2015 (Shen et al JAMA Network Open 2022):

[5] Gbolahan 0, Hashemi-Sadraei N, Yash S et al. Time to treatment initiation and its impact on real-world survival in metastatic colorectal cancer and pancreatic cancer. Cancer Med. 2023 Feb;12(3): 3488-3498.doi: 10.1002/cam4.5133. Epub 2022 Aug 17. https://doi.org/10.1002/cam4.5133

[6] Österlund P, Salminen T, Soveri L-M et al. Repeated centralized multidisciplinary team assessment of resectability, clinical behavior, and outcomes in 1086 Finnish metastatic colorectal cancer patients (RAXO): A nationwide prospective intervention study. Lancet Reg Health Eur. 2021 Jan 29;3:100049. doi: 10.1016/j.lanepe.2021.100049. eCollection 2021 Apr.

[7] Osterlund E, Glimelius B. Temporal development in survival, and gender and regional differences in the Swedish population of patients with synchronous and metachronous metastatic colorectal cancer. ACTA ONCOLOGICA 2022, VOL. 61, NO. 10, 1278–1288. https://doi.org/10.1080/0284186X.2022.2126327

[8] Zineddine FA, Zaineddine MA, Yousef A et al. Survival improvement for patients with metastatic colorectal cancer over twenty years. *NPJ Precis. Onc.* 7, 16 (2023). https://doi.org/10.1038/s41698-023-00353-4.

For mCRC, a comprehensive assessment is recommended: medical history, physical examination, complete blood count and biochemical laboratory testing with CEA and optionally CA-19-9, and imaging primarily with CT of thorax, abdomen and pelvis (Cervantes et al Ann Oncol 2022). Additional imaging techniques include ultrasound, magnetic resonance imaging, and/or [18F]2-fluoro-2-deoxy-D-glucose-positron emission tomography. For biomarker testing, the following are recommended by ESMO (for ESMO Scale for Clinical Actionability of molecular Targets, ESCAT, see Mateo et al. Ann Oncol 2018[9]):

• Testing for MMR status and KRAS, NRAS exon 2, 3 and 4 and BRAF mutations is recommended in all patients at the time of mCRC diagnosis [I, A].

• RAS testing is mandatory before treatment with anti-EGFR mAbs and can be carried out on the primary tumour or other metastatic sites [III, A].

• BRAF mutation status should be assessed simultaneously with the evaluation of RAS, for prognostic assessment [I, B] and for the option of treatment with cetuximab-encorafenib [I, A].

• dMMR/MSI testing in mCRC can assist in genetic counselling for Lynch syndrome [II, B].

• dMMR/MSI status is also recommended as the initial molecular work-up in metastatic disease for its predictive value for the use of ICIs [I, A].

• Identification of HER2 amplification by IHC or FISH is recommended in RAS-wt patients to detect those who may benefit from HER2 blockade [III, B].

• Testing of other biomarkers including ALK and ROS1 gene fusions, mutations of PIK3CA and HER2 activating mutations is not recommended outside clinical trials [IV, D].

• In the rare event that an NTRK fusion is detected by IHC and/or comprehensive genomic analysis, treatment with larotrectinib or entrectinib is recommended [III, A].

• Testing for DPD deficiency has to be conducted before initiating 5-FU-based ChT [III, A].

3.1.8. Management

For the European context, the Clinical Practice Guideline for mCRC by ESMO is the most relevant (Cervantes et al. Ann Oncol 2022). For an advanced CRC systemic therapy with a non-curative intent follows the continuum of care concept, exposing the patient to all active medicinal products sequentially. 1st line therapy is usually followed by maintenance therapy. After 2nd line therapy, 3rd line and beyond therapy can be considered. Current ESMO guidance is summarised in Figure 2 and Figure 3.

[9] Mateo J, Chakravarty D, Dienstmann R et al. A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). Ann Oncol. 2018 Sep 1;29(9):1895-1902. doi: 10.1093/annonc/mdy263

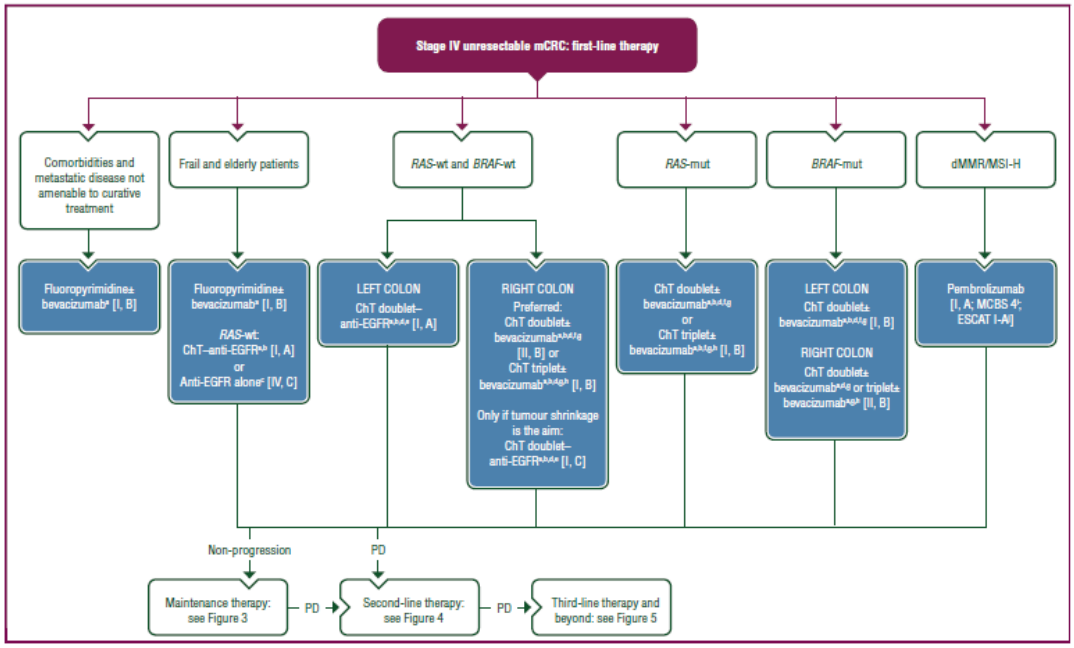


Figure 2. Management of stage IV unresectable mCRC in first-line therapy. Purple: general categories or stratification; blue: systemic anticancer therapy; white: other aspects of management.

5-FU, 5-fluorouracil; ChT, chemotherapy; dMMR, deficient mismatch repair; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; FDA, Food and Drug Administration; FOLFIRI, leucovorin—5-fluorouracil—irinotecan; FOLFOX, leucovorin—5-fluorouracil—oxaliplatin; FOLFOXIRI, leucovorin—5-fluorouracil—oxaliplatin—irinotecan; MCBS, ESMO-Magnitude of Clinical Benefit Scale; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; mut, mutant; PD, progressive disease; PS, performance status; S-1, tegafur—gimeracil—oteracil; wt, wild-type.

[a]In patients presenting with cardiotoxicity and/or hand-foot syndrome on 5-FU or capecitabine-based ChT, S-1 may be used as an alternative [III, B].

[b]Additional details on treatments and drug combinations can be found under the section 'Management of advanced and metastatic disease without potential conversion' (subsections 'First-line treatment' and 'Second-line treatment').

[c]In frail or elderly patients unable to tolerate ChT whose tumours are left-sided and RAS-wt.

[d]FOLFIRI—cetuximab ESMO-MCBS v1.1 score: 4; FOLFOX4—panitumumab ESMO-MCBS v1.1 score: 4; mFOLFOX6—panitumumab ESMO-MCBS v1.1 score: 3.[i]

[e]FOLFOX4—panitumumab ESMO-MCBS v1.1 score: 4; modified FOLFOX6—panitumumab ESMO-MCBS v1.1 score: 3; for FOLFIRI—cetuximab ESMO-MCBS v1.1 score: 4.[i]

[f]In a very selected population.

[g]CAPOX— or FOLFOX4—bevacizumab ESMO-MCBS v1.1 score: 1.[i]

[h]A triplet with FOLFOXIRI plus bevacizumab is an option for selected patients with good PS and without comorbidities [I, B; ESMO-MCBS v1.1 score: 2].[i]

[i]ESMO-MCBS v1.1[165] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).

[j]ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[164] See Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.10.003, for more information on ESCAT scores.

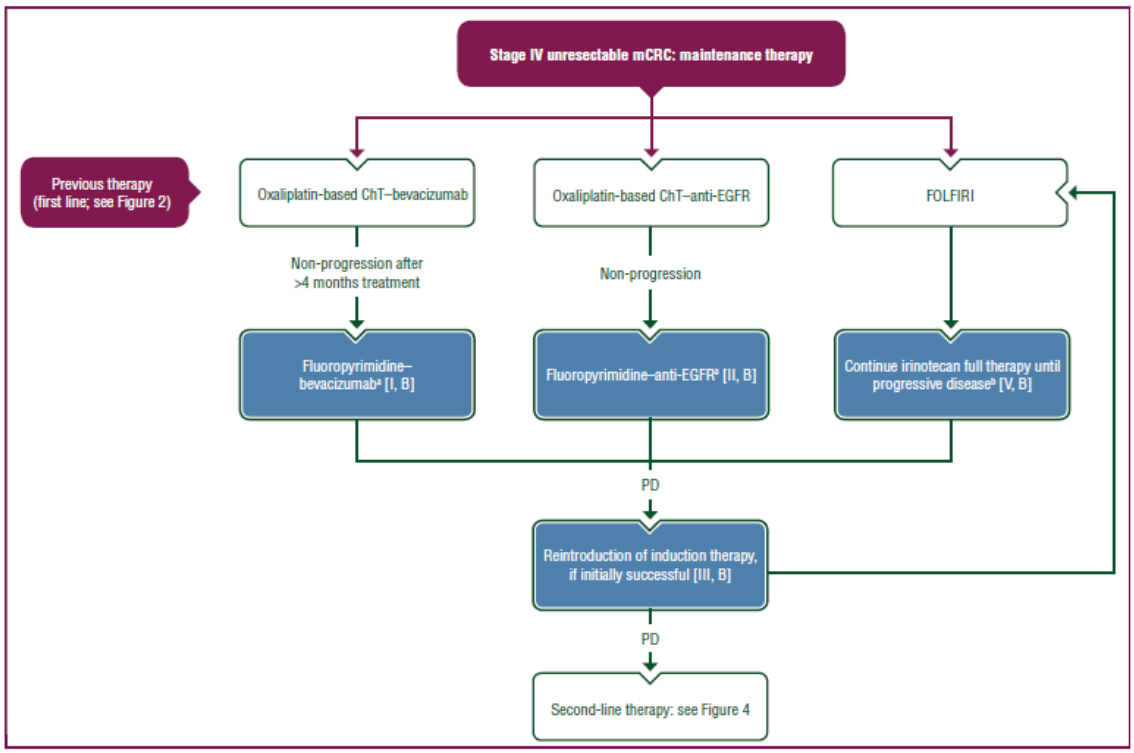


Figure 3. Management of stage IV unresectable mCRC with maintenance therapy. Purple: general categories or stratification; blue: systemic anticancer therapy; white: other aspects of management.
5-FU, fluorouracil; ChT, chemotherapy; EGFR, epidermal growth factor receptor; FOLFIRI, leucovorin—5-fluorouracil—irinotecan, mCRC, metastatic colorectal cancer; PD, progressive disease; S-1, tegafur—gimeracil—oteracil.
[a]In patients presenting with cardiotoxicity and/or hand-foot syndrome on 5-FU or capecitabine-based ChT, S-1 may be used as an alternative [III, B].
[b]Due to the lack of a cumulative toxicity of FOLFIRI.

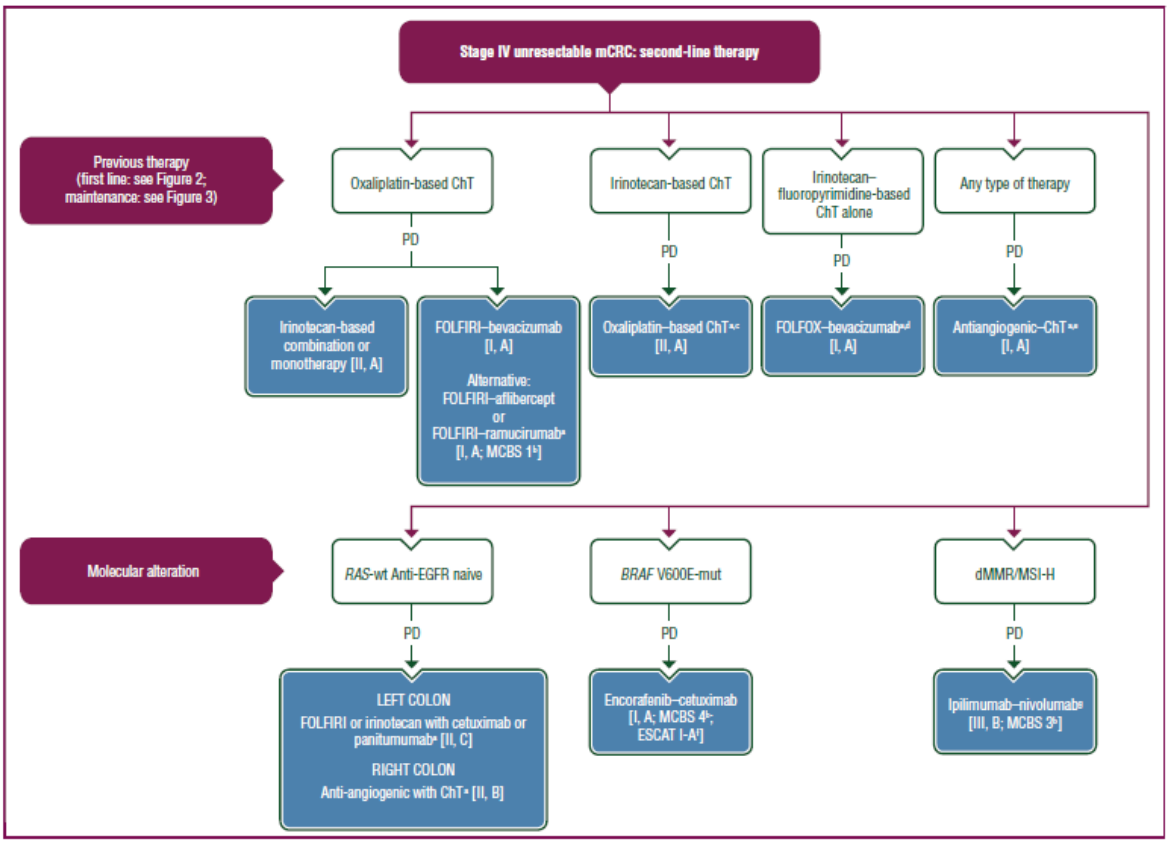


Figure 4. Management of stage IV unresectable mCRC in the second line. Purple: general categories or stratification; blue: systemic anticancer therapy; white: other aspects of management.

5-FU, fluorouracil; CAPOX, capecitabine—oxaliplatin; ChT, chemotherapy; dMMR, deficient mismatch repair; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; FDA, Food and Drug Administration; FOLFIRI, leucovorin—5-fluorouracil—irinotecan; FOLFOX, leucovorin—5-fluorouracil—oxaliplatin; MCBS, ESMO-Magnitude of Clinical Benefit Scale; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; mut, mutant; PD, progressive disease; PTL, primary tumour location; S-1, tegafur—gimeracil—oteracil; wt, wild-type.

[a]In patients presenting with cardiotoxicity and/or hand-foot syndrome on 5-FU or capecitabine-based ChT, S-1 may be used as an alternative [III, B].

[b]ESMO-MCBS v1.1[165] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).

[c]FOLFOX or CAPOX, if no contraindications.

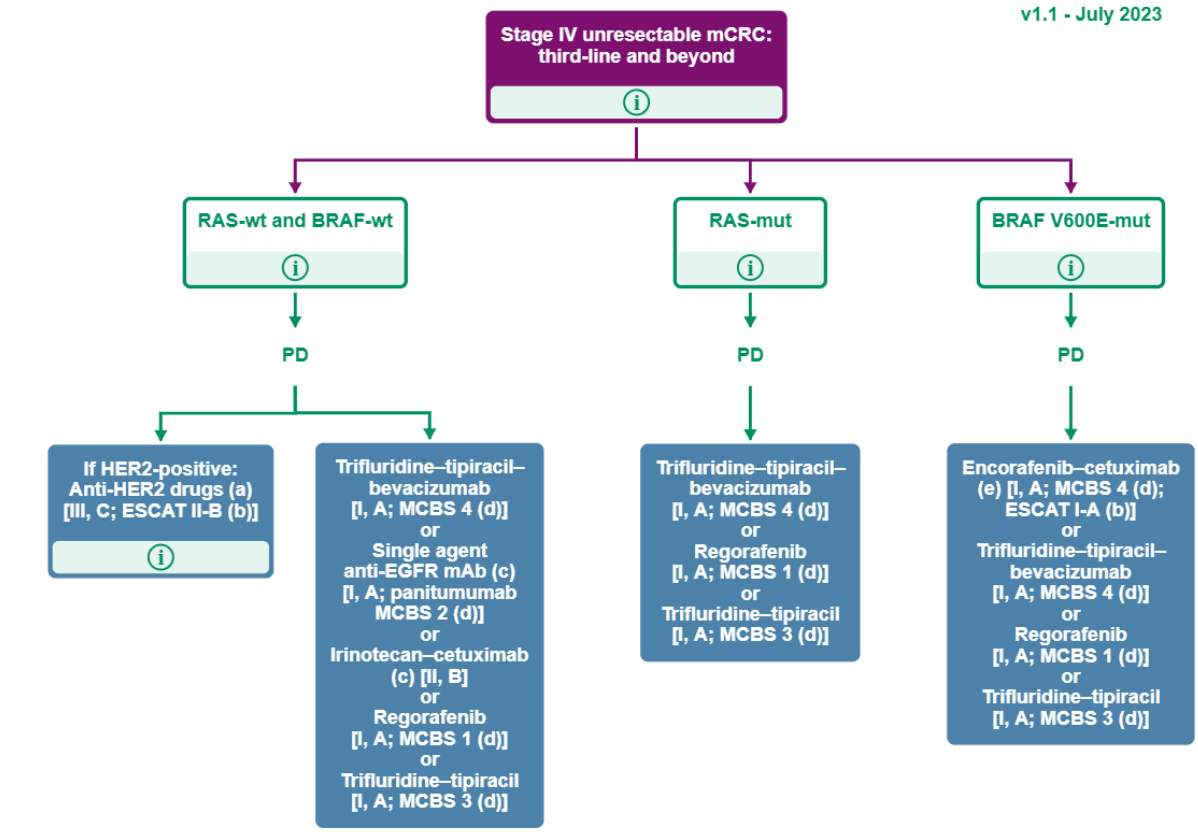
[d]Bevacizumab can be combined with ChT doublet (a fluoropyrimidine with oxaliplatin or irinotecan, depending on the first-line ChT backbone delivered) [I, A; ESMO-MCBS v1.1 score: 1].

[e]With or without previous first-line treatment with bevacizumab and independently of *RAS* mutational status and the PTL.

[f]ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[164] See Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.10.003, for more information on ESCAT scores.

[g]Indicated for immunotherapy-naive patients.

Figure 2: 1st line, maintenance therapy after 1st line, and 2nd line therapy recommendations by ESMO (Cervantes et al. Ann Oncol 2022)



Purple: general categories or stratification; blue: systemic anticancer therapy; white: other aspects of management.

EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; mAb, monoclonal antibody; MCBS, ESMO-Magnitude of Clinical Benefit Scale; mCRC, metastatic colorectal cancer; mut, mutant; PD, progressive disease; wt, wild-type.

(a) For a summary of recommended anti-HER2 regimens for mCRC see Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2022.10.003.

(b) ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and

Precision Medicine Working Group. (Mateo, 2018) See Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.10.003, for more information on ESCAT scores.

(c) In *RAS*-wt patients not previously treated with anti-EGFR monoclonal antibodies.

(d) ESMO-MCBS v1.1 (Cherny, 2017) was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).

(e) Treatment for *BRAF*-mut patients if not used in the second line.

Figure 3: 3rd line and beyond therapy as recommended by ESMO (Cervantes et al. Ann Oncol 2022, updated in ESMO Metastatic Colorectal Cancer Living Guidelines, v1.1 July 2023)

Antiangiogenic therapy in mCRC (adapted from ESMO guidelines, Cervantes et al. Ann Oncol 2022):
In the 1st line setting of mCRC, the only antiangiogenic medicinal product that has shown better outcomes in combination with ChT is bevacizumab, a selective VEGF-A inhibitor. Bevacizumab can be continued in maintenance therapy after 1st line, combined to a fluoropyrimidine. In patients previously treated with bevacizumab in the 1st line setting, maintaining bevacizumab in combination with 2nd line ChT (oxaliplatin or irinotecan-based, switching depending on the 1st line treatment delivered) demonstrated improvement in the primary endpoint of OS. In 2nd line therapy alternatives to bevacizumab are aflibercept and ramucirumab. Aflibercept is a recombinant fusion protein that blocks the activity of VEGF-A and B, as well as placental growth factor, by acting as a high-affinity ligand trap.

Ramucirumab is a human mAb that targets the extracellular domain of VEGF receptor 2. Each of these antiangiogenics in combination with ChT has demonstrated improved OS in the 2nd line treatment of mCRC.

Further summary of recommendations by ESMO for 3rd and further line treatment is included below. Additionally, larotrectinib or entrectinib can be considered for NTRK fusion positive mCRC. Of note, medicinal products against HER2 in mCRC have currently no approval in the EU and have not been incorporated in Table 1, below, for 3rd line and beyond therapies.

- Reintroduction of the initial induction therapy can be considered after second-line therapy, as long as the patient did not progress during the induction course of first line ChT [III, B].
- Regorafenib is recommended in patients pre-treated with fluoropyrimidines, oxaliplatin, irinotecan and biologics, if available, or in earlier lines of therapy following oxaliplatin and irinotecan regimen failure, depending on local approvals [I, A, ESMO-MCBS v1.1 score: 1].
- Trifluridine-tipiracil is recommended in patients pre-treated with fluoropyrimidines, oxaliplatin, irinotecan and biologics, if available, or in earlier lines of therapy following oxaliplatin and irinotecan regimen failure, depending on local approvals [I, A; ESMO-MCBS v1.1 score: 3].
- For BRAF V600E-mutated, pre-treated mCRC patients, encorafenib-cetuximab is recommended as the best option in third line [I, A; ESMO-MCBS v1.1 score: 4; ESCAT: I-A].
- In RAS-wt and BRAF-wt patients not previously treated with EGFR antibodies, cetuximab and panitumumab are recommended as single agents [I, A; panitumumab ESMO-MCBS v1.1 score: 3].
- In irinotecan-refractory patients, cetuximab-irinotecan is recommended over cetuximab alone [II, B].
- Administering an alternative anti-EGFR antibody, if a patient is refractory to one of the other anti-EGFR antibodies, is not recommended [I, E].
- In patients maintaining RAS-wt status, rechallenge with anti-EGFR mAbs may be an option in selected patients [III, C].
- In HER2-positive patients with mCRC, treatment with HER2 dual blockade is optionally recommended.

Table 1: Additional information for MAs in 3rd line and beyond for mCRC in the EU since 2013.

Medicinal product(s)	Trial	Design	Prior regimens for metastatic cancer	N; allocation	Results for primary endpoint	MA by EC
Encorafenib-cetuximab[1)]	ARRAY-818-302	Phase 3 Encorafenib, binimetinib & cetuximab vs encorafenib & cetuximab vs cetuximab & irinotecan OR cetuximab and FOLFIRI	1 prior line 65.2%:66.4%:65.6% 2 prior lines 34.4%:33.6%:33.9%	665; 1:1:1	Median OS 9.3 (8.2, 10.8) vs 9.3 (8.0, 11.3) vs 5.9 (5.1, 6.57) months ORR 26.8% vs 19.5% vs 1.8%	2020
Regorafenib[2)]	CORRECT	Phase 3 Regorafenib vs. placebo	52% with ≤3 lines	760; 2:1	Median OS 6.4 vs. 5.0 months, HR	2013

					0.77 (0.64, 0.94)	
Trifluridine-tipiracil[3)]	RECOURSE	Phase 3 Trifluridine-tipiracil vs. placebo	46.5% with >3 lines	800; 2:1	Median OS 7.1 vs. 5.3 months, HR 0.68 (0.58, 0.81)	2016
Trifluridine-tipiracil-bevacizumab[4)]	SUNLIGHT	Phase 3 Trifluridine-tipiracil-bevacizumab vs. trifluridine-tipiracil	5% with 1 prior line 92% with 2 prior lines 3% with >2 prior lines	492; 1:1	Median OS 10.8 months vs. 7.5 months, HR 0.61 (0.49-0.77)	2023

[1)] EMA/CHMP/271532/2020; data shown only for the phase 3 part, not for the safety lead-in

[2)] SmPC for regorafenib

[3)] EMA/CHMP/287846/2016

[4)] SmPC for trifluridine-tipiracil

An extension of indication for trifluridine-tipiracil with bevacizumab for 3rd line treatment was approved by the EC in 2023. This was based on SUNLIGHT, a phase 3 RCT comparing trifluridine-tipiracil and bevacizumab to trifluridine-tipiracil (Prager et al NEJM 2023[10]). 492 patients with no more than two ChT regimens for advanced cancer were randomised in 1:1. The median number of prior regimens for metastatic cancer was 2. 71.95% of patients had been previously treated with an anti-VEGF antibody. The median OS was 10.8 vs. 7.5 months (HR for death, 0.61; 95% CI, 0.49 to 0.77; P<0.001). The median PFS was 5.6 months in the trifluridine-tipiracil-bevacizumab group and 2.4 months in the trifluridine-tipiracil group (HR for PD or death, 0.44; 95% CI, 0.36 to 0.54; P<0.001). The combination has been incorporated in ESMO living guidelines as of July 2023.

After the patient has exhausted available therapies, a significant unmet need prevails.

3.2. About the product

Fruquintinib is a small molecule TKI of VEGFR -1, -2, and -3. Signalling by VEGFs via the *VEGFR plays a key role in tumor angiogenesis and tumor growth, and targeting of the VEGF signalling pathway is a well-accepted strategy for anticancer therapy (Duda, 2007; Jayson, 2016).

According to the Applicant, fruquintinib was found to inhibit VEGFR-1, -2, and -3 kinases with IC50 of 33, 35, and 0.5 nM, respectively. Kinase selectivity studies showed that fruquintinib did not significantly inhibit the kinases related to cell cycle or cell proliferation, including cyclin-dependent kinases 1, 2, and 5; the EGFR; the transmembrane tyrosine kinase receptor (c-Met) (IC50 > 10 μM) and did not show appreciable inhibitory activity against a panel of 264 different kinases.

The final approved indication is:

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.

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

[10] * Prager G, Taieb J, et al. Trifluridine–Tipiracil and Bevacizumab in Refractory Metastatic Colorectal Cancer. N Engl J Med 2023; 388:1657-1667

cycle of 28 days. Treatment should be continued until disease progression or unacceptable toxicity occurs.

3.3. Type of application and aspects on development

The following table summarizes history of EU regulatory interactions during the development program of fruquintinib.

Table 2: EU regulatory interactions during the development of fruquintinib

Date	Description
26 March 2020	Scientific Advice on quality, pre-clinical and clinical development was received on 26 March 2020 (EMA/CHMP/SAWP/138519/2020: Procedure No.: EMEA/H/SA/4402/1/2020/III)
24 July 2020	EU paediatric study waiver (Reference ID: EMA/PDCO/260701/2020) was granted on 09 September 2020 (EMA decision P/0360/2020)
06 July 2021	Request to CHMP to confirm eligibility for submission of application for EU Marketing Authorization for Fruzaqla. CHMP confirmed eligibility for submission for EU Marketing Authorisation under Article 3 (1) on 22 July 2021
05 August 2021	Name Review Group (NRG) accepted the name Emsorzi on 17 December 2021
17 February 2022	NRG accepted the name Fruzaqla on 24 May 2022
23 September 2022	Letter of Intent submitted outlining HUTCHMED's proposal to submit a MAA by 26 May 2023
13 December 2022	EMA pre-submission interaction feedback received on 13 December 2022
28 February 2023	Rapporteur and Co-Rapporteur Pre-MAA Submission Meeting

CHMP = Committee for Medicinal Products for Human Use; EMA = European Medicines Agency; EU = European Union; MAA = Marketing Authorisation Application; PDCO = Paediatric Committee; SAWP = Scientific Advice Working Party

3.4. Quality aspects

3.4.4. Introduction

The finished product is presented as hard capsules containing 1 mg and 5 mg of fruquintinib as active substance.

Other ingredients are:

- Capsule content: Maize starch, Cellulose microcrystalline (E460), Talc (E553b)
- Capsule shell (1 mg hard capsules only): Gelatin, Titanium dioxide (E171), Tartrazine (E102), Sunset yellow FCF (E110)
- Capsule shell (5 mg hard capsules only): Gelatin, Titanium dioxide (E171), Allura red AC (E129), Brilliant blue FCF (E133)
- Printing ink: Shellac (E904), Propylene glycol (E1520), Potassium hydroxide, Iron oxide black (E172)

The product is available in high-density polyethylene (HDPE) bottle (45 mL) with polypropylene (PP) child resistant closure and a HDPE desiccant cartridge containing silica gel. Each bottle contains 21 hard capsules.

3.4.5. Active substance

General information

The chemical name of fruquintinib is 6-[(6,7-Dimethoxyquinazolin-4-yl)oxy]-N,2-dimethyl-1-benzofuran-3-carboxamide corresponding to the molecular formula $C_{21}H_{19}N_3O_5$. It has a relative molecular mass of 393.39 g/mol and the following structure:

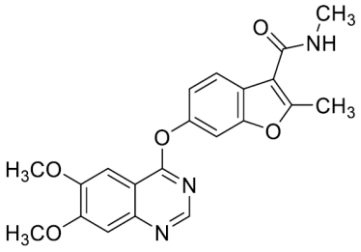


Figure 4: Active substance structure

The chemical structure of fruquintinib was elucidated by a combination of IR (infrared) and UV/Vis (ultraviolet/visible) spectroscopy, MS (mass spectrometry), ^{1}H-, ^{13}C-, ^{13}C-DEPT (distortionless enhancement by polarization transfer), COSY (^{1}H - ^{1}H correlation spectroscopy), HSQC (heteronuclear singular quantum correlation) and HMBC (heteronuclear multiple bond correlation) nuclear magnetic resonance (NMR techniques). Absolute structure was confirmed by single crystal X-ray diffraction analysis. Physical-chemical characterization included hygroscopicity, solubility, particle size distribution, pKa and determination of partition/distribution coefficient. The solid-state properties of the active substance were measured by thermal analysis (differential scanning calorimetry - DSC) and XRPD (X-ray powder diffraction). Fruquintinib has a non - chiral molecular structure.

The active substance is a non-hygroscopic white to off-white powder, particle size distribution D90 ≤ 15 µm, 1 µm ≤ D50 ≤ 5 µm, D10 ≤ 2 µm, and a low aqueous solubility at 37°C (0.7 µg/mL in water, 129.9 µg/mL in 0.1 mol/L HCl solution, 0.9 µg/mL in pH 4.5 acetate buffer, 0.9 µg/mL in pH 6.8 phosphate buffer).

Polymorphism has been observed for fruquintinib. Polymorph screening has been performed in different solvent systems. Several solid state forms were observed in the study. Distinct XRPD patterns were observed for the studied polymorphic forms, which allowed the development of a discriminating XRPD method for monitoring the relevant forms in development and stability studies and during manufacturing. All fruquintinib batches generated to date, including those used in all clinical studies, using the current manufacturing process were produced as Form I.

The applicant requested fruquintinib to be considered as a new active substance (NAS). During the assessment, a Major Objection was raised concerning the applicant's justification of fruquintinib NAS claim, requesting additional information about database searches performed by the applicant for structurally related substances in relation to the therapeutic moiety of the claimed NAS. The applicant has adequately addressed this issue and, therefore, fruquintinib is to be qualified as a new active substance in itself as it was concluded that it is not a constituent of a medicinal product previously authorised within the European Union.

Manufacture, characterisation and process controls

The proposed regulatory starting materials are adequately justified in line with ICH Q11 and are controlled using acceptable specifications. The fruquintinib manufacturing process is adequately described. Reaction schemes are presented including reagents, catalysts and solvents. Material inputs and yields for each step and manufacturing scale for commercial process are given. Relevant process parameters, reaction times and temperatures are included in the synthesis narrative. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Adequate in-process controls (IPCs) are applied during the synthesis and critical process parameters (CPPs) have been identified in the milling and polymorphic transformation steps. Proven acceptable ranges (PARs) and normal operating ranges (NORs) are presented and justified for these steps, but no design space is claimed, which is acceptable.

The current fruquintinib active substance manufacturing process involves no aseptic or sterilisation steps. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Fruquintinib has been assessed for related substances, residual solvents, elemental impurities, genotoxic impurities, nitrosamine impurities, and degradation products. Thorough discussion of potential and actual impurities is provided and supported by spike-purge studies and batch analysis data. The level of details on the experiments is adequate and impurities were well discussed with regards to their origin and characterised. Impurities are controlled in starting materials and intermediates specifications where relevant and supported by batch data.

Residual solvents (including potential contaminants) are controlled according to ICH Q3C. Only acetone, acetonitrile, and tetrahydrofuran, which all are used in the final manufacturing step, are likely to be present in the final active substance based on the accumulated data and thus are controlled in the active substance specification by limits consistent with ICH Q3C Option 1. Throughout the manufacture of fruquintinib, no benzene is used nor formed in any steps. Residual benzene from 2 potential sources of solvents, acetone and toluene, has been assessed and it was concluded that a test for benzene in the active substance specification is not necessary.

A risk assessment for elemental impurities that may be present in the active substance from potential sources of starting materials, reagents, manufacturing equipment, and the active substance container closure system has been performed per ICH Q3D. Based on the risk assessment and following confirmatory testing, it was concluded that testing for each elemental impurity in the active substance specification in not necessary.

Fruquintinib (itself not genotoxic) is evaluated for the treatment of patients with advanced or metastatic colorectal cancer, for which ICH S9 applies. As such, potential genotoxic impurities may be managed consistent with the concepts outlined in ICH Q3A/B. None of the impurities are found above the qualification threshold, but the applicant has nevertheless evaluated potential genotoxic impurities in accordance with ICH M7 based on the projected treatment duration of less than 10 years. After assessment of all starting materials, intermediates, reagents, and impurities, several potential genotoxic impurities have been identified. By demonstrating understanding of fate, purge and associated process controls that ensure that the level of potential genotoxic impurities is below acceptable limits in the active substance, no additional testing in the active substance is required.

There are no nitrosating agents, recovered solvents, reagents or catalysts used in any fruquintinib manufacturing process steps and adequate specification for nitrate and nitrite at purified water level are set in place. Therefore, the risk of nitrosamine impurity formation in fruquintinib active substance has been assessed is low.

Manufacturing process development is adequately described and the applicant shows good process understanding. The synthetic route has remained mainly the same throughout development from early toxicological studies to late-stage clinical studies, apart from a few process and operational modifications made to ensure the quality of the active substance and a robust process. In addition, a transfer of the manufacturing process from the sites used for clinical active substance batches to the commercial manufacturing site occurred during development. All changes introduced have been presented in sufficient detail and have been justified. It has been demonstrated that the changes did not have a significant impact on the quality of the product and that the quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process at the proposed commercial manufacturer.

The active substance is packaged in a low-density polyethylene (LDPE) bag which complies with Commission Regulation (EU) 10/2011, as amended. This bag is closed and then placed in a triple-layered laminated outer bag consisting of polyethylene terephthalate (PET), aluminium and polyethylene (PE), which is heat sealed. The choice of the container closure system is considered justified.

Specification

The active substance specification includes tests for: appearance, identity (IR, HPLC), polymorphic form (XRPD), assay (HPLC), impurities (HPLC), residual solvents (GC), water content (KF), residue on ignition (Ph. Eur.) and particle size distribution (laser light diffraction). The proposed active substance specification includes relevant testing parameters. The specification was established taking into account applicable ICH and EU guidelines and compendial considerations, as well as manufacturing capability, batch analysis data and stability results. During the assessment, the limit of total impurities has been tightened upon request. The omission of microbial control has been adequately justified by the applicant by demonstrating that the active substance is not capable of supporting microbial growth or viability. The control strategy of impurities has been detailed in the characterisation of the active substance section and is considered acceptable.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data are provided for a total of 21 active substance batches, ranging from early toxicological batches to process validation batches manufacturing using the proposed commercial process. Overall, the batch analysis results show that the manufacturing process can produce active substance with consistent quality.

Stability

Fruquintinib stability studies were conducted at accelerated conditions (40 °C/ 75% relative humidity [RH]), intermediate conditions (30 °C/ 65% RH) and long-term conditions (25 °C/ 60% RH) in accordance with ICH Q1A(R2).

Stability studies were conducted on 3 primary stability batches of fruquintinib manufactured at the commercial site, at the commercial scale, by the previous Process 3.0 and packaged in the proposed commercial packaging, up to 48 months under long-term and intermediate conditions and up to 6 months under accelerated conditions. In addition, a process verification batch was manufactured at the commercial site, using the commercial scale and by the commercial Process 3.1 and was placed on stability. The 6-month timepoint under accelerated conditions and the 12-month timepoint under both long-term and intermediate conditions have been completed.

The following parameters were tested*:* appearance, identification by IR, polymorphic form, related substances, water content, particle size distribution, assay and microbial limits. The analytical methods used in the stability studies were the same as for release and were demonstrated to be stability indicating.

The stability results indicate no clear trends and no significant changes compared to batch release results across all testing conditions and tested batches. Considering that the Process 3.0 and 3.1 are identical (differing solely in redefinition of the starting material during process development and consequently inclusion of the first step of fruquintinib synthesis under GMP) and that batches prepared by Process 3.0 and those prepared using the commercial Process 3.1 are equivalent based on comparability data, the proposed active substance retest period of 60 months when stored below 30°C is endorsed based on the presented stability data.

Fruquintinib active substance was also exposed to different stress conditions (high temperature of 60°C, high humidity of 90% RH, or under light exposure as per ICH Q1B, Option 2). There were no significant changes in the test results for appearance, identification by IR, polymorphic form, related substances, water content, particle size distribution or assay compared to the initial results. Forced degradation studies were carried out using acidic, basic and oxidative conditions. Degradation products were well separated, peak purity of fruquintinib was good and the mass balance close to 100%.

In conclusion, the stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 60 months in the proposed container and stored below 30 °C.

3.4.6. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is presented as immediate release hard capsules containing 1 mg or 5 mg of fruquintinib as active substance, described as follows:

- 1 mg strength: Opaque hard gelatin capsule, size 3 (approximate length 16 mm), with a yellow cap and a white body imprinted with "HM013" over "1mg" in black ink.
- 5 mg strength: Opaque hard gelatin capsule, size 1 (approximate length 19 mm), with a red cap and a white body imprinted with "HM013" over "5mg" in black ink.

The choice of pharmaceutical form/strengths adequately addresses the proposed dosing regimen. The composition of fruquintinib 1 mg and 5 mg finished product, of the hard gelatin capsule shells and of the black ink used for the text print on the pre-printed capsules are provided in the dossier.

All excipients are well known and commonly used pharmaceutical ingredients. There are no novel excipients used in the finished product formulation. The gelatin capsules are of animal origin. The transmissible spongiform encephalopathy (TSE)/bovine spongiform encephalopathy (BSE) compliance statement from the gelatin capsules manufacturer and the applicable Certificates of Suitability (CEPs) for gelatin granted by the European Directorate for the Quality of Medicines (EDQM) have been presented and demonstrate compliance with the EMA Note for guidance on transmissible spongiform encephalopathy (TSE) (EMA/410/01 rev.3).

The full list of excipients is included in section 6.1 of the SmPC and in paragraph 3.4.4 of this report. Tartrazine, Sunset yellow FCF and Allura red are azo colouring agents, for which applicable warning text has been inserted in the Product information. All excipients (including those included in the composition of the imprinting ink and capsule shells) are compliant with Ph. Eur. standards and, where

applicable, have adequate specifications for their control. Overall, the selection of each excipient in the proposed level have been adequately discussed and justified. The compatibility between the active substance and excipients has been demonstrated based on the stability results.

The fruquintinib finished product was developed to meet the quality requirements of a standard immediate-release capsule, which can be swallowed easily, allows flexible dose adjustments and self-administration for patients, that meets compendial and other relevant quality standards throughout the assigned shelf-life. The critical quality attributes identified were: identification, assay, content uniformity, dissolution, related substances and microbial limits. The key development considerations, the potential impact on the quality target product profile (QTPP) and on critical quality attribute (CQAs), and the resulting control strategies are summarized in Table 3.

Table 3: Key development considerations and resulting control strategy

Item	QTPP/CQA Impact	Control Strategy
Drug substance particle size needed to be controlled	Dissolution	Drug substance manufacturing milling step with confirmation as part of the drug substance specification
Powder cohesion due to drug substance of fine particle size negatively impacts powder flowability and ultimately content uniformity	Content uniformity	The excipients of microcrystalline cellulose and corn starch were added to improve the flowability, and the process of premixing and sieving were developed to decrease agglomeration.
Chemical and physical stability	Dissolution Related substances Polymorphic form	Formulation and process developed, and stability confirmed by stress, accelerated, and long-term stability testing
Critical process parameters with acceptable ranges were needed in order to ensure appropriate dissolution profiles and content uniformity	Content Uniformity Dissolution	Critical process parameters defined for final blending uniformity and capsule filling weight

Abbreviations: CQA=critical quality attribute; QTPP=quality target product profile.

Consequently, dry blending of active substance and excipients and subsequent capsule filling was chosen as manufacturing process for finished product. The manufacturing process has not been changed significantly from initial clinical batches to the large-scale production batches, including pivotal clinical batches. The capsule fill formulation of 1 mg and 5 mg capsules also remained unchanged during the clinical development stages. The only difference between the proposed commercial capsule shells and those used in the global Phase 3 study is in the imprint on the capsule shells. Thus, the formulations used in clinical trials are representative of the commercial formulation.

No overages are used in the formulation of fruquitinib finished product.

Pilot and production scale batches have been manufactured to determine suitable process parameters (PPs) such as blending times of capsule fill and encapsulation speed. The critical process parameters (CPPs) ranges were determined through studies conducted on large scale batches.

Various studies have been conducted in order to establish an appropriate dissolution method for the testing of the finished product. As presented under the active substance section, fruquintinib is considered a low solubility compound. The solubility of fruquintinib is pH-dependent. Several different dissolution methods have been used at different stages of development. A summary has been presented regarding the dissolution methods used, in addition to a clarification for the background for the changes made to the methods. Dissolution method optimisation throughout development was

adequately justified. The change of the dissolution method in relation to the stability results is further discussed below in Stability.

The development of the dissolution method has been described in details and the proposed method is found acceptable. The discriminatory power of the proposed dissolution method has been shown to discriminate changes to material properties. Results have been presented for clinical batches tested with proposed dissolution method. Dissolution results have also been presented in support of the transfer of the manufacturing process from the Hutchmed Limited China (Hutchmed) site to the additional STA Pharmaceutical Switzerland SA (STA Couvet) site. Comparison of dissolution profiles has been performed between pivotal clinical batches and manufacture transfer batches STA Couvet. The dissolution profiles are comparable across both manufacturing sites and for both finished product strengths.

The primary packaging is a high-density polyethylene (HDPE) bottle (45 mL) with polypropylene (PP) child-resistant closure and a HDPE desiccant cartridge containing silica gel. The material complies with Ph. Eur. and EC requirements. The proposed pack size is 21 hard capsules. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The fruquintinib finished product is manufactured, filled, packaged, and tested in accordance with GMP. A flow diagram, supported also by narrative description of the manufacturing process and selected CPPs/IPCs, is provided in the dossier. The manufacturing process has been described in sufficient level of detail. In-process controls during the finished product manufacture have been established based on the manufacturing process development studies and are considered adequate for this type of pharmaceutical form.

The manufacturing process consists of sieving, weighting of materials, sequential addition of active substance and excipients, blending steps, following encapsulation. Hold times for final blend and bulk capsules have been proposed and are considered adequately justified.

In the initial submission, process validation data was presented only for the Hutchmed site, but not for the STA Couvet site. Therefore, during the assessment, a Major Objection (MO) was raised to request for process validation data for the finished product batches manufactured at this site. The MO was adequately resolved by the applicant by providing the requested data by the end of the procedure. It was therefore demonstrated that the manufacturing process at both sites is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product specifications include appropriate tests for this kind of dosage form: appearance (visual inspection), identification (HPLC, UV), assay (HPLC), related substances (HPLC), content uniformity (HPLC/Ph. Eur.), dissolution (HPLC/Ph. Eur.), water content (Karl Fischer/Ph. Eur.) and microbial limits (Ph. Eur.).

The parameters included in the finished product specification are found adequate to control the quality of the finished product at release and during shelf-life. Adequate justification was provided by the applicant for the omission of polymorphic form testing from the finished product release and shelf-life specification, based on active substance stability results, the nature of the finished product manufacturing process where no unit operations involving moisture, heat or other processing stresses

are involved, and by presenting supportive XRPD testing results on representative finished product batches, all indicative of the polymorphic stability at finished product level.

During the assessment, a MO was raised to request additional justification of the proposed specification limit for dissolution of the finished product. Upon provision of additional batch data with intentional variations in the critical quality attributes that impact dissolution of the active substance and the bioavailability of the finished product, the applicant was able to demonstrate the discriminatory ability of the dissolution method at the proposed specification limit (Q≥80% in 30 minutes). Therefore, the MO was resolved (see also discussion regarding dissolution in Stability).

Impurities in the finished product may be derived from the active substance and may also be degradation products produced during manufacture, storage, and/or transportation of the finished product. Based on the data provided, it was demonstrated that no degradation occurs during manufacture of the finished product capsules and that fruquintinib capsules had similar degradation impurity profiles as active substance when conducted under similar conditions. Thus, following the assessment, acceptance criteria at release for specified, unspecified and total impurities were tightened upon request, to align with the active substance specification.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on 6 batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

No solvents are used in the finished product manufacturing process. Active substance and the excipients used in the manufacture of the capsules all comply with ICH Q3C(R8). Thus, the absence of a test for residual solvents is justified.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that the risk of nitrosamine impurities in the finished product is low and is well below the ICH Q3A/B thresholds taking into account the ICH S9 indication. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for batches from different stages of development, originating from both Hutchmed and STA Couvet sites, and they show consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability results have been presented for 6 production scale/primary stability batches (3 batches for each strength) of finished product manufactured at Hutchmed site up to 12 months under 25 ºC/ 60% RH storage conditions, up to 18 months under long term conditions (30ºC/65% RH) and up to 6

months under accelerated conditions (40ºC/75% RH) according to the ICH guidelines. In addition, stability data for 2 technology transfer batches (1 batch for each strength) of finished product manufactured at STA Couvet site up to 6 months under long term conditions (30ºC/65% RH) and under accelerated conditions (40ºC/75% RH) were provided. The active substance used the finished product batches studied throughout stability was manufactured at the proposed active substance manufacturing site. The batches of medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

The following parameters were tested*:* appearance, related substances, dissolution, water content, assay and microbial limits. The analytical methods used in the stability studies were the same as for release and were demonstrated to be stability indicating.

For the primary stability finished product batches manufactured at Hutchmed site, there was no significant change in the results of all test items compared with the initial time point and all results met the requirements of the specification. Important to note is that the dissolution method has changed during development, the proposed commercial dissolution method has been used starting with the 12-month time point for the 1 mg and 5 mg strength capsules stored at 25°C/60% RH and 30°C/65% RH storage condition.

For the technology transfer batches manufactured at STA Couvet site, stability data indicate no clear trends, apart from the dissolution results that showed a more pronounced variation compared to the primary stability batches manufactured at Hutchmed site. To further mitigate any concerns with regards to this apparent downtrend, the applicant provided supporting dissolution stability data up to 48 months under long term conditions (25ºC/60% RH and 30ºC/65% RH) for pivotal clinical batches manufactured at Hutchmed site (1 batch for each strength), up to 24 months under long term conditions (25 ºC/60% RH and 30 ºC/65% RH) for the 6 primary stability batches manufactured at Hutchmed site, up to 12 months under long term conditions (30 ºC/65% RH) for the 2 technology transfer batches (1 batch for each strength) manufactured at STA Couvet site and up to 3 months under long term conditions (30 ºC/65% RH) and accelerated conditions (40 ºC/75% RH) for 5 PPQ batches (3 batches of 1 mg strength and 2 batches of 5 mg strength - stability for the third PPQ batch was restarted due to a sample handling error) manufactured at STA Couvet site. This additional data showed a consistent dissolution trend throughout the entire stability profile of the product. The apparent downtrend observed initially for the STA Couvet batches after 6 months was not continued, as shown by the dissolution results at the 9-month and 12-month timepoint, suggesting rather an atypical result for the 6-month timepoint. Dissolution testing results from two additional testing laboratories further supported this conclusion. The preliminary root cause analysis performed by the applicant indicates a testing execution error due to analyst inexperience. However, given the marked fluctuations in the dissolution results during storage for the finished product batches manufactured at STA Couvet, the root cause should be investigated and, if applicable based on the findings, the applicant should make a proposal for a control strategy of this root cause or further development of the dissolution method (Recommendation).

Based on the totality of the evidence, it can be concluded that the proposed shelf-life of 24 months with storage condition "*This medicinal product does not require any special temperature storage conditions. Store in the original container to protect from moisture. Keep the bottle tightly closed. Do not remove desiccant from the bottle*", as stated in the SmPC (section 6.3), can be considered acceptable. Taking into account that there was a change in the dissolution method used during the stability study that could have an impact on the results interpretation and trend assessment, and due to the fluctuations in drug release rate, the applicant should also monitor and report stability results for the STA Couvet PPQ batches every 3 months for up to 24 months (Recommendation).

One primary stability batch each of 1 mg and 5 mg fruquintinib capsules were selected for stress testing. These batches were manufactured at Hutchmed site, by the commercial process and at the commercial scale, and then packaged into HDPE bottles. The bottles were each packaged into a carton. Stress testing was performed simultaneously on unpackaged capsules under conditions of high temperature (60°C), high humidity (75% RH), and exposure to light (an illumination of not less than 0.5 × 104 lux and near-ultraviolet energy of not less than 1.0 watt/m^2) for 10 days at each condition and capsules packaged in HDPE bottles under the light-exposure condition only. These light exposure requirements comply with ICH requirements (Q1B, Option 2). The stress testing results showed that the unpackaged fruquintinib capsules as well as capsules in HDPE bottles (light exposure only) had no significant effect on the appearance, assay, related substances and dissolution under the conditions of high temperature (60°C), light exposure and high humidity of 75% RH. Although the moisture of unpackaged fruquintinib capsules significantly changed under those conditions, there was no significant change in the moisture of fruquintinib capsules packaged in HDPE bottles. This showed that HDPE bottle packaging sufficiently protected the capsules from moisture uptake and that the selection of the packaging was suitable.

Adventitious agents

Gelatin obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatin used in the manufacture is provided.

3.4.7. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During the procedure, three Major Objections were raised on quality grounds concerning (1) incomplete justification of the fruquintinib New Active Substance claim, (2) lack of process validation data for the finished product manufactured at STA Couvet site and (3) insufficient justification of the proposed specification limit for dissolution of the finished product. The Major Objections, as well as all the other concerns, have been satisfactorily resolved.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product which pertain to stability of the finished product manufactured at the STA Couvet site. These points are put forward and agreed as recommendations for future quality development.

3.4.8. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on TSE safety.

3.4.9. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The root cause for the fluctuations in dissolution rate during stability studies for the finished product manufactured at STA Couvet site should be investigated by the applicant and the outcome of the investigation should be reported to the Agency. If applicable based on the findings, the applicant should make a proposal for the control strategy of this root cause or further development of the dissolution method.
2. The applicant should monitor and report to the Agency the stability results every 3 months for up to 24 months for the STA Couvet PPQ batches.

3.5. Non-clinical aspects

3.5.4. Introduction

Fruquintinib (HMPL-013) is a broad tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFR)-1, -2, and -3. Signalling by vascular endothelial growth factor (VEGF) via VEGFR plays a key role in tumour angiogenesis and tumour growth and targeting of the VEGF signalling pathway is a well-accepted strategy for anticancer therapy, including colorectal cancer.

As fruquintinib is intended for use in oncology, the nonclinical development program was designed in accordance with the International Council for Harmonisation (ICH) S9 guidance and ICH S9 Questions and Answers document. Acceptable justifications for missing studies in the MAA dossier were provided.

The suitability of non-clinical study package was evaluated during the EMA/CHMP/SAWP/138519/2020. It was concluded that the package, despite the missing GLP-status, can be accepted with certain conditions:

-The applicant was asked to indicate where there are diversions from OECD GLP and to explain the potential impact on the reliability of the data

-It was agreed that a 3-month rat study will be conducted in the US and no new repeat-dose toxicity study in dogs was recommended.

3.5.5. Pharmacology

3.5.5.1. Primary pharmacodynamic studies

In vitro

Primary pharmacodynamic (PD) studies of fruquintinib included studies using *in vitro* human cell systems, mouse xenograft models and a mouse PK/PD study. *In vitro* assays showed that fruquintinib was broad TKI and primarily targets the VEGFR family receptors, VEGFR-1, -2, and -3 with IC_{50}s of 33 nM, 35 nM, and 0.5 nM, respectively. Fruquintinib inhibited VEGFR kinases at the cellular level and in an engineered cell line HEK-293-KDR which overexpresses VEGFR2. Fruquintinib suppressed VEGF-A stimulated VEGFR2 phosphorylation with an IC_{50} of 0.0006 μM and inhibited the phosphorylation of its downstream signal molecules, including AKT, ERK, Src kinase, and P38. In primary cultured HUVECs, fruquintinib similarly inhibited VEGF-A-stimulated activation of VEGFR2 and its downstream signalling molecules. Selectivity profiling of fruquintinib at 1 μM against 264 kinases using [^{32}P- ATP] incorporation assay revealed more than 50% kinase activity inhibition rate against 16 kinases. Fruquintinib showed ~80% inhibition of rearranged during transfection (RET) and fibroblast growth factor receptor (FGFR)-1 kinases, with IC_{50}s of 128 and 181 nM, respectively. The 50% to 80% inhibition of platelet-derived growth factor receptor α (PDGFRα), FGFR2, c-kit (stem cell factor

receptor), and FGFR3 was observed with IC_{50}s of 601, 553, 458, and 738 nM, respectively. Thus, fruquintinib is at least 3-fold more selective for VEGFR1 and 2 over RET and FGFR1. Moreover, only VEGFR1, 2, 3 had IC_{50} values that were below the unbound steady state maximum observed concentration (C_{max}) of 38 nM at the recommended dosage of 5 mg once daily (QD) in a 28 day cycle in patients.

M11, the major circulating metabolite of fruquintinib observed in human plasma, was also pharmacologically active in inhibiting VEGFR2 kinase activity and VEGFR2 phosphorylation, albeit being significantly less potent.

M11 is 2-fold less potent than fruquintinib (M11: IC_{50} = 28 nM, fruquintinib: IC_{50} = 15 nM) and 10-fold less potent in cellular assays after studying activity of fruquintinib and M11 on VEGFR2 (study oncology 2021-013-01). The parent molecule, fruquintinib showed comparable IC_{50} on VEGFR1 and VEGFR2, both involved in angiogenesis pathway. M11 was observed to be 2.5-fold less potent than fruquintinib on VEGFR1 (M11: IC_{50} = 71 nM, fruquintinib: IC_{50} = 28 nM). Fruquintinib inhibited tubular formation in cultured HUVECs by 94% at a concentration of 300 nM. Inhibition of neovascularization at fruquintinib doses ≥0.1 nmol was also demonstrated in the chorioallantoic membrane angiogenesis model using chick embryo. Fruquintinib had low cytotoxicity in 11 human tumour cell lines and normal human primary cells (HUVEC). After 48-hour incubation at concentrations ranging from 2 nM to 30 μM (9 nm to 20 μM for HUVECs) IC50 values were >30 μM except for HUVECs for which IC_{50} was 18.7 μM.

The PD assays on phosphorylation of VEGFR2 and not the inhibitory activities on VEGFR1 and 3 in cellular assays. VEGF signalling through VEGFR2 has been established in the literature as the major angiogenic pathway, while VEGFR1 plays a secondary role (Dvorak 2002; Shalaby et al. 1995; Shibuya 2011). VEGFR3 has been shown to play a key role in lymphangiogenesis; however, the ability of fruquintinib to inhibit this biological process *in vivo* has not been investigated. Only *in vitro* results are available.

Fruquintinib effects on the immune system were observed in nonclinical species.

In vivo

In vivo pharmacology studies with fruquintinib consist of xenograft models bearing various human cancer cell lines. In addition, a PK/PD study was conducted with fruquintinib to assess suppressed VEGF-induced VEGFR2 phosphorylation in lung tissues of nude mice. Fruquintinib demonstrated dose-dependent and reproducible tumour growth inhibition for the following human xenograft models in BALB/c nude mice: BGC-823, HT-29, Caki-1, and NCI-H460. Fruquintinib at 2.5 mg/kg inhibited VEGFR2 phosphorylation in the lungs of nude mice in a time-dependent manner and completely inhibited VEGFR2 phosphorylation for 4 hours post-dose. The concentrations of fruquintinib in plasma correlated well with target inhibition, and a plasma drug concentration of greater than 424 ng/mL (4 hours after the 2.5 mg/kg dose) completely inhibited VEGFR2 phosphorylation. Studies conducted in the murine colon cancer CT26.WT model showed that fruquintinib exerted an antitumour angiogenesis effect, significantly reduced the number of immunosuppressive macrophages in tumour tissues, and further enhanced the antitumour effect when it was combined with an anti-PD-L1 or anti-PD-1 antibody, suggesting that fruquintinib has an immunomodulatory effect on the tumour microenvironment.

3.5.5.2. Secondary pharmacodynamic studies

In secondary pharmacodynamic study with 87 receptors, ion channels, and enzymes included in the panel, no inhibition or binding was higher than 50% for any of the targets.

3.5.5.3. Safety pharmacology programme

In vitro safety pharmacology studies assessing the potential for delayed ventricular repolarization (i.e., hERG assay) was conducted with fruquintinib and its major human metabolite (M11). Fruquintinib did not inhibit hERG channels, resulting in an IC_{50} value of >13.08 µM, based on the actual concentrations. IC_{50} for M11 was > 6.05 µM. These IC_{50} values are more than 380- and 1000-fold greater than the unbound human steady-state C_{max} at the proposed therapeutic dose of 5 mg daily of fruquintinib indicating a low potential for QTc prolongation. Overall, there were remarkable differences in inhibition-% between the test cells. The applicant acknowledges that there was a wide range of percent human hERG current inhibition in the definitive assay with fruquintinib (ranging from -7.30 to +12.26% at 20 µM) and the exact cause for this variability is unknown. These inter-cell variations resulted in high standard deviations in dataset, which in turn raise questions about the correctness of the calculated IC_{50} values. Moreover, at fruquintinib concentration of 20 µM inhibition-% in 2 of 4 cells was even negative. As a result, there was no concentration proportionality in hERG current inhibition (%). Therefore, it not fully agreed with the Applicant's claim that the hERG current inhibition at all of the fruquintinib tested concentrations (1, 3, 10, and 20 µM nominal concentrations) were substantially below a 50% inhibition level which raised no concerns for a QT. Precipitation was observed at 20 µM fruquintinib in the non- GLP dose range-finding assay after 4 hours of preparation, but not in the GLP-compliant definitive hERG assay within 2 hours after preparation; thus, this concentration was used as the high concentration in the definitive assay. In the definitive assay, no precipitate was observed at any concentration when used within 2 hours of preparation; therefore, there is no effect on the assay results. The nominal concentration of 20 µM resulted in a post-perfusion concentration of 13 µM, although the concentrations of the working solutions were verified to be within 96% to 100% of nominal concentrations, and the concentrations of the samples for homogeneity analysis were within 97% to 101% of nominal values. All of the working solution concentrations met the protocol-specified acceptance criteria. Per protocol and to ensure appropriate reporting of the study results, the post-perfusion concentration was used to conservatively calculate the IC_{50}, to account for any nonspecific binding of the test article to the perfusion system.

In *in vivo* safety pharmacology studies, single oral administration of fruquintinib at dose levels ranging from 0.5 to 10 mg/kg had no effect on motor coordination or behavioural activities in mice. Furthermore, results on electrocardiograms (ECGs), blood pressure, and respiratory rate in anesthetized beagle dogs orally administered with single doses of fruquintinib ranging from 0.085 to 0.34 mg/kg indicated that fruquintinib had no adverse effect on the cardiovascular and respiratory systems at these doses. In addition, no ECG, respiratory, or CNS changes were attributed to fruquintinib at doses up to 0.12 mg/kg/day, the highest dose administered, in beagle dogs during a 13-week OECD GLP compliant toxicity study. The 13-week dog toxicity study in beagle dogs was performed based on findings from a GLP audit conducted in 2020 and was primarily intended to bridge the 39-week toxicity study in beagle dogs. In addition to providing bridging toxicity data, ECGs were added to this study to verify findings from the safety pharmacology study (Report 0849PH1 which was completed in 2009). The dosing in study 0849PH1 was a single oral gavage of the test article suspension in 0.5% CMC-Na while in study 8449374 oral capsules were administered for 13 weeks at dose levels significantly lower than those in study 0849PH1. In the 13-week study, no fruquintinib-related effects were noted on ECG measurements, blood pressure, respiration rate, pulse oximetry or neurological examinations at any dose level. No abnormal ECG waveforms or arrhythmias were attributed to fruquintinib during the qualitative assessment of the ECGs.

3.5.5.4. Pharmacodynamic drug interactions

Studies were conducted to investigate the efficacy of fruquintinib alone, or in combination with molecular targeted therapies such as EGFR and cMET inhibitors, on tumour growth in xenograft models bearing various human tumours and with chemotherapeutic agents or an immune checkpoint inhibitor (anti-PD-L1 or anti-PD-1) on tumour growth in syngeneic models bearing murine tumour. A synergistic or additive antitumour effect was observed in these nonclinical tumour models.

3.5.6. Pharmacokinetics

Methods of Analysis

The validated methods (LC-MS/MS) are standard laboratory methods suitable for the quantification of the components of the liquid samples such as plasma. The assay procedures for the measurement of fruquintinib and the main metabolite M11 in rat, dog and guinea pig plasma samples was validated in terms of accuracy, precision, stability, sensitivity (LLOQ) and selectivity. The described sample preparation technique included protein precipitation and subsequent dilution, however, not all validation reports described the sample preparation in detail showing low quality in reporting. The internal standards for method validation were HMPL-012 (study HMPL-013-ADME) or phenacetin (studies 1054MV1, 1054MV2) or CMB (other studies) providing sufficient robustness as described in the validation reports. The sensitivity of methods was considered suitable for the purpose as well as the sample stability under storage (>21 days). No interference with the endogenous substances in the plasma samples were observed in the validation process of different methods.

Absorption

The PK/TK data was collected from mouse, rat, dog and guinea pig studies as well as from *in vitro* studies with relevant human cell types. The *in vivo* administration routes were IV and oral, the planned administration route in humans is oral.

Fruquintinib is a highly permeable compound without suggested P-gp inhibition potential *in vitro* (Caco-2 cells).

PK/TK data was collected for up to 13-weeks in rats and dogs after once daily oral dosing. There was slight increase in AUC_{0-t} of the last day (28/91 days) over the first day in rats and clearer increase in AUC_{0-t} in dogs. In the 39-week repeat-dose study with dogs, an increase in the AUC_{0-t} was observed suggesting accumulation of fruquintinib in dogs. The increase in C_{max} and AUC_{0-t} in rats was higher than dose-proportional in the dose range 0.5-2.0 mg/kg whereas in dogs and guinea pigs the increase was dose-proportional. Food intake had no impact in the oral PK studies.

The single-dose study with [14C]-fruquintinib in rats (report RTC00357) suggested absolute oral bioavailability of 145.87% for males and 71.69% for females without any discussion by the Applicant on the unexpected high value reported for males. In addition to this, data reported in study report 8453891 (*in vivo* genotoxicity study) showed no increase in exposure (mean C_{max} and AUC_{0-24}) when fruquintinib dose was increased from 500 to 2000 mg/kg/day, causing uncertainty on the reliability of conclusions of the rat micronucleus and alkaline comet assay. Please see *Toxicology*-section for further details.

Based on the C_{max} values collected from the PK/TK studies with a wide dose range in rats and dogs, the pharmacokinetics of fruquintinib is suggested to be linear, however, the increases in C_{max} were slightly lower than dose proportional in dog studies.

After IV administration to dog at 0.3 mg/kg and to rat at 1 mg/kg, clearance was 0.07-0.09 L/h/kg or 8.017 mL/min/kg indicating a low clearance of fruquintinib in both species. Volume of distribution was 1.56-1.72 L/kg in dogs indicating some distribution to tissues in dogs, and 650 mL/kg in rats.

No clear gender differences were observed in dogs, however, more variation between genders was recorded in rats especially in C_{max} and AUC values.

T_{max} was 2.7 to 4 hours after single oral administration in fasted dogs, 0.22-1.7 after IV administration of dogs and 1.8 to 2.3 hours after single oral dosing in rats. Mean half-life ranged from 11.5 to 15.7 hours after singe oral administration and 13.4 to 14.6 after IV administration in dogs whereas it was 1.72-2.60 hours after single oral and 1.03 hours after IV administration in rats. The oral bioavailability after one dose (0.1, 0.3 or 1.0 mg/kg) was 64.9%, 52.8% and 46.9% in dogs. After a single dose (0.5, 1.0 or 2.0 mg/mg) in rats, the oral bioavailability was 24.9%, 46.6% and 61.7%.

Studies with the metabolites M9 and M11 after oral administration of dogs and rats showed lower exposure compared to the fruquintinib with no gender differences.

No sufficient safety margins for the clinical exposure have been reached in non-clinical studies. Please see *Toxicokinetics*-section for further details.

Distribution

The plasma protein binding (PPB) properties of fruquintinib were evaluated in mouse, rat, dog and human plasma using a rapid equilibrium dialysis method. Drug concentrations used were 1, 3 and 10 μM. The PPB of fruquintinib appeared to be concentration independent in all tested species as PPB rates of fruquintinib were 91.2%, 92.7%, and 92.8% in mouse, 96.2%, 95.6%, and 96.5% in rat, 87.3%, 88.7%, and 88.2% in dog, and 95.4%, 95.3%, and 95.3% in human plasma.

For the main metabolite M11, the PPB properties were tested with same method in mouse, rat, dog, monkey and human plasma. PPB rates were similar: 96.8%, 96.6%, 94.8%, 95.6%, and 97.7% in mouse, rat, dog, monkey, and human.

The R_B rates of fruquintinib were investigated in blood from human, dog and rat. The R_B at 10 and 60 minutes was 0.458 and 0.601 in human, 0.709 and 0.733 in rat and 0.851 and 0.792 in dog blood. Only one concentration (1 μM) was used, and therefore the concentration-dependent blood-to-plasma partition preference cannot be evaluated.

The protein binding of fruquintinib was studied in human liver microsomes with concentrations 1 and 10 μM. When the protein content was 0.2 mg/mL, the binding rates were -3.57% and 1.58% and when the protein content was 0.5 mg/mL, the binding rates were 15.2% and 24.3%, suggesting a capability of fruquintinib to bind proteins in concentration-dependent manner.

In vivo studies with oral and IV administration of rats with [14C]fruquintinib showed blood-to-plasma ratios 0.34-1.28 (IV) and 0.51-1.01 (oral) suggesting no significant binding to cellular components.

The tissue distribution study with [14C]fruquintinib on non-pigmented (5/sex) and pigmented (10/males) rats with a single oral dose (2 mg/ml) showed maximum concentrations of the radioactivity 0.5-4 hours post-dose in tissues regardless of the gender. Different sampling schedules were used in non-pigmented (0.5, 4, 24, 168 hr) and pigmented (0.25, 2, 4, 8, 24, 48, 168, and 504 hr) rats.

The ratio of the total radioactivity based on AUC in whole blood and plasma was approximately 0.5, suggesting that [14C]fruquintinib and its metabolites were mainly distributed to plasma. The radioactivity was mainly recorded from metabolic and excretory organs (males: liver, small intestine wall, large intestine wall, urinary bladder wall, and kidney; females: liver, small intestine wall, large intestine wall, kidney, and harderian gland) and the distribution in brain/CNS was low in non-pigmented rats.

Metabolism

The metabolism of fruquintinib was investigated in several *in vitro* studies and one *in vivo* rat study. M10 has been identified as a major metabolite of fruquintinib in human liver microsomes, with M1, M7 and M2 as the secondary metabolites. However, in the human plasma the major metabolite was M11 that is converted from M10. The studies comparing different species (mice, rats, dogs, monkeys and humans) suggest that the metabolites for different species are similar. However, the results in the preliminary study DMPKR20150076-E-01 identified only M1+M7 (O-demethylation), M2 (hydroxylation) and M3 (mono-oxydation) and not the main metabolite M10. Study DMPKR20160009-E-01 identified more metabolites: M11 (O-demethylation) and M10 (hydroxylation) that were also identified in all investigated species (rats, dogs, monkeys, humans) but the relative amounts of metabolites were different. The species comparison suggests that metabolites in dog represent mostly the metabolites in human but that the rat also has same metabolites present, although in a different ratio.

The role of CYP enzymes in the metabolism of fruquintinib was investigated in the *in vitro* studies in human liver microsomes. The preliminary study DMPKR20150079-E-01 investigated the metabolism of fruquintinib to M1+M7 and M3 and not the main metabolite M10. In addition, the percentages shown in these two reports concerning metabolism to M1+M7 and M3 represent large variation. According to the study DMPKR20160003-E-01 the formation of M10 was mainly mediated by CYP3A4 (77.7%) and CYP2C9 (28.1%) and FMO (23.0%). However, the study DMPKR20190006-E-01 suggest that CYP3A4 has a contribution of no less than 92.5% to the fruquintinib metabolism and CYP2C8, CYP2C9, and CYP2C19 only small contribution (0.529%, 0.241%, and 0.015%). It is agreed based on the presented data that CYP3A4 seems to be the main enzyme involved in the metabolism of fruquintinib, however, due to the large variability between the data from different NC studies, clinical PK data is needed to confirm the observation.

No gender differences were recorded in the metabolic stability or microsomal metabolism in the species tested. The hepatic extraction is expected to be low.

The *in vivo* study in rats shows different metabolite profile than studies with human plasma M2 being the most dominant metabolite in the plasma instead of M11 in the human plasma. The value of this study in the analysis of the fruquintinib metabolism is questioned due to the major differences between rat and human in the relative amounts of metabolites.

Excretion

The *in vivo* excretion was studied in rats after single-dose administration of fruquintinib. The majority of fruquintinib related radioactivity was excreted in faeces (males 69.65%, females 73.11%). Smaller, but relevant, fraction was excreted in urine (males 24.47%, females 20.23%). In the BDC rat, bile accounted for approximately 33% of the excreted radioactive dose. The excretion was fast as almost all radioactivity was excreted within 48 hr post-dose. No information on excretion into milk is provided.

Pharmacokinetic drug interactions

Fruquintinib as an inducer of CYPs

Fruquintinib was not considered an inducer of CYP1A2, CYP2B6, or CYP3A4 *in vitro.*

Fruquintinib as inhibitor of CYPs

IC50 values >50 μM were determined for CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 indicating no inhibition by fruquintinib. IC50 value > 12.5 μM was determined for CYP2B6, indicating possible inhibition by fruquintinib, however, 12.5 μM was the highest dose tested so the dose selection was not successful for the experiment.

Fruquintinib did not show time-dependent inhibition potential on CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 in pooled human liver microsomes.

M11 as inhibitor of CYPs

IC50 values >50 μM were determined for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1 indicating no inhibition by M11. IC50 value of 38 μM for CYP 3A4/5 demonstrated a weak inhibition of CYP 3A4/5 by M11.

M11 or M9 did not show time-dependent inhibition potential on CYP1A2, CYP2C9, CYP2D6, and CYP3A4/5 in pooled human liver microsomes.

Fruquintinib as substrate of transporters

Fruquintinib was not a substrate of OATP1B1 or OATP1B3 transporters *in vitro* and was unlikely to be substrate of efflux transporters such as P-gp.

Fruquintinib as an inhibitor of transporters

The data indicate that fruquintinib has the potential to inhibit P-gp and BCRP *in vitro* but no inhibitory effects on OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, and MATE2-K.

M9 and M11 as an inhibitor of transporters

The metabolites M9 and M11 demonstrated weak inhibition on P-gp and potential to inhibit BCRP *in vitro*. M11 was an inhibitor of OATP1B1, OATP1B3, MATE1, and MATE2-K and had no inhibitory effect on OAT1, OAT3, and OCT2.

No other PK studies were performed.

3.5.7. Toxicology

3.5.7.1. Single dose toxicity

The non-GLP single dose toxicity studies were performed in 2 species, rats and dogs. The maximum tolerated dose (MTD) for rats was 2000 mg/kg and for dogs 1000 mg/kg, the only dose used in both studies.

In the single-dose rat study, a statistically significantly decreased body weight was observed in male rats but not in females, corresponding with observed clinical finding diarrhoea observed during days 11-14. The microscopic changes included haemorrhage and congestion of mucosa in stomach; dilatation of biliary duct accompanied with mild hyperplasia and necrosis of epithelial cells in the mucosal surface and mild inflammatory cell infiltration in the mucosa; haemorrhage and/or congestion of mucosa in duodenum together with mild multiple small focal inflammatory cell infiltration in the mucosa.

In the dog study, decreased activity, food consumption and body weight as well as diarrhoea and haematochezia were observed between days 2-17 in male and female dogs. These effects were fully (female) or partially (male) recovered at the end of the observation period. As only one dog/sex was used, the interpretation of the data is unsecure.

The results suggest that GI-tract is the target organ of toxicity in both species.

3.5.7.2. Repeat dose toxicity

28-day rat and dog study, 26-week rat and 39-week dog study were conducted in compliance with NMPA GLP, and 13-week rat and dog studies were conducted in compliance with OECD GLP, however, in a test facility located in China (not part of the OECD MAD mutual data sharing agreement).

Rats

Three pivotal repeat dose toxicity studies were conducted in Sprague-Dawley rats with fruquintinib in National Shanghai Center for New Drug Safety Evaluation and Research (non-GLP, 2009 and 2012) and Covance Pharmaceutical R&D (Shanghai) Co., Ltd (Covance - Shanghai; 13-week GLP study, 2021). The dosing schemes were 0, 2, 20, 60 mg/kg in 28-day study; 0, 0.3, 0.6, 1.2/2.4 (increased from day 44 onwards) in the 13-week study, and 0, 0.5/ 0.25 (decreased from day 50 onwards), 1.5/ 0.75 (decreased from day 50 onwards), 5/3/1.5 (decreased from days 29 and 50 onwards), 10/6 (decreased from day 29 onwards) in the 26-week study. TK analyses were conducted for all the repeat-dose studies at all dose levels.

It is stated in the 13-week study report that on Day 44 of the dosing phase, as no severe toxicity was noted for animals administered 1.2 mg/kg/day and the exposure tested was generally lower than previous toxicity studies, the dose level for this group was increased to 2.4 mg/kg/day through the end of dosing phase. The differences in the exposure levels between studies were estimated to be due to the inter-study variability with the rats used in these studies originating from different vendors.

Fruquintinib-related mortality was observed in 28-day study (60 mg/kg/day), and in the 26-week study (10/6 mg/kg/day) due to the liver and kidney damage. In the 13-week study, moribundity-induced sacrifice in the 1.2/2.4 mg/kg/day group was due to the hunched posture, thinness, red discoloured nasal discharge, broken teeth, and discoloured skin.

In all rat studies, abnormal/broken teeth were observed possibly causing the decrease in food consumption and body weight and thin appearance/activity loss of rats. In the 26-week study, no NOEAL could be identified, and in the 13-week study Applicant suggested the lowest dose 0.3 mg/kg/day as the NOAEL as the clinical chemistry findings observed at this dose level were not associated with any adversity.

The toxicity profile determined in the non-GLP studies (4-week studies and 26-week study with an intermediate 13-week analysis) appears affected a larger number of target organs than observed in GLP pivotal study (13-week study). It is noticed that exposures achieved in the 13-week study was lower than in 4- and 26-week study and could be the reason of not detecting of the target organs. The extended toxicity profile is reported in RMP and in SmPC section 5.3. However, non-GLP studies presented limited animal per group and no complete histopathology analysis for intermediate groups; thus, these studies are considered to be limited of value. However, it is acknowledged that an extended toxicity profile is consistent with those obtained for already marketed anti-VEGFR1, 2 and 3 products, and the use of toxicity profile obtained from the supportive studies therefore is accepted. The value of the additional 13-week study in rat presented a limited value and is questionable from 3R perspective.

The identified target organs of fruquintinib toxicity were liver, kidney, adrenal gland, thymus, spleen, bone marrow (sternum), and femur. The clinical chemistry findings in rats supported the conclusions for liver changes, for other recorded clinical pathology findings such as lower reticulocyte and platelet count the mechanism was not identified. In the dog studies, the clinical pathology changes were associated with general inflammation.

Dogs

Three pivotal repeat dose toxicity studies were conducted in Beagle dogs with fruquintinib in National Shanghai Center for New Drug Safety Evaluation and Research (4 and 39-weeks non-GLP, 2009 and 2012) and Covance Pharmaceutical R&D (Shanghai) Co., Ltd (Covance - Shanghai; 13-week GLP study, 2021). The dosing schemes were 0, 0.03, 0.1, 0.3 mg/kg in 4-week study, 0, 0.03, 0.06, 0.12 in 13-week study and 0, 0.01, 0.03, 0.1/0.06 (decreased from day 15 onwards), 0.2/0.12 (decreased from day 15 onwards) in the 39-week study. TK analyses were conducted for all the repeat-dose studies at all dose levels; in the 4-week study in non-GLP-settings.

Dose levels in the repeat-dose dog studies were low due to the high mortality rate in the studies. In the 4-week study, NOAEL was set as 0.1 mg/kg/day and in the 39-week study NOAEL was set as 0.03 mg/kg/day. No NOAEL could be set in 13-week study, the 0.03 mg/kg/day being the LOAEL of the study. In all studies, dogs showed signs of general toxicity with decreased body weight and activity and decreased food consumption (not detectable in 13-week study as additional canned food was provided).

High level of fruquintinib-related mortality was observed in 4-week study at 0.3 mg/kg/day, but no dead or moribund animals were found in 0, 0.03 and 0.1 mg/kg/day groups. In the 39-week study, 2 female dogs in the high dose group experienced moribundity/death. In the 13-week study all animals survived to their scheduled sacrifice.

No relevant ECG findings nor significant changes in blood pressure or heart rate were recorded in any of the repeat-dose dog studies.

The non-GLP dog studies identified liver, kidney, GI-tract, adrenal gland, and immune system (thymus and spleen, and lymph nodes in the 39-week study) as target organs. The recorded deaths in the 39-week study were due to hepatotoxicity, nephrotoxicity, GI-toxicity, and immunosuppression. No teeth effects were recorded. The toxicity profile determined in the supportive studies differs from the one observed in the GLP-study, suggesting only adrenal gland and femur as target organs, whereas also duodenum, kidney, liver, spleen, thymus and lymph node (26-week study) were target organs in supportive studies.

In the 13-week study, fruquintinib-related histopathology was observed in adrenal gland, femur, and femur marrow. In the high dose group, abnormal teeth (brown) were recorded, this finding was still present after the recovery period. Signs of irritation (red discoloured oral mucosa and oral mucosa ulceration) were also recorded. The applicant suggested that the oral mucosal lesions and teeth findings are class-effects for VEGFR inhibitors. In the clinical settings, stomatitis and oral pain (gingival pain, oral pain, toothache) has been noted to fruquintinib-treated subjects. The SmPC section 4.8 lists these effects.

3.5.7.3. Genotoxicity

Fruquintinib was not recorded to have genotoxic potential in GLP-compliant *in vitro* and *in vivo* studies (performed in Labcorp Early Development Laboratories Ltd, UK; 2022).

Fruquintinib did not induce mutations when adequately tested in histidine-requiring strains of Salmonella typhimurium (TA98, TA100, TA1535, TA1537 and TA102) at concentrations up to 5000 µg/plate in the absence and presence of a rat liver metabolic activation system (±S9). No *Escherichia coli* was included in the assay, this is accepted per OECD TG471.

In an *in vitro* mammalian chromosome aberration study in CHO cells, fruquintinib was negative at the presence and absence of metabolic activation. Increases in the frequency of cells with numerical aberrations, which exceeded the concurrent vehicle controls and the normal range, were observed in

cultures treated with fruquintinib following 3-hour treatments (with a 17-hour recovery) in the presence of S9.

There were no positive findings in the *in vivo* combined micronucleus and comet assay expect for one rat in 500mg/kg group. The TK data demonstrated no increase in the exposure (C_{max} and AUC_{0-24} values) when dose was increased from 500 to 2000 mg/kg/day. No clinical observations were recorded, which is not in line with the results in the single-dose toxicity study in male rats (0849AD1), however, the adversity was not observed until day 11 in the earlier study. The exposure at the low dose is 28-fold above the human AUC and 38-fold above the human C_{max}, indicating low risk of genotoxicity in clinical settings. No mortality was observed in any of the treatment groups.

Only male rats were used as no TK/PK differences were recorded in the previous studies.

3.5.7.4. Carcinogenicity

Carcinogenicities studies were not submitted as part of this application.

3.5.7.5. Reproductive and developmental toxicity

The reproductive and development toxicity study program consisted of 3 rat studies, one (8449387) being GLP-compliant.

Fertility and early embryonic development

A non-GLP compliant fertility and early embryonic development study were conducted in male and female rats with dosing of 0.05, 0.15, or 0.5 mg/kg/day of fruquintinib for females and 0.3, 1, or 3 mg/kg/day for males. The background of different dosing schemes was not provided by the Applicant. For males, the NOAEL for general toxicity was set as 0.3 mg/kg, however, no effects in fertility parameters were recorded. This is in line with the GLP-compliant 13-week repeat-dose toxicity study in rats (8426159) and dogs (8449374) sperm analysis parameters with no findings in sperm motility, percentage, caudal epididymal weight or sperm density. For females, the common NOAEL for fertility and general toxicity (0.5 mg/kg) was set based on no maternal toxicity or changes in mating, pregnancy parameters or oestrous cycle parameters were seen in the highest dose tested. For the early embryonic development, NOAEL 0.15 mg/kg was set as number and percent of viable foetuses was drastically decreased with dose of 0.5 mg/kg, with increased number and percent of resorption and post-implantation loss.

Historical control data generated in the test facility for copulation (90-100%) and conception (70-96%) indices were submitted. In males, values in all groups including concurrent controls were outside of the historical control range. The highest values were reported in the low and mid dose groups, and a 13% decrease in the high dose group vs. concurrent controls was noted. A treatment-related effect on male fertility is to be considered in the high dose group. In females, the conception index was outside of the historical control range in the high dose group only suggesting a drug-related effect.

Overall, the Applicant has submitted additional data highlighting a decrease in rat fertility at the high dose levels of 3 mg/kg (male) and 0.5 mg/kg (female). This is based on copulation and conception indices being outside of the historical control range and lower than those reported in other groups, including concurrent controls.

Further clarification was also requested regarding any treatment-related effect on preimplantation loss in view of the higher values noted especially from the mid-dose level. The applicant noted that there was no test-article related effect on this parameter in the embryo-foetal study; this is not unexpected in study wherein the study is initiated from implantation. It was also explained that the

preimplantation loss values in all groups lied within the historical controls. In view of the historical control range value (0-100%), it would be suggested to take into consideration the mean historical control value (14.6% per litter) which is in line with the value reported in controls of the rat embryofoetal toxicity study no. 1054RB1 conducted at the same test facility (14.35%). Although less relevant, historical control ranges for preimplantation loss in SD rats generated at other testing facilities could be considered as general indicators for this parameter; a range of 1.8-16.4% was reported in the facility where the pivotal EFD study was conducted (study 8449387), whereas maximal historical control values reported at various Charles River testing facility in fertility studies[11] were in general below 18.5% with one exception at 20.8% (Montreal site).

Embryo-foetal development

Embryo-foetal developmental studies were conducted in rats. Based on the preliminary non-GLP study, the dosing regimen for GLP-compliant study (8449387) was selected.

Signs of general toxicity was seen in the main study (8449387) with the high dose group (0.25 mg/kg), but no maternal mortality was observed. Piloerection and macroscopic thymus observations were observed in all treatment groups, and decreased activity, head bobbing, ataxia and irregular respiration in groups treated with 0.1 mg/kg and 0.25 mg/kg. These effects were transient and dose responsive. The maternal NOAEL was set as 0.1 mg/kg/day.

Teratogenicity was observed in foetuses after fruquintinib administration of ≥0.1 mg/kg/day. These severe external, visceral, and skeletal anomalies affected primarily the head (cranial meningocele), tail (short, bent), tongue (protruding), blood vessels (absent or malpositioned), heart (ventricular septal defect), thymus (malpositioned), and developing skeleton (notably vertebrae).

The TK parameters showed dose-proportional increase. The metabolite M11 could not be detected as the values were below the limit of quantification. This is expected with the known metabolite profile of fruquintinib in rats.

Based on the GLP-compliant embryo-foetal developmental study, the maternal NOAEL was set to 0.1 mg/kg/day and foetal NOAEL as 0.025 mg/kg/day. These dose levels did not induce significant maternal toxicity and corresponded to 0.05-fold and 0.21-fold, respectively, the exposure levels at the maximum recommended human dose.

Fruquintinib or M11 are not genotoxic and 200-fold safety margin based on LOAEL (0.1 mg/kg/day) in the rat EFD study (no. 8449387) is derived. If the NOEAL from the same study (0.025 mg/kg/day) is used, the safety factor is 48 (C_{max} measured on GD17 in maternal animals 18.70 ng/mL). ICH S5(3) indicates only minor concern for effects limited to occurred at more than 25-fold human exposure, and therefore no male contraception is required.

This toxicological profile is consistent with the pharmacological activity of fruquintinib. Additional embryo-foetal development studies are not required considering the significant developmental toxicity observed in rats.

3.5.7.6. Toxicokinetic data

The systemic exposure of fruquintinib increased dose proportionally. Some accumulation was observed in dog studies. No obvious sex differences were recorded. The TK data collected from GLP-compliant 13-week rat study (8426159) and dog study (8449374) are presented in the below table.

[11] https://www.criver.com/products-services/safety-assessment/toxicology-services/developmental-and-reproductive-toxicology-dart/historical-control-data

Table 4: TK data for 13-week rat studies

Study ID	Daily Dose (mg/kg)	Animal AUC (ng*h/ml)		C_{max} (ng/ml)		T_{max} (h)	
		♂	♀	♂	♀	♂	♀
8426159	0.3	1530	1630	268	401	2	1
	0.6	2150	4360	497	760	2	2
	1.2/2.4	18200	13600	2230	2050	4	2
8449374	0.03	312	284	18	17.1	4	2
	0.06	594	802	35.5	41.5	4	2
	0.12	1820	1140	129	80.4	2	2

The gender-combined systemic exposure (AUC) at the NOAEL in rats at 0.3 mg/kg (1580 ng*h/mL, not 1640 ng*h/mL as presented by the Applicant) and LOAEL in dogs at 0.03 mg/kg (298 ng*h/mL) or HNSTD in dogs suggested by the Applicant (0.12 mg/kg - 1480 ng*h/mL) were lower than human systemic exposure at the therapeutic dose level (5 mg/day). The safety margins (total AUC ratio) derived from the GLP-compliant 13-week rat and dog study NOAELs are 0.3 and 0.05, respectively. For the embryo-foetal development, the safety factor derived from the NOEAL is 0.02.

The systemic exposure of the metabolite M11 was evaluated in the 13-week rat and dog studies. M11 showed dose-proportional increase without apparent accumulation.

3.5.7.7. Local Tolerance

The applicant has not provided a discussion on the local tolerance of the fruquintinib.

In repeat-dose rat studies, the oral gavage administration was used. This may silence the possible effects in the beginning of the GI-tract and, on the other hand, the experimental model itself may cause stress and irritation on the GI-tract of rat. Therefore, the dog studies are foreseen as a better model to evaluate the local tolerance of fruquintinib.

In the GLP-complaint repeat-dose 13-week study, red discoloured oral mucosa, oral mucosa ulceration and brown teeth were reported in animals administered 0.12 mg/kg/day; red or brown oral mucosa was reported also in dogs dosed with 0.06 mg/kg/day.

3.5.7.8. Other toxicity studies

Metabolites

The TK of fruquintinib was evaluated in the repeat-dose toxicity studies and reproductive and developmental toxicity studies. M11, the identified major human metabolite was confirmed to be present in rat and dog 13-week studies but at lower levels (2% and 6 % respectively) than in human (17%). The plasma levels of M11 (HM5025423) were measured in the rat micronucleus assay and M11 exposures are in the clinical range and could be considered qualified. A GLP standard battery was performed with fruquintinib.

Phototoxicity

The phototoxicity was studied in the guinea pig single-dose study (more than 100 animals). The study was performed in Shanghai Innostar, China but claimed by the Applicant to be GLP-compliant and inspected by EU inspectors (Belgium). Fruquintinib absorbs at 238 nm and 320 nm with molar extinction coefficients of the maximum absorptions above 1000 $L.mol^{-1}.cm^{-1}$. Furthermore, the distribution study with 14C-labelled fruquintinib showed distribution of the total radioactivity to the melanin-containing tissues (such as eye, uveal tract, pigmented skin, *etc*). According to ICH S10 stepwise approach, an *in vitro* study is preferred as the second step in order to reduce the number of

used animals. It is noticed that fruquintinib is almost insoluble in water and therefore the *in vitro* test was not performed. The phototoxicity study demonstrated no phototoxicity in skin of guinea pigs treated with fruquintinib. As fruquintinib data shows maximum absorbance of 238nm and some absorbance at 320 nm (< 400 nm), the phototoxicity testing in eye is not required.

3.5.8. Ecotoxicity/environmental risk assessment

Table 5: Summary of main study results

Substance (INN/Invented Name): Fruquintinib			
CAS-number (if available): 1194506-26-7			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	logDow = 2.8 at pH 5 log Kow= 2.9 at pH 7 log Kow =2.9 at pH 9	Potential PBT N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	Values at pH 5, 7 and 9 are < 4.5	not B
	BCF		not B
Persistence	log K_{ow}		not P
Toxicity	log K_{ow}		not T
PBT-statement:	The compound is not considered as PBT nor vPvB.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC surfacewater, Fpen refined based on prevalence of the indication, and treatment region	0.00049	µg/L	> 0.01 threshold N
Other concerns (e.g. chemical class)			N

Fruquintinib and its metabolites are considered of no immediate concern for the environment based on results of OCDE 107 study and PEC surface water calculation.

Results of GLP-compliant OCDE 107 study are presented to justify that fruquintinib is not considered to be a persistent, bioaccumulative and toxic (PBT) or a very persistent and very bioaccumulative (vPvB) substance.

To determine PEC surface water, if 0.01 is used as default value as mentioned in the current available guideline, the resulting value is above the action limit of 0.01 µg/L (0.025 µg/L). The applicant refined Fpen value based on prevalence values of CRC and posology. These data are acceptable and explained that the median duration of treatment in the fruquintinib arm was 3.7 months. Therefore, the PEC surface water used with the refined values is acceptable and below the action limits.

As fruquintinib has potentially toxic effect on fertility, it has the potential of acting as a sexual endocrine disrupting compound.

3.5.9. Discussion on non-clinical aspects

Primary pharmacodynamics

In vitro assays showed that fruquintinib was a broad TKI and primarily targets the VEGFR family receptors, VEGFR-1, -2, and -3 with IC_{50}s of 33 nM, 35 nM, and 0.5 nM, respectively. Therefore, the

substance is a broad TKI and primarily targets the VEGFR family receptors. The unbound C_{max} value of 34.3 nM at the clinical recommended human dose (5 mg once daily) is around or higher than IC_{50} values of VEGFR1, 2 and 3 and lower than other tested kinases IC_{50}. In cellular assays, only the inhibitory activity was confirmed on VEGFR2 phosphorylation (around 1 nM) and on proliferation of HUVECs (around 1 nM). Studies performed in vitro with cancer cell lines and ex vivo with chorioallantoic membrane model demonstrated that anti-angiogenic effect was responsible to the observed anti-tumor effect and that cytotoxic effect of fruquintinib was limited. Selectivity profiling of fruquintinib at 1 μM concentration against 264 kinases revealed more than 50% activity inhibition rate against 16 kinases. Fruquintinib showed ~80% inhibition of rearranged during transfection (RET) and fibroblast growth factor receptor (FGFR)-1 kinases, with IC50s of 128 and 181 nM, respectively. The 50% to 80% inhibition of platelet-derived growth factor receptor α (PDGFRα), FGFR2, c-kit (stem cell factor receptor), and FGFR3 was observed with IC50s of 601, 553, 458, and 738 nM, respectively. Thus, fruquintinib is at least 3-fold more selective for VEGFR1 and 2 over RET and FGFR1.

It is appreciated that sunitinib was used as a comparator in these studies. Sunitinib presented a lower selectivity on the kinase profile and presented cytotoxicity activity on cancer cell lines.

VEGF signalling through VEGFR2 has been established in the literature as the major angiogenic pathway, while VEGFR1 plays a secondary role (Dvorak 2002; Shalaby et al. 1995; Shibuya 2011). Pharmacodynamic studies thus focused on fruquintinib inhibition of VEGFR2. VEGFR3 has been shown to play a key role in lymphangiogenesis; however, the ability of fruquintinib to inhibit this biological process *in vivo* has not been investigated and only *in vitro* results are available. Fruquintinib effects on the immune system were observed in nonclinical species and their clinical relevance is reflected in the risk management plan (RMP). *In vivo* proof-of-concept was also sufficiently demonstrated xenografted mice models (colon, lung, kidney and gastric cancer model). Fruquintinib supressed tumour growth in a dose-dependent manner with an effect similar than sunitinib at the highest fruquintinib tested dose. In addition, tissues analysis collected from these models confirmed thought CD31 analysis, an angiogenesis marker, that the observed anti-tumour effect is mediated via an anti-angiogenesis mechanism of action.

Finally, lately in the development (2021), an additional assay of biochemical activity (2021-013-01) was performed to compare inhibitory activity of fruquintinib and its metabolite M11 on VEFGR2. M11 is 2-fold less potent than fruquintinib (M11: IC_{50} = 28 nM, fruquintinib: IC_{50} = 15 nM) and 10-fold less potent in cellular assays. The contribution of M11 to the PD activity appears negligible compared to the parent fruquintinib at the clinical C_{max} corrected with the protein binding affinity (M11 unbound C_{max} = 4.47 nM). M11 kinase activity on the VEGFR1 was shown to be 2.5-fold in comparison to fruquintinib and therefore not having meaningful contribution to the overall pharmacological activity of fruquintinib).

Safety pharmacology

In vitro safety pharmacology studies assessing the potential for delayed ventricular repolarization (i.e., hERG assay) was conducted with fruquintinib and its major human circulating metabolite (M11). Fruquintinib did not inhibit hERG channels, resulting in an IC_{50} value of >13.08 μM, based on the actual concentrations. IC_{50} for M11 was > 6.05 μM. These IC_{50} values are more than 380- and 1000-fold greater than the unbound human steady-state C_{max} at the proposed therapeutic dose of 5 mg daily of fruquintinib indicating a low potential for QTc prolongation. A wide range of percent human hERG current inhibition in the definitive assay with fruquintinib (ranging from -7.30 to +12.26% at 20 μM) and the exact cause for this variability is unknown. As a result, there was no concentration proportionality in hERG current inhibition (%). The inter-cell variations raise concerns of the calculated IC50 values. Precipitation was observed at 20 μM fruquintinib concentration in the non- GLP dose range-finding assay after 4 hours of preparation, but not in the GLP-compliant definitive hERG assay

within 2 hours after preparation; thus, this concentration was used as the high concentration in the definitive assay. In the definitive assay, no precipitate was observed at any concentration when used within 2 hours of preparation; therefore, there is no effect on the assay results. The nominal concentration of 20 µM resulted in a post-perfusion concentration of 13 µM. All of the working solution concentrations met the protocol-specified acceptance criteria. The post-perfusion concentration was used to conservatively calculate the IC50, to account for any nonspecific binding of the test article to the perfusion system.

A pivotal 13-week oral capsules toxicity and toxicokinetic study in beagle dogs with a 4-week recovery (study 8449374) in compliance with OECD GLP was conducted to bridge a previous cardiovascular and respiratory study in anesthetized beagle dogs following single oral gavage (Study 0849PH1) in compliance with NMPA GLP. No fruquintinib-related effects were noted on ECG measurements up to 0.12 mg/kg/day. However, the margins of exposure are very limited (0.4-0.9 for fruquintinib and 0.07-0.2 for M11). Nevertheless, the current clinical experience is sufficient to address the uncertainties raised by the limited margins of exposures and this issue need to be assessed in clinical safety with the current large clinical experience.

Effects on the central nervous system was assessed in a dedicated mice study (0849PB1 as non-GLP compliant. Fruquintinib had no effect on the motor activity, behavior, or coordination in this study. Similarly, the dedicated study to assess respiratory function (0849PH1) was declared as non-GLP compliant; fruquintinib had no effect on respiratory system. There is no observed effect in the repeated-dose toxicity studies, however, the exposures in animals in the entire non-clinical package are too limited to determine the clinical relevance. No further non-clinical data is requested.

Pharmacodynamic Drug Interactions

Studies were conducted to investigate the efficacy of fruquintinib alone, or in combination with molecular targeted therapies such as EGFR and cMET inhibitors, on tumour growth in xenograft models bearing various human tumours and with chemotherapeutic agents or an immune checkpoint inhibitor (anti-PD-L1 or anti-PD-1) on tumour growth in syngeneic models bearing murine tumour. A synergistic or additive antitumour effect was observed in these nonclinical tumour models.

Pharmacokinetics

The PK program is considered adequate; however, the planning of *in vivo* studies including species selection should have been more careful and only necessary *in vivo* studies should have been conducted in respect with 3R principles. Metabolite M11 was studied only in recent studies (2021).

The methods of analysis described in the dossier were considered adequate and suitable for the purpose.

In general, the PK studies performed for the present application are considered sufficient and support the oral route of administration. Fruquintinib is rapidly absorbed, mainly distributed in the metabolic and excretory organs (gastrointestinal tract, liver, and kidney) and into melanin-containing tissues. The most abundant metabolite of fruquintinib in human plasma was M11 (> 10% of the fruquintinib-derived total AUC), also called HM5025423 or M379-3. M11 is produced by O-demethylation and converted primarily from M10, with M10 production mediated by CYP3A4/5. Metabolite M11 was present at different levels across species: around 2% in rat, 6% in dog, 8% in guinea pig and 17% in humans. Rat was selected as a representative species for the *in vivo* study.

The majority of these tissues are listed as sites of very common adverse reactions in SmPC Section 4.8. Notably, fruquintinib showed distribution to melanin-containing tissues inducing a need for phototoxicity testing.

The safe use of fruquintinib during breast-feeding has not been established. It is not known whether fruquintinib or its metabolites are excreted in human milk. There are no animal data on the excretion of fruquintinib in animal milk. A risk to the breastfeeding newborns/infants cannot be excluded.

Breast-feeding should be discontinued during treatment and for 2 weeks after the last dose.

No effects on CYP metabolism were suggested but the concomitant P-gp and BCRP substrates may be affected by fruquintinib treatment. This interaction is described in SmPC section 4.5.

Fruquintinib was predominantly excreted *via* faeces.

Toxicokinetics

No interspecies comparison or safety margin calculations were presented. The safety margins (total AUC ratio) derived from the GLP-compliant 13-week rat and dog study NOAELs are 0.3 and 0.05, respectively. For the embryo-foetal development, the safety factor derived from the NOEAL is 0.02).

The data analysis suggests that the concomitant P-gp and BCRP substrates may be affected by fruquintinib treatment. This interaction is described in SmPC section 4.5.

Toxicology

The applicant presented a comparison of the Chinese GLP, OECD GLP and FDA GLP and submitted the audit report (Covance/LapCorp, 2020).

It is acknowledged that the test facility which performed the two 13-week studies and the one for phototoxicity and hERG studies were periodically and successfully inspected by the Belgium authorities; thus, these studies could therefore be considered as GLP compliant. All other single- or repeated-dose studies are claimed as non-GLP compliant. Given the indication was in the scope of ICH S9 guideline, the two 13-week GLP compliant studies could be considered as the only pivotal studies in the submitted non-clinical package.

The identified target organs of fruquintinib toxicity were liver, kidney, adrenal gland, thymus, spleen, bone marrow (sternum), and femur. NOAELs were low or could not be set, demonstrating high toxicity of fruquintinib.

Some questions and concerns raised from the newly performed GLP-compliant bridging studies (13-week rat and dog studies). The applicant discussed the differences in the exposure levels of the 13-week GLP-compliant study in rats and the older studies, explaining that the differences in the exposure levels between studies were estimated to be due to the inter-study variability with the rats used in these studies originating from different vendors. It is noticed that exposures achieved in the 13-week rat study were lower than in 4- and 26-week studies and could be the reason of not detecting the target organs. Overall, the toxicity profile determined in rat and dog in the non-GLP studies (4-week studies and 26 or 39-week studies with an intermediate 13-week analysis) appears affected a larger number of target organs than the one observed in GLP pivotal studies (two 13-week studies). The applicant discussed the discrepancy observed in terms of target organs between GLP and non-GLP studies and especially the toxicity profile determined after 13-week in dog in dedicated 13-week study and the one determined at the intermediate analysis at 13-weeks in chronic study, explaining that the differences in dog age and feeding during the studies may have affected on the sensitivity of the animals. Overall, it remains unclear why the dogs in the 13-week studies expressed different toxicity profile, as the exposure levels were considered similar between the studies. However, as the extended toxicity profile observed in the supportive Chinese studies reflects the known adversity of VEGFR-inhibitors, this issue is not argued further.

The applicant has discussed mechanisms of the toxicity observed in every target organ. Even though some mechanisms are not completely identified, it could be concluded that all toxicity observed are

related to the pharmacologic activity of the molecule. Therefore, the observed toxicity in animals is considered relevant for the treated patients. This is reflected in SmPC Section 5.3 and RMP PART II Module SII.

Carcinogenicity studies were not performed and are not required for pharmaceuticals intended for the treatment of advanced cancer (ICH S9).

In vitro genotoxicity studies did suggest that fruquintinib was non-genotoxic compound. The *in vivo* genotoxicity study in rats showed no increase in the exposure levels when dose was increased from 500 to 2000 mg/kg/day. no genotoxicity was recorded at approximately 28-fold exposure levels above the human AUC and 38-fold above the human C_{max}.

The non-clinical package demonstrated the absence of margins of fruquintinib exposure. Metabolite M11 was confirmed to be present in rat and dog 13-week studies but at lower levels (2% and 6 % respectively) than in human (17%). A GLP genotoxicity standard battery was performed with fruquintinib. Therefore, it could be concluded that no genotoxic potential was observed after exposures at clinical range.

Reproductive and developmental toxicity studies show high foetal toxicity, e.g., decreased number of live foetuses and severe external, visceral and skeletal abnormalities in foetuses. In the non-GLP fertility and early embryonic development study, there was a decrease in rat fertility at the high dose levels of 3 mg/kg (male) and 0.5 mg/kg (female). This is based on copulation and conception indices being outside of the historical control range and lower than those reported in other groups, including concurrent controls. This conclusion is implemented in the SmPC sections 4.6 and 5.3.

The absence of second species in the embryo-foetal development studies can be accepted as clearly positive results for the induction of malformations and embryo-foetal lethality was demonstrated after administration of low doses of fruquintinib in rat studies (ICH S9).

As regards early embryonic development, the doubling of the %preimplantation loss noted in that study at 0.5 mg/kg compared to concurrent controls is considered as treatment-related taking into consideration the apparent dose-related increase in preimplantation loss in the fertility study conducted with fruquintinib, the mean historical control value of 14.6% per litter for this parameter at the testing facility, as well as historical control data generated in other testing facilities. This conclusion is implemented in the SmPC sections 4.6 and 5.3.

The SmPC section 4.6 addresses the risk for severe foetal toxicity by setting a requirement for highly effective contraception use in woman of childbearing potential. The lack of safety margin for clinical exposure creates an uncertainty in regards with fertility effects induced by fruquintinib that is managed in the SmPC sections 4.6 and 5.3.

Local tolerance has not been studied or discussed based on the data collected from the repeat-dose toxicity studies in dogs (e.g., effects in oral mucosa of dogs). The observed oral and teeth effects were considered to be class effect VEGFR inhibitors. The risk of stomatitis and oral pain in clinical settings is identified in the SmPC section 4.8.

As fruquintinib was shown to be distributed to melanin-containing tissues such as eye, uveal tract and pigmented skin, a phototoxicity study was conducted. No phototoxicity in skin was reported, however, the eye phototoxicity was not investigated as fruquintinib data shows maximum absorbance below 400 nm. The performance of the *in vivo* phototoxicity study was questionable given the already collected large clinical data at this time (FRESCO).

ERA

Fruquintinib (and its metabolites) is not a PBT substance and there is no immediate concern for the environment based on results of OCDE 107 study and PEC surface water calculation. However, to confirm the Applicant's conclusion, more information was required during the assessment.

The applicant presented results of GLP-compliant OCDE 107 study to justify that fruquintinib is not considered to be a persistent, bioaccumulative and toxic (PBT) or a very persistent and very bioaccumulative (vPvB) substance.

To determine PEC surface water, if 0.01 is used as default value as mentioned in the current available guideline, the resulting value is above the action limit of 0.01 µg/L (0.025 µg/L). The applicant refined Fpen value based on prevalence values of CRC and posology. These data are acceptable and explained that the median duration of treatment in the fruquintinib arm was 3.7 months. Therefore, the PEC surface water used with the refined values is acceptable and below the action limits.

As fruquintinib has potentially toxic effect on fertility, it has the potential of acting as a sexual endocrine disrupting compound.

3.5.10. Conclusion on the non-clinical aspects

The non-clinical data submitted support this application.

3.6. Clinical aspects

3.6.4. Introduction

GCP aspects

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 6: List of all clinical trials with fruquintinib

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Healthy Subjects or Diagnosis of Patients	Countries Involved
Bioavailability (BA) Studies					
Pharmacology; Phase 1	2012-013-00CH2	PK and safety (Food Effect)	Randomised, single-centre, open-label, single-dose, 2-Cycle, Crossover	Healthy Chinese male subjects	China
Pharmacology; Phase 1	2020-013-00US1	PK and safety (Food effect and DDI)	Open-label, randomised, 3-Period, 2-Sequence	Healthy subjects	USA
Comparative BA and Bioequivalence (BE) Studies					
Pharmacology; Phase 1	2013-013-00CH2	PK and safety	Randomised single-centre, open-label, single-dose, 2-Period, Crossover	Healthy Chinese male	China
Pharmacology; Phase 1	2014-013-00CH5	PK and safety	Randomised single-centre, open-label, single-dose, 2-Period, Crossover	Healthy Chinese male	China

Healthy Subject PK and Initial Tolerability Studies					
Pharmacology; Phase 1	2015-013-00CH2	PK and safety (ADME)	Single-centre, open-label, single-dose	Healthy Chinese male	China
Patient PK and Initial Tolerability Studies					
Monotherapy; Phase 1	2009-013-00CH1	Safety, PK, and preliminary efficacy	Single-centre, open-label, dose-escalation	Patients with malignant solid tumour for whom either standard therapy had proven ineffective or standard systemic therapy did not exist.	China
Monotherapy; Phase 1/1b	2015-013-00US1	Safety, PK, and preliminary efficacy	Multi-centre, open-label	Dose Escalation: patients with advanced solid tumours Expansion: patients with advanced solid tumours (Cohort A), with refractory mCRC (Cohorts B and C), and with metastatic breast cancer (Cohorts D and E).	USA
Intrinsic Factor PK Studies					
Pharmacology; Phase 1	2021-013-00US1	PK and safety	Open-label, single-centre	Subjects without cancer who have moderate or mild (if enrolled) hepatic impairment and healthy subjects with normal hepatic function	USA
Pharmacology; Phase 1	2021-013-00US2	PK and safety	Open-label, single-centre	Subjects without cancer who have moderate or severe renal impairment and healthy subjects with normal renal function	USA
Extrinsic Factor PK Studies					
Pharmacology; Phase 1	2020-013-00US2	PK and safety (DDI)	Single-centre, open-label, 2-Part, 2-Period fixed sequence crossover	Healthy subjects	USA
Pharmacology; Phase 1	2021-013-00US3	PK and safety (DDI)	Open-label, 2-part, 2-period fixed sequence	Healthy subjects	USA
Controlled Clinical Studies pertinent to the claimed indication					
Monotherapy, Phase 3	2019-013-GLOB1/ FRESCO-2	Efficacy, safety, and PK	Randomised, double-blind, placebo-controlled, multicentre	refractory mCRC	Australia, Austria, Belgium, Czech Republic, Estonia, France, Germany, Hungary, Italy, Japan, Poland, Spain, United Kingdom, USA
Monotherapy, Phase 3	2013-013-00CH1/ FRESCO	Efficacy and safety	Randomised, double-blind, placebo-controlled, multicentre	advanced CRC who had progressed after 2nd-line and above standard chemotherapy	China

Monotherapy, Phase 2	2012-013-00CH1	Efficacy and safety	Randomised, double-blind, placebo-controlled, multicentre	advanced CRC who had progressed with 2 or more lines of standard chemotherapy	China
Monotherapy, Phase 2	2014-013-00CH1	Efficacy and safety	Randomised, double-blind, placebo-controlled, multicentre	advanced non-squamous NSCLC who had progressed after 2nd-line standard chemotherapy	China
Monotherapy, Phase 3	2015-013-00CH1/FALUCA	Efficacy and safety	Randomised, double-blind, placebo-controlled, multicentre	advanced non-squamous NSCLC who had progressed after second-line standard chemotherapy	China
Uncontrolled Clinical Studies					
Monotherapy, Phase 1b	2012-013-00CH3	Safety, PK, and preliminary efficacy	Open-label, 2 centre	advanced CRC who had failed 2 lines or more of standard chemotherapy.	China
Combination therapy, Phase 1b/2	2014-013-00CH3	Safety, PK, and preliminary efficacy	Open-label, multicentre, dose escalation, dose expansion	Advanced gastric cancer	China
Combination therapy, Phase 2	2016-013-00CH1	Efficacy, safety	Open-label, single-arm, 2-centre,	Non-squamous NSCLC with EGFR-sensitizing mutations	China
Combination therapy, Phase 1b/2	2018-013-00CH3	Efficacy, safety	Open-label, dose escalation, dose expansion	Dose Escalation: Various cancers Dose Expansion: mCRC	China
Combination therapy, Phase 1b/2	2020-013-00US3	Efficacy, safety	Open-label, safety lead-in, dose expansion	Advanced or metastatic colorectal cancer, triple negative breast cancer or endometrial cancer	USA
Studies shown for clarity but no clinical reports included in the MAA					
Combination therapy, Phase 2/3	2022-013-00CH1	Efficacy, safety, PK	Randomised, active- controlled, open-label, multicentre	Advanced renal cell carcinoma	China
Combination therapy; Phase 3	2017-013-00CH1 (FRUTIGA)	Efficacy and safety	Randomised, double-blind, placebo-controlled, multicentre	advanced gastric cancer (as 2nd-line therapy)	China
Post marketing surveillance (Non-interventional); Phase 4	2018-013- 00CH2	Safety	Multicentre, double cohort	Advanced CRC who had failed at least 2 lines of standard systemic therapies (Cohort 1) or other indications suitable for treatment according to investigator judgment (Cohort 2)	China

3.6.5. Clinical pharmacology

3.6.5.1. Pharmacokinetics

Pharmacokinetics of fruquintinib has been investigated in 13 clinical studies:

- 5 clinical pharmacology studies in healthy subjects (mass balance, drug-drug interactions (DDI) with strong CYP3A inhibitor and inducer, DDI with P-gp and BCRP substrates, hepatic and renal impairment studies)
- 4 biopharmaceutic studies (dose escalation and food effect study, 2 bioequivalence studies, food effect and DDI with PPI)

- 4 studies in patients with metastatic colorectal cancer, mCRC (phase 1 and phase 3 studies in China and US)

In addition, 11 studies without PK (studies with other cancers or combination studies) have been conducted.

Table 7: Clinical Studies and Analyses Relevant to Fruquintinib Clinical Pharmacology

Type of Study	Study Number	Description	Population	Dose
Single-Dose PK	2012-013-00CH2	PK and food effect	Healthy	PK: fruquintinib 2, 3, or 4 mg single dose Food effect: fruquintinib 4 mg single dose
	2013-013-00CH2	Bioequivalence (manufacturers change)	Healthy	Fruquintinib 5 mg single dose
	2014-013-00CH5	Bioequivalence (manufacturers change)	Healthy	Fruquintinib 5 mg single dose
	2015-013-00CH2	Mass balance	Healthy	5 mg/100 µCi [^{14}C]fruquintinib single dose
	2020-013-00US1	Food effect	Healthy	Fruquintinib 5 mg single dose
Multiple-Dose PK	2009-013-00CH1	Safety, tolerability, efficacy, and PK	Patient	Fruquintinib 1, 2, 4, 5, or 6 mg single dose Fruquintinib 1, 2, 4, 5, or 6 mg QD (continuous) Fruquintinib 5 or 6 mg QD 3/1
	2012-013-00CH3	Safety, tolerability, efficacy, and PK	Patient	Fruquintinib 4 mg QD (continuous) Fruquintinib 5 mg QD 3/1
	2015-013-00US1	Safety, tolerability, efficacy, and PK	Patient	Fruquintinib 3 and 5 mg QD 3/1
	2019-013-GLOB1	Efficacy, safety, tolerability, and PK	Patient	Fruquintinib 5 mg QD 3/1
DDI - Victim	2020-013-00US1	DDI with PPI	Healthy	Fruquintinib 5 mg single dose Rabeprazole 40 mg QD
	2020-013-00US2	DDI with itraconazole (CYP3A4 inhibitor) and rifampin (CYP3A4 inducer)	Healthy	Fruquintinib 5 mg single dose Itraconazole 200 mg twice a day Rifampin 600 mg QD
DDI - Perpetrator	2021-013-00US3	DDI with dabigatran (P-gp substrate) and rosuvastatin (BCRP substrate)	Healthy	Fruquintinib 5 mg single dose Dabigatran 150 mg single dose Rosuvastatin 10 mg single dose
Specific Population	2021-013-00US1	HI (moderate) versus normal hepatic function	Healthy and HI	Fruquintinib 2 mg single dose (moderate HI) Fruquintinib 5 mg single dose (normal)
	2021-013-00US2	RI (severe, moderate) versus normal renal function	Healthy and RI	Fruquintinib 2 mg single dose (severe RI) Fruquintinib 5 mg single dose (moderate RI and normal)
Cardiovascular safety	HMPI-PMX-FRUQ-2785-QTc	Effect on ECG, fruquintinib concentration-QTc relationship	Patient	Fruquintinib 5 mg QD 3/1

Analytical methods

Fruquintinib was quantitated in human plasma by two validated protein precipitation - LC-MS/MS methods. The methods were fully validated at Covance China. The initial method HMPHPP was used in the early phase of clinical studies to measure the concentrations of fruquintinib and metabolites M2 and M7. The second method (HM13HPP) was used for quantification of fruquintinib and metabolites M9 and M11 in the majority of clinical studies. This method was transferred to Covance US and

successful partial validation was performed. Comparability of the results between two sites (Covance Indianapolis and Covance Shanghai) were demonstrated with cross-validation.

Fruquintinib and its metabolites were quantitated in human urine and faeces by validated protein precipitation - LC-MS/MS methods.

A non-labelled structural analogue of fruquintinib, CMB, was used as internal standard. CMB has similar physical-chemical properties as fruquintinib and comparable matrix factor and close retention times.

Absorption

After oral administration of fruquintinib, the median time to achieve peak plasma fruquintinib concentration (T_{max}) was approximately 2 hours. Fruquintinib showed a second absorption peak approximately 24 hours after drug administration. Absolute bioavailability has not been evaluated in humans but at least 60 % of the drug dose is absorbed based on the percent of radioactivity excreted in urine (Study 2015-013-00CH2). Following repeat once-daily dosing, fruquintinib exposure (C_{max} and AUC_{0-24h}) increased in a dose-proportional manner across the dose range of 1 to 6 mg (0.2 to 1.2 times the recommended dosage). Following administration of fruquintinib 5 mg once daily for 21 days with 7 days off of each 28-day cycle in patients with advanced solid tumours, steady state of fruquintinib was achieved after 14 days, and the mean accumulation based on AUC_{0-24h} was 4-fold relative to a single dose. At the recommended dose of 5 mg of fruquintinib, the geometric mean (%CV) C_{max} and AUC_{0-24h} for fruquintinib at steady state were 300 ng/mL (28%) and 5880 ng*h/mL (29%), respectively.

Food effect on pharmacokinetics of fruquintinib was studied in two clinical trials after single dose of Fruquintinib 4 mg or 5 mg (Studies 2012-013-CH2 and 2020-013-00US1, respectively). Concomitant high-fat meal slightly decreased C_{max} of fruquintinib by 17% but not AUC when compared to administration in the fasted state after 4 mg of fruquintinib, with median T_{max} delayed by 1 hour. Food intake had no clinically significant effect on the exposure of fruquintinib and metabolite M11 following a single 5 mg dose of fruquintinib.

Bioequivalence of fruquintinib manufactured at three different manufacturing sites was investigated in two clinical studies (Studies 2012-013-CH002 & 2014-013-00CH05). The 90 % confidence intervals were within the prespecified acceptance range 80-125 % for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ in both studies.

Distribution

Fruquintinib was approximately 95 % bound to human plasma proteins in vitro and binding is not concentration dependent. Fruquintinib is mainly bound to human serum albumin. Binding of the active metabolite M11 to plasma proteins was 97.7 %. Mean whole blood-to-plasma ratios ranged from 0.41 to 0.81, suggesting no significant binding to cellular components.

The volume of distribution of fruquintinib was 44.0 L in healthy subjects. The PopPK model-predicted Vz/F at steady state for a 70-kg patient with cancer was estimated as 48.5 L.

Elimination

Excretion and metabolism were studied after giving radiolabelled fruquintinib to healthy subjects (n=6). A single dose of 5 mg/100 µCi [14C]fruquintinib was given to investigate absorption and excretion of fruquintinib and to identify chemical structures of the main metabolites in plasma, urine and faeces. (Study 2015-013-00CH2)

Radioactive fruquintinib was absorbed rapidly with a median t_{max} of 2 hours in plasma and blood. Systemic exposure to radioactivity in blood was approximately 0.6-fold (range 0.41-0.81) of that in plasma, based on mean C_{max} and AUC_{∞} values indicating limited distribution of fruquintinib and/or its metabolite into blood cells.

In plasma, unchanged [14C]fruquintinib was the major circulating radioactive component average accounting for 72.48% of the total radioactivity. C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ values of fruquintinib in plasma were lower than that of the total radioactivity indicating the presence of metabolites of plasma. Totally 8 different metabolites were discovered from plasma. The circulating metabolite M11 accounted for > 10% of the exposure level of fruquintinib in plasma whereas M9 accounted for 2.6% of its parent drug and the amount of metabolite M409 was 4.46 % of total AUC. All other metabolites accounted for less than 1.5 % of total AUC.

The mean arithmetic half-life of fruquintinib was about 33 hours and about 51 hours for the circulating metabolite M11 after a single dose of 5 mg/100 µCi of [14C]fruquintinib to healthy subjects.

Total recovery of [14C]fruquintinib was approximately 90.1% of the radioactive dose. About 60 % of the dose was excreted in urine and about 30 % in faeces. Unchanged drug was the minor component detected in excreta, accounting on average for 5.34 % and 0.5% of the dose in faeces and urine, respectively.

Biotransformation pathways of fruquintinib include mono-oxidation and di-oxidation, N- or O-demethylation, O-dequinazoline moiety, amide bond hydrolysis, glucuronidation, and sulfation. Glucuronidation and sulfation were the main phase II metabolic pathways observed. Twenty-two metabolites were identified as part of the in vivo study 2015-013-00ch2. No-human specific metabolites were detected.

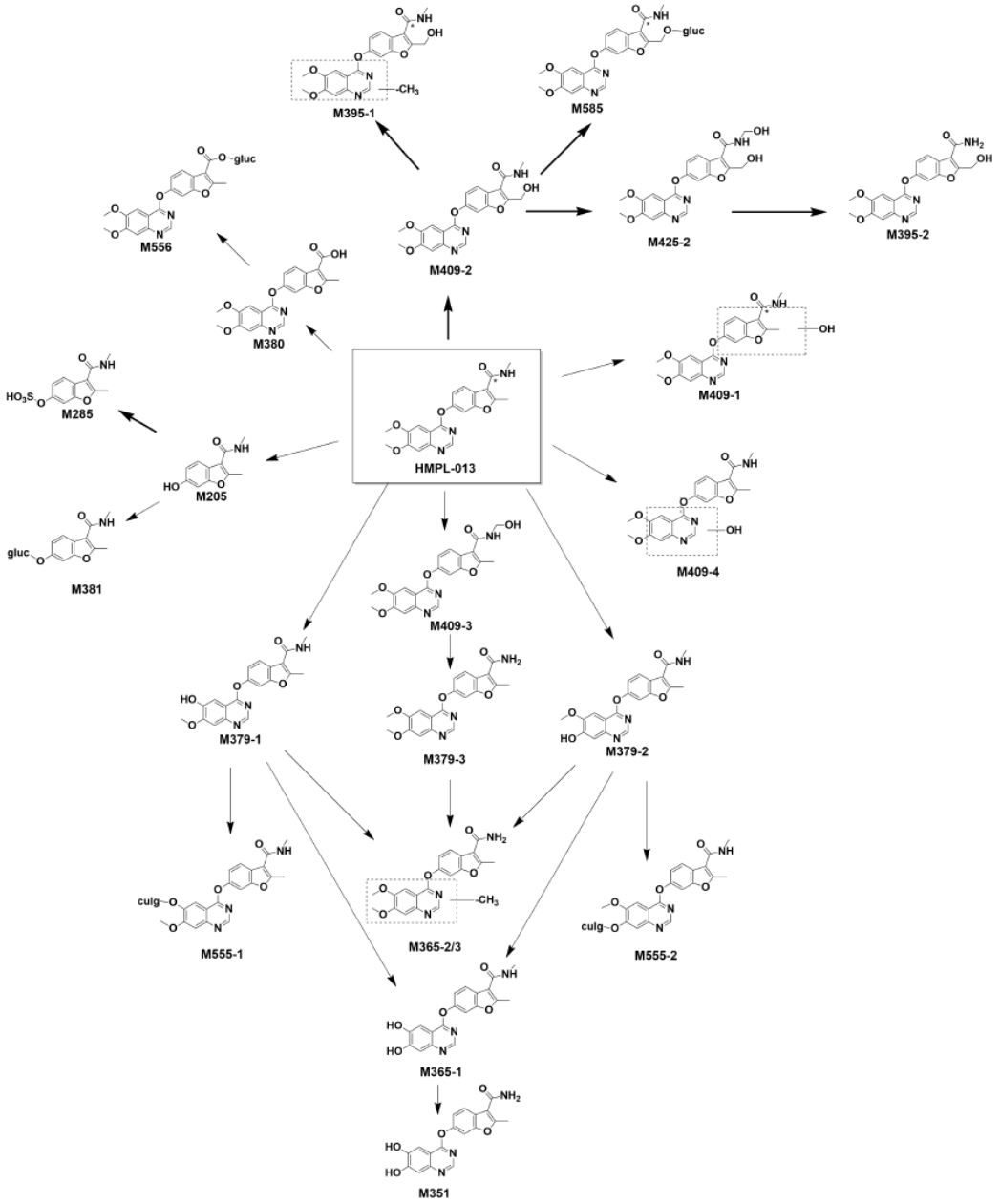


Figure 5. Possible Metabolite Pathways of Fruquintinib in Humans (Study 2015-013-00CH2)

Unchanged [14C]fruquintinib was a minor radioactive component in urine samples, average accounting for 0.50% of the dose. Three major metabolites in urine, M285, M381 and M409-4, accounted for 10.48%, 21.16% and 8.92% of the dose, respectively.

Unchanged [14C]fruquintinib accounted for 5.34% of the dose. Three major metabolites in faeces, M205, M365-2 and M380, accounted for 2.29%, 3.30% and 2.59% of the dose, respectively.

In several studies where rich PK sampling was performed (Studies 2012-013-00ch2, 2015-013-00ch2, 2020-013-00us1) a clear rebound of fruquintinib concentrations occurred approximately at 24h post-dose. The reason for the second peak is unknown.

Dose proportionality and time dependencies

The PK parameters C_{max}, AUC_{0-t} and AUC_{0-inf} of fruquintinib increased proportionally after single dose of 2 mg, 3 mg and 4 mg of fruquintinib in healthy subjects (Study 2012-013-00CH2). Plasma fruquintinib exposure also increased linearly in patients with cancer over the tested dose range of 1 to 6 mg after

single dose and linearity was also noticed after continuous dosing with doses 1 to 6 mg QD (Study 2009-013-00CH1). Dose proportionality was also observed in Study 2015-013-00US1 where patients with cancer received multiple doses of fruquintinib 3 and 5 mg QD 3/1.

Fruquintinib CL/F following a single dose of fruquintinib was similar to that after multiple doses indicating the PK of fruquintinib is independent of time. In Study 2009-013-00CH1, fruquintinib CL/F following a single dose of 4 mg was 12.8 mL/min after the first dose while apparent clearance at steady state (CLSS/F) values after multiple doses of 4 mg QD were 13.4 mL/min (C1D14) and 13.5 mL/min (C1D28).

Special populations

Elderly

Age was not found to be a predictor of fruquintinib PK within the population PK model. The following table summarises the number of elderly subjects with PK data available.

Table 8: PK data on elderly

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
PK Trials	175/557	33/557	0/557

Disease State

PK of fruquintinib has been investigated in four clinical studies in patients with cancer.

In the first study performed in China (2009-013-CH1) dose escalating of fruquintinib 1 mg, 2 mg, 4 mg, 5 mg and 6 mg was studied to determine the maximum tolerated dose (MTD) and in the second part of the study the study was expanded and explored another dosage regimen (3/1) at 5- and 6-mg QD. Fruquintinib was rapidly absorbed after a single oral administration with detectable drug concentration in plasma at 0.5-hour postdose and reached T_{max} at 2.5 hours. Fruquintinib exposure increased linearly with dose over the studied dose range of 1 to 6 mg.

Similar fruquintinib exposure (C_{min}, C_{max}, and AUC from time 0 to 24 hours [AUC_{0-24}]) was observed between Days 14 and 28 indicating fruquintinib concentration reached steady state after 14 days of continuous QD dosing. M11 concentrations were not investigated in this study 2009-013-00CH1 performed in the early state of development.

In study 2012-013-00CH3 the patients were randomised into the fruquintinib 4 mg QD continuous dosing group (n=20) or the fruquintinib 5 mg QD 3/1 group in the randomised comparison stage (n=20). In addition, another 22 Chinese patients were recruited to the 5 mg QD 3-week on/ 1-week off group in the expansion stage. Following continuous dosing of fruquintinib 4 mg QD, plasma fruquintinib concentration reached steady state by 14 days after dosing. Fruquintinib exposure accumulated by 2- to 4-fold after multiple dosing. The mean steady-state plasma exposure level was slightly higher in the fruquintinib 5 mg QD 3/1 group (AUC_{0-24}: 5889 h•ng/mL) than the fruquintinib 4 mg QD continuous group (AUC_{0-24}: 5584 h•ng/mL). Fruquintinib was almost completely eliminated after 1 week of drug discontinuation, which is expected as half-life of fruquintinib has been estimated to be about 42 hours in patients. The amount of fruquintinib (~17 ng/ml) remained in plasma accounted for approximately 5% of C_{max} on the last day of the 1-week drug discontinuation period. M11 concentrations were not investigated in the study.

Fruquintinib 3 mg (dose-escalation phase) or 5 mg (dose-escalation and dose-expansion phases) was administered QD for 3 on/1 off for every 28-day treatment cycle in a multicenter study in patients with

advanced solid tumors (2015-013-00US1). 14 patients were enrolled in the dose-escalation phase (7 patients at 3 mg dose level and 7 patients at 5 mg dose level) and 87 patients were enrolled in the dose-expansion phase. Steady state concentrations of fruquintinib were reached on 14 days of treatment after continuous dosing of 3 or 5 mg QD. With repeated QD dosing to steady state, fruquintinib mean accumulation ratio was approximately 4.1-fold for AUC_{0-24} and 3.4-fold for C_{max}. Daily fluctuations in fruquintinib plasma concentrations were low, with a peak-to-trough ratio of approximately 1.5. The pharmacokinetic parameters AUC and C_{max} for fruquintinib increased dose-proportionally as seen in the dose-normalized PK values. PK parameters clearance (11.1-17.5 ml/min) and effective half-life (55.5-65.0 hrs) were similar at different dose-levels and on different treatment days. Although the accumulation ratio of the metabolite M11 is large being 31, accumulation across multiple cycles is not expected due to one-week drug holiday. This was confirmed by simulations from a population PK model. For both fruquintinib and M11, model-predicted Cycle 1 and steady-state C_{max}ss and C_{min}ss were essentially the same for the QD 3/1 regimen.

In a global, multicenter, randomised, placebo-controlled, double-blind Phase 3 trial FRESCO-2 (2019-013-GLOB1) the patients were randomised in a 2:1 ratio to either 5 mg fruquintinib plus BSC treatment group or placebo plus BSC treatment group. Samples for fruquintinib and metabolite M11 were collected at pre-specified time-points from different cycles and the PK data from this study were included in the PopPK analysis report HMPI-PMX-FRUQ-2785-PPKER.

The PopPK analysis reported a 9.08% lower in the typical value of Vz/F of fruquintinib in healthy subjects as compared to patients with cancer. This small difference is unlikely to result in any meaningful difference in fruquintinib exposure between the 2 populations.

Sex

No dedicated clinical study evaluating the effect of sex on the PK of fruquintinib has been conducted. In the PopPK analysis, a statistically significant sex effect on the clearance of fruquintinib and clearance of M11 was identified, with females having 17% lower parent and metabolite clearance than males, independent of bodyweight.

Body Weight

No dedicated clinical study evaluating the effect of body weight on the PK of fruquintinib has been conducted. The results from PopPK indicated that body weight was a significant covariate on fruquintinib and M11 PK, with fruquintinib and M11 clearances and volumes of distribution increasing with increasing body weight. However, the predicted fruquintinib exposure at steady state was < 20% difference between patients at 48 kg or 108 kg as compared to a 70-kg patient. The predicted M11 exposure at steady state was < 50% difference between patients at 48 kg or 108 kg as compared to a 70-kg patient, and M11 is not found to have significant relationship with any AEs based on the safety E-R analysis.

Hepatic Impairment

Fruquintinib is metabolised primarily via the hepatic route, with less than 6% of the administered dose recovered as unchanged drug in urine and faeces (Study 2015-013-00CH2). In the PopPK analysis, no statistically significant effects on the PK of fruquintinib or M11 were identified for mild HI (based on NCI ODWG) (data not shown). A dedicated PK study is being conducted to evaluate the effect of moderate HI (ChildPugh-Class B) on the PK of fruquintinib following administration of a single oral dose of fruquintinib in subjects who do not have cancer (2021-013-00US1). The PK results indicated no clinically significant difference in exposure to fruquintinib and M11 in subjects with moderate HI compared to historical data in healthy subjects.

The effect of severe HI on the PK of fruquintinib will not be studied because it is unlikely that patients with mCRC, who have severe HI, will be able to tolerate the hepatic function abnormal AEs that are sometimes seen after multiple doses of fruquintinib.

Renal Impairment

Fruquintinib is extensively metabolised in the liver and eliminated mainly by renal clearance, with a lesser contribution by biliary excretion into faeces. Results from a mass balance study (2015-013-00CH2) indicated that approximately 60% of the administered dose was excreted renally in the form of metabolites. A dedicated PK study was conducted to investigate the PK of fruquintinib in subjects with moderate (CLCR: 30 to 59 mL/min) or severe (CLCR: 15 to 29 mL/min) RI (2021-013-00US2). The PK results indicated that exposures to fruquintinib in subjects with moderate (N = 8) or severe (N = 8) RI were similar compared to subjects with normal renal function when dose normalised to 5 mg (data not shown). The geometric mean ratio (GMR) of subjects with severe renal impairment to normal renal function for Cmax, AUC0-t and AUC0-inf were 0.89, 0.97 and 1.01, respectively. In patients with moderate impaired renal function the GMR ratio for Cmax, AUC0-t and AUC0-inf was 0.95, 1.06 and 1.07, respectively. The 90 % CIs contained unity for Cmax, AUC0-t and AUC0-inf for both subjects with severe and moderate impairment. Total plasma clearance of fruquintinib after extravascular administration (CL/F) was comparable in subjects with severe renal impairment (15.0 ml/min) and in subjects with moderate renal impairment (14.2 ml/min) versus in subjects with normal renal function (15.0 ml/min). The exposure parameters of M11 C_{max}, AUC_{0-t} and AUC_{inf} were lower in subjects with moderate and severe renal impairment compared to subjects with normal renal function when dose normalized to 5 mg. In the PopPK analysis, no statistically significant effects on the PK of fruquintinib or M11 were identified for mild or moderate RI (CLCR from 32.6 to < 90 mL/min). The effects of end-stage-renal disease or hemodialysis on the PK of fruquintinib and M11 have not been studied.

Race and Ethnicity

No dedicated clinical study evaluating the effect of race on the PK of fruquintinib has been conducted. In general, fruquintinib exposures appear similar between Western and Chinese patients. In the PopPK analysis, no statistically significant effects on the PK of fruquintinib or M11 were identified for race (White, Black, Asian, and other races) and country (Japanese versus Chinese versus rest of the world). Similarly, no statistically significant effects on the PK of fruquintinib or M11 were identified for ethnicity (Hispanic/Latino versus non-Hispanic/Latino) (data not shown).

Genetic Differences

The effects of genetic polymorphism on the PK of fruquintinib have not been evaluated. Fruquintinib is metabolised via multiple metabolic reactions, including mono-oxidation and di-oxidation, N- or O-demethylation, O-dequinazoline moiety, amide bond hydrolysis, glucuronidation, and sulfation, mediated by CYP enzymes, non-CYP enzymes and phase 2 enzymes. CYP3A4 is the main CYP involved in producing the major metabolite M11. To date, no major pharmacogenetic differences in CYP3A4 variants have been identified. Low expression of CYP3A4 protein associated with the CYP3A4*22 allele has been reported, suggesting that the CYP3A4*22 allele may play a role in the individual differences in drug clearance mediated by CYP3A4. Clinically, the association between CYP3A4*22 mutation and decreased activity of CYP3A4 has been reported, and a lower dose of medications that are sensitive substrates of CYP3A4 (eg, statin or tacrolimus) may be needed. However, a rather low frequency of CYP3A4*22 mutation (global minor allele frequency of 2.1%; 5% in Caucasians, and 0% in Asians) limits broader contribution to overall CYP3A variability.

Pharmacokinetic interaction studies

Acid-reducing agents

Fruquintinib exhibits pH-dependent solubility in aqueous media. Acid-reducing agents such as a PPI, H2-antagonist, or antacid may affect the solubility and absorption of fruquintinib. Results from a clinical study showed that coadministration of a single dose of fruquintinib 5 mg with rabeprazole, a PPI, resulted in similar exposure of fruquintinib and its major metabolite M11 compared to fruquintinib alone (2020-013-00US1) (data not shown).

Effect of CYP3A inhibition on fruquintinib PK

In vitro results indicated that fruquintinib can be metabolised by several metabolic enzymes. CYP3A4 is the main CYP contributing to the metabolism of fruquintinib. Its major metabolite M11 is likely produced by CYP3A4 (DMPKR20160003-E-01). Therefore, strong inhibitors of CYP3A may have a potentially clinically relevant effect on the PK of fruquintinib.

Results from a clinical study showed that coadministration with itraconazole, a strong CYP3A inhibitor, did not affect the systemic exposure of fruquintinib and decreased the systemic exposure of the M11 metabolite by approximately half, following a single dose of fruquintinib 5 mg (2020-013-00US2) (data not shown). The inhibition of CYP3A4 activity by itraconazole decreased the M11 exposure but had limited effect on the systemic exposure of the parent drug. The decrease in M11 metabolite exposure with coadministration of itraconazole is in line with the formation of M11 being mediated by CYP3A4. Since M11 has no clinically meaningful contribution to the total pharmacological activity of fruquintinib, DDI between fruquintinib and itraconazole is not deemed clinically significant. The results of this study also suggested that CYP3A is not the only major metabolic enzyme contributing to the metabolism of fruquintinib.

A PBPK model was used to predict the likely outcomes of interaction of fruquintinib with steady-state itraconazole (strong CYP3A4 inhibitor), fluconazole and erythromycin (moderate CYP3A4 inhibitors), cimetidine (weak CYP3A4 inhibitor), rifampin (strong CYP3A4 inducer), efavirenz (moderate CYP3A4 inducer), and dexamethasone (weak CYP3A4 inducer) administered with a single 5 mg dose in patients with cancer indicated changes in fruquintinib and M11 exposure.

The PBPK model was used prospectively to simulate the extent of the DDI between fruquintinib with sensitive P-gp probe substrate digoxin and sensitive BCRP probe substrate rosuvastatin during daily administration of 5 mg fruquintinib to steady state. All simulations were performed under steady-state conditions. No clinically significant DDIs were predicted following administration of multiple doses of 5 mg QD fruquintinib with sensitive P-gp probe substrate digoxin, the simulated AUCinf and Cmax ratios of digoxin with and without administration of fruquintinib were < 1.25-fold under simulated steady-state conditions for fruquintinib (data not shown). No clinically significant DDIs were predicted for fruquintinib and M11 effect on sensitive BCRP probe rosuvastatin AUCinf, following administration of multiple doses of 5 mg QD fruquintinib. Specifically, the simulated AUCinf ratio of rosuvastatin with and without administration of fruquintinib was < 1.25-fold under simulated steady-state conditions for fruquintinib. However, a potential for a weak interaction (Cmax GMR $\geq$ 1.25-fold to < 2.00-fold) was predicted based on the simulated change in rosuvastatin Cmax.

Effect of CYP3A induction on fruquintinib PK

As fruquintinib is metabolised by CYP3A, the potential of a strong inducer of CYP3A to affect the PK of fruquintinib cannot be excluded.

Results from a clinical study showed that coadministration with rifampin, a strong CYP3A inducer, had no significant effect on Cmax of fruquintinib but decreased the extent of systemic exposure substantially by 65% based on AUC following a single dose of fruquintinib 5 mg (2020-013-00US2).

Coadministration with rifampin had a marginal effect on the AUCs of M11 metabolite but increased Cmax by 2.3-fold. The effects of rifampin on the PK of fruquintinib and M11 are possibly due to several factors. Rifampin is a strong inducer of CYP3A and moderate inducer of CYP2C9, both of which are involved in the metabolism of fruquintinib. Therefore, induction of these CYP enzymes by rifampin resulted in a significant increase in the overall clearance of fruquintinib. The minimal change in AUC of M11 may represent the net effect of increased formation and elimination rate of M11 that both processes were inducible by rifampin.

Because a significant interaction with a strong CYP3A inducer was observed, PBPK modelling was used to predict the effects of moderate and weak CYP3A inducers. Based on this PBPK analysis, efavirenz (a moderate CYP3A inducer) and dexamethasone (a weak CYP3A inducer) were predicted to decrease fruquintinib AUC by approximately 28% and 9%, respectively, but have no impact on fruquintinib Cmax.

To compensate for the effect on fruquintinib PK due to enzyme induction, the dose of fruquintinib should theoretically be increased to 14 mg QD 3/1 when used concomitantly with a strong CYP3A inducer or to 7 mg QD 3/1 with a moderate CYP3A inducer. However, fruquintinib was evaluated up to 6 mg (QD continuous and QD 3/1) in Chinese patients (2009-013-00CH1) and up to 5 mg QD 3/1 in Western patients (2015-013-00US1); no PK, safety and efficacy data are available at doses > 6 mg QD 3/1.

Effect of fruquintinib on the pharmacokinetics of P-gp and BCRP substrates

Based on in vitro data, fruquintinib inhibited P-gp and BCRP-mediated efflux with in vitro IC50 values of 4.6 and 1.3 μM, respectively. The maximum expected concentration in the intestinal lumen on the apical side of the enterocytes (Igut) was 50.8 μM at a dose of 5 mg. The IC50 values for P-gp and BCRP were lower than the 0.1*Igut cutoff value according to the EMA Guideline on the Investigation of Drug Interactions, therefore the likelihood of a clinically relevant interaction with P-gp or BCRP substrate cannot be excluded.

Results from a clinical study showed that coadministration of a single dose of 5 mg fruquintinib with dabigatran etexilate, a P-gp substrate, or rosuvastatin, a BCRP substrate, resulted in no clinically relevant changes in the systemic exposure of dabigatran or rosuvastatin (2021-013-00US3). A PBPK model was developed to further evaluate the effects on P-gp and BCRP substrates after repeat dosing of 5 mg fruquintinib to steady state. Based on PBPK analysis, fruquintinib was predicted to increase the exposure of digoxin, a P-gp substrate, by approximately 7% for Cmax and 6% for AUCinf, and increase the exposure of rosuvastatin by approximately 28% for Cmax and 19% for AUCinf.

In the multiregional Phase 3 clinical study of fruquintinib in patients with mCRC (FRESCO-2), the protocol stipulated that patients should avoid concomitant use of medications that are sensitive substrates of P-gp or BCRP where possible. If the use of these concomitant medications could not be avoided for medical reasons, the Investigator was advised to monitor the patient more frequently for adverse reactions associated with the P-gp or BCRP substrate and consider dose reduction of the P-gp or BCRP substrate medication. A review of concomitant medication use in 2 Phase 3 studies showed there was minimal usage of medications that are sensitive substrates of P-gp or BCRP in patients with mCRC. Sensitive P-gp or BCRP substrates are those with a greater than or equal to 2-fold increase in exposure when coadministered with a P-gp or BCRP inhibitor. In FRESCO-2, 26 out of 691 patients (approximately 4%) who were enrolled and treated received concomitant sensitive substrates of P-gp or BCRP. In the 2013-013-00CH1 study conducted in China, none of the 415 enrolled patients were treated with sensitive substrates of P-gp or BCRP. In the 691 patients enrolled in FRESCO-2 who received concomitant P-gp or BCRP sensitive substrates, no AEs/serious AEs were observed that would suggest any PK interaction between the agents and investigational product fruquintinib.

Population PK model

The applicant has fitted a population PK model to time-concentration data of six clinical studies, including five phase 1 studies and one phase 3 study. The population PK model is relevant in predicting pharmacokinetics in special populations, and in providing the exposure estimates to be used in exposure-response and exposure-safety modelling.

The population PK model features one-compartment PK of the parent compound with absorption lag-time, and first-order absorption and elimination. The M11 metabolite PK is modelled with an assumption that 7.25% of the parent compound transforms to the metabolite. The metabolite elimination follows first-order kinetics.

During population PK model building, dose was not included within formal covariate search procedures. However, during structural model development, dose was tested as a covariate of relative bioavailability, and dose failed to produce a statistically significant improvement within the model. Consequently, dose proportionality was considered to be confirmed, at least within the scope of population PK modelling.

Population PK model plots of residuals as a function of time did not reveal major trends of residuals either in fruquintinib concentrations or M11 concentrations as a function of time. This suggests that there are no time-dependent trends in fruquintinib or M11 metabolite PK. If there were time-dependent changes in PK, then there would be trends visible in residuals because the popPK model assumes no time dependencies.

The population PK model found no correlation between fruquintinib clearance and creatinine clearance. Within the population PK dataset, most of the subjects were classified as having normal renal function (337 subjects [60.5%]), and 177 subjects (31.8%) as having mild renal impairment. There were 42 patients (7.5%) classified with having moderate renal impairment, and no subjects with severe renal impairment. The population PK model supports the notion that no dose adjustment is required for patients with mild and moderate renal impairment.

The population PK model found no correlation between fruquintinib clearance and hepatic function. Within the population PK dataset (which did not include patients from the dedicated hepatic impairment study), based on NCI hepatic impairment categorization, 421 subjects (75.6%) of the subjects had normal hepatic function, 133 subjects (23.9%) had mild hepatic impairment, 2 patients (0.4%) had moderate hepatic impairment, and 1 subject (0.2%) had missing hepatic function. There were no patients with severe hepatic impairment.

During the covariate selection procedure, since sex and weight were highly correlated, only weight was investigated on CL/F and CLM/F as it was considered more physiologically relevant. However, female CL/F and CLM/F appeared markedly decreased compared to male subjects. Moreover, the exposure-safety analyses found an association between sex and risk of any grade proteinuria. The applicant was requested to use the final population PK model and to test the inclusion of sex on both CL/F and CLM/F. The applicant provided the requested data, and it was confirmed that female sex is associated with a 17% lower fruquintinib clearance and 17% lower M11 metabolite clearance when compared to males of identical bodyweight.

The population PK model found weight to be a statistically significant predictor of fruquintinib and M11, but bodyweight changes within the 5th and 95th percentiles of body weight in the analysis dataset (48 and 108 kg, respectively), when compared to a reference subject of 70kg bodyweight, resulted in expected exposure range within 80-125% of AUCss, Cmaxss and Cminss in the patient population. For M11, the AUC_{SS} values for subjects at the 5th and 95th of body weight were predicted to be 49% higher and 37% lower, respectively, than AUCSS for a 70-kg subject. The exposure-safety analyses found no relationship between AEs and M11 exposure. The concentration-QTc analysis did find M11

concentration to be a better predictor of QTc prolongation than fruquintinib concentration. However, there is a sufficient safety margin of 3.4-fold between the clinically observed M11 Cmax and the M11 concentration that is predicted to cause a mean QTc change of 10ms or higher. The M11 concentration increases occurring due to high bodyweight are still within the safety margin, and are not expected to cause QTc prolongation, thus suggesting that weight effect on M11 exposure is not clinically meaningful.

For drug-drug interaction predictions of the impact of moderate CYP3A4 inhibitors and CYP3A4 inducers on fruquintinib PK, the Applicant has used a PBPK model. However, for the simulations to be acceptable, the PBPK model would need to be reliably informed about the relative contribution of CYP3A4 on fruquintinib metabolism. Unfortunately, the exact contribution of CYP3A4 and CYP2C9 to fruquintinib metabolism is unclear, with conflicting results from in vitro studies and the clinical DDI study.

As a consequence of the unidentifiability of the CYP3A enzyme contribution to overall metabolism of fruquintinib, the PBPK model cannot be used to predict the impact of moderate CYP3A4 inhibitors and CYP3A4 inducers on fruquintinib PK. The applicant was instructed to omit the mention of moderate CYP3A4 inducer effect PBPK predictions from the SmPC, but to leave in a statement that moderate CYP3A4 inducers are not recommended; and the Applicant complied.

The PBPK model was also used to predict the impact of repeated-dosing fruquintinib on P-gp substrate digoxin exposures, and BCRP substrate rosuvastatin exposures. There were clinical DDI data available of single-dose fruquintinib effect on P-gp substrate dabigatran etexilate exposures, and on BCRP substrate rosuvastatin exposures, which were used to verify the PBPK model. The applicant was requested to omit the PBPK predictions of repeated-dose fruquintinib effects on rosuvastatin PK from the SmPC because the PBPK model with regard to BCRP has not been verified with a sufficient number of substrates. Moreover, the Applicant was requested to omit the PBPK predictions of repeated-dose fruquintinib effects on digoxin PK because digoxin is not a sensitive P-gp probe. The applicant complied, and the SmPC only contains information of single-dose fruquintinib PK effects on BCRP and P-gp probe substrates, which is acceptable.

Pharmacokinetics using human biomaterials

See Analytical methods.

3.6.5.2. Pharmacodynamics

Mechanism of action

Fruquintinib, a small molecule antitumor quinazoline class tyrosine kinase inhibitor (TKI), is a highly selective and potent inhibitor of the vascular endothelial growth factor receptor (VEGFR), which include subtypes VEGFR1, VEGFR2, and VEGFR3. Signalling by vascular endothelial growth factors (VEGFs) via the VEGFR plays a key role in tumour angiogenesis and tumour growth, and targeting of the VEGF signalling pathway is a well-accepted strategy for anticancer therapy. Fruquintinib inhibits VEGFR1, 2, and 3 with 50% inhibitory concentrations (IC50) of 33, 35, and 0.5 nM, respectively. M11, the major circulating metabolite of fruquintinib observed in human plasma, also inhibits VEGFR2 kinase activity and VEGFR2 phosphorylation but the cellular activity of M11 is 10-times less potent compared to the parent fruquintinib. Kinase selectivity studies showed that fruquintinib did not significantly inhibit the kinases related to cell cycle or cell proliferation, including cyclin-dependent kinases 1, 2, and 5; the epidermal growth factor receptor (EGFR); the transmembrane tyrosine kinase receptor (c-Met) (IC50 > 10 μM) and did not show appreciable inhibitory activity against a panel of 264 different kinases. Nonclinical mechanism of action (MoA) for fruquintinib was also demonstrated in studies with cultured

human umbilical vein endothelial cells and human tumour cell lines. Dose-dependent inhibition of tumour growth was shown in mice bearing different human tumour xenografts. Low potential for off-target effects for fruquintinib based on screening in binding, enzyme, and uptake assays supports its high selectivity for VEGFR inhibition.

Primary and Secondary pharmacology

No specific studies on pharmacodynamics (PD) biomarker were conducted in healthy subjects with fruquintinib. Nor were studies conducted on PD biomarker in cancer patients with fruquintinib. Currently there are no *in vitro* biomarker tests for patient selection or for prediction of response, therefore, no specific studies on pharmacodynamics were conducted. Nonclinical PK/PD studies in mice and tumour growth inhibition studies in a variety of human tumour xenograft models formed the basis for dose selection for further clinical development.

No specific secondary pharmacology endpoint studies were conducted with fruquintinib. Exposure-response and concentration-QTc analyses based on data from a subset of cancer patients in Phase 3 FRESCO-2 study were conducted.

Concentration-QTc modelling

The applicant has conducted concentration-QTc modelling on the basis of PK data from a subset of patients in phase 3 study 2019-013-GLOB1. A pre-defined concentration-QTc model has been fitted to these data, and has been used to make predictions of QT prolongation for the two-week fruquintinib and M11 metabolite geometric mean Cmax, using the upper bound of 90% CI of the QT change as the main criterion, as instructed by the ICH E14 R3 guideline. A custom decorrelation was performed to separate the effect of heart rate from QTc. This custom decorrelation is referred as QTcP. Additionally, the concentration-QTc analysis was repeated with Fridericia's corrected QT times, which are referred as QTcF. M11 metabolite concentrations predicted QTc prolongation better than fruquintinib concentrations. The main prediction is that the upper bound of the 90% CI of mean ΔΔQTcP will exceed 10 msec at 3.4-fold higher than the observed two-week GM Cmax of M11, and fruquintinib concentrations at twice the steady-state fruquintinib Cmax will result in upper bound of the 90% CI of the predicted mean ΔΔQTcP of 3.96 ms. A sensitivity analysis using Fridericia's correction to decorrelate heart rate and QTc time resulted in predictions of a clinically relevant ΔΔQTcF at an M11 concentration 2.3-fold higher than the observed GM two-week M11 Cmax, and a mean ΔΔQTcF of <10 ms at twice the fruquintinib GM steady-state Cmax. Taken together, the possibility of a 10 ms QTc prolongation can be excluded in normal clinical use.

Exposure-response

The efficacy E-R analyses for OS and PFS were conducted using data pooled from 368 patients with mCRC from Study 2019-013-GLOB1(N = 328) and Cohort B of Study 2015-013-00US1 (N = 40). All subjects received a dosing regimen of 5 mg QD 3/1. Two sets of analyses were done for OS and PFS, one using CminSS based on the starting dose and the other based on CminSS adjusted for RDI. There was no statistically significant E-R relationship of OS with fruquintinib CminSS identified in either analysis; the 95% CIs of the CminSS hazard ratios included 1. In the analyses for PFS, fruquintinib CminSS had statistically significant hazard ratios >1 (data not shown). However, the PFS E-R relationship is not considered clinically meaningful in the context of a lack of an E-R relationship for the primary endpoint of OS, as well as the PFS-related treatment benefit of fruquintinib relative to placebo in Study 2019-013-GLOB1 (stratified hazard ratio [95% CI] for PFS of 0.321 [0.267, 0.386], p < 0.001). There were insufficient data to conduct and E-R analysis for ORR.

Exposure-safety

The safety E-R analysis was conducted based on data from a total of 515 patients pooled from 4 clinical studies (2019-013-GLOB1, 2015-013-00US1, 2009-013-00CH1, and 2012-013-00CH3) that included a wide range of fruquintinib doses (1 to 6 mg) and 2 different regimens (QD continuous versus QD 3/1). Statistically significant and positive correlations were identified between model-predicted fruquintinib or M11 exposure measures (AUCave, CmaxSS, or CmaxSS + regimen) and the following AEs:

- Dermatological toxicity, any grade and Grade ≥ 3: fruquintinib AUCave and CmaxSS + regimen
- Haemorrhage, any grade: fruquintinib AUCave and CmaxSS + regimen
- Proteinuria, any grade and Grade ≥ 3: fruquintinib CmaxSS + regimen
- Hepatic function abnormal, Grade ≥ 3: M11 AUCave

After the covariate analyses were performed for the above safety endpoints with statistically significant E-R relationships, the E-R relationships for any-grade dermatological toxicity, any-grade proteinuria, and Grade ≥ 3 hepatic function abnormal were no longer statistically significant (data not shown). Grade ≥ 3 dermatological toxicity was the only safety endpoint that continued to have a statistically significant relationship with fruquintinib exposure (CmaxSS) and QD regimen. Any-grade hemorrhage and Grade ≥ 3 proteinuria showed a statistically significant association with the QD regimen but not exposure. Due to the low occurrence of Grade ≥ 3 dermatological toxicity (8.3%) and Grade ≥ 3 proteinuria (2.7%), the E-R results for these AEs should be interpreted with caution. There were no E-R relationships identified for other safety endpoints investigated (i.e., any-grade or Grade ≥ 3 hypertension, Grade ≥ 3 hemorrhage, or any-grade hepatic function abnormal) with fruquintinib or M11 exposure.

Heart Rate-Corrected QT Interval

Consistent with the in vitro findings, the safety pharmacology study in anesthetized Beagle dogs at doses up to 0.34 mg/kg single dose and the collected ECGs in the 4-, 13-, and 39-week repeat-dose toxicity studies in dogs (highest dose: 0.3 mg/kg/day) did not reveal any dose-related changes in QTc (Module 2.6.2 Section 4.2.2.1). In addition, no ECG changes were attributed to fruquintinib in the 4-, 13-, and 39-week repeat-dose dog toxicity studies (highest doses 0.3, 0.12, and 0.2/0.12 mg/kg/day, respectively).

3.6.6. Discussion on clinical pharmacology

Pharmacokinetics

Pharmacokinetics of fruquintinib has been investigated in nine studies in healthy subjects and in four studies in patients with cancer. In general, the **analytical methods** are acceptable and properly validated. The performance of the bioanalytical methods was satisfactory during the sample analysis and the handling of samples was adequate. The reasons for reanalysis of samples and for repeating analytical runs are considered acceptable. Incurrent sample reanalysis data is acceptable. All study samples were analysed within the established long-term stability.

The applicant confirmed that a new assay for fruquintinib and its active metabolite M11 in human plasma using an isotope-labelled internal standard will be used for LC-MS/MS analyses of PK samples in future clinical studies conducted by Takeda.

Absorption of fruquintinib is fast being about 2 hours after single dose of 5 mg. Cmax and AUC increase dose-proportionally between doses 1-6 mg both after single and multiple doses. PK of fruquintinib is linear and independent of time. 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.

The apparent volume of distribution of fruquintinib is approximately 48.5 L. Plasma protein binding of fruquintinib is approximately 95% *in vitro* and mainly bound to human serum albumin.

Clearance and half-life are independent of the dose clearance being about 11.1-17.5 ml/min and effective half-life 55.5-65.0 hrs after multiple doses of fruquintinib in patients with cancer (# 2015-013-00US1).

Elimination half-life is about 42 hours in patients. Fruquintinib was approximately 95 % bound to human plasma proteins in vitro and is not concentration dependent. The apparent clearance (CL/F) of fruquintinib is 14.8 mL/min at steady-state after once daily dosing in patients with advanced solid tumours. 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 faeces (5% of the dose as unchanged fruquintinib).

The manufacturing site had no effect on bioavailability of fruquintinib as demonstrated in two bioequivalence studies (2013-013-00CH2 & 2014-013-00CH5). Concomitant food did not have significant effect on absorption of fruquintinib so the product can be taken with or without concomitant food (#2012-013-00CH2 & 2020-013-00US1) (data not shown).

The effect of **sex** on the PK of fruquintinib was not considered clinically relevant. Therefore, no dose adjustment is necessary for sex based on PK findings.

The effect of moderate and severe **renal impairment** (#2021-013-00US2) and the effect of mild and moderate **hepatic impairment** (2021-013-00US1) on PK of fruquintinib have been studied. The results indicate that moderate or severe renal impairment and moderate hepatic impairment does not affect PK of fruquintinib. Fruquintinib dose adjustment in patients with mild, moderate and severe RI is not warranted. No dose adjustment is deemed necessary for patients with mild or moderate HI. Fruquintinib is not recommended in patients with severe hepatic impairment. This was included in section 4.2 of the SmPC.

The effects of **genetic polymorphism** on the PK of fruquintinib were not evaluated. Overall, considering: 1) the involvement of multiple enzymatic pathways; 2) that fruquintinib PK exposure was not affected when co-administered with a strong CYP3A inhibitor; and 3) no differences in PK exposure and associated variability was observed between Asian and other races, genetic polymorphism is not expected to have a clinically meaningful impact on fruquintinib metabolism.

Three **interaction studies** were performed for fruquintinib. Solubility of fruquintinib is pH dependent increasing under acidic conditions, but a proton pump inhibitor rabeprazole (40 mg) had no effect on PK of fruquintinib or metabolite M11 (#2020-013-00US1). Based on these results, no dose adjustment for fruquintinib when coadministered with acid-reducing agents is necessary. A strong CYP3A inhibitor itraconazole (200 mg) did not affect PK of fruquintinib, based on these results, no dose adjustment for fruquintinib is necessary when coadministered with any kind of CYP3A inhibitor. A strong CYP3A inducer (rifampin), however, decreased fruquintinib AUC by 65% (#2020-013-US2). Therefore, coadministration of fruquintinib with a strong or moderate CYP3A inducer should be avoided and alternate concomitant medication with no or minimal CYP3A induction potential should be considered. No dose adjustment is necessary when coadministered with weak CYP3A inducers. Fruquintinib did not change clinically significantly AUC and Cmax of a P-gp substate of dabigatran. Neither were there seen

clinically significant changes in AUCs and Cmax of rosuvastatin (a BCRP substrate) with coadministration of fruquintinib compared to alone (2021-013-00US3). Based on the totality of data, no dose adjustment for concomitant medications that are substrates of P-gp or BCRP is necessary when coadministered with fruquintinib.

The applicant fitted a **population PK model** to time-concentration data of six clinical studies. The population PK model supports the notion that no dose adjustment is required for patients with mild and moderate renal impairment.

The PK model was used to test the inclusion of sex on both CL/F and CLM/F, and it was confirmed that female sex is associated with a 17% lower M11 metabolite clearance when compared to males of identical bodyweight. While statistically significant, this finding was not considered clinically relevant, and thus not necessary to include in the SmPC. It was also confirmed that the population PK model with sex effect predicts highly similar individual exposures when compared to the population PK model without sex effect. Thus, the exposure estimates used in the exposure-efficacy and exposure-safety analyses are appropriate, and do not need to be updated because of this new finding of sex effect on parent and metabolite clearance.

The population PK model found weight to be a statistically significant predictor of fruquintinib and M11. However, it was shown that the effect of weight on fruquintinib and M11 metabolite PK does not lead to a clinically meaningful exposure differences between patients.

Pharmacodynamics

Currently there are no *in vitro* biomarker tests for patient selection or for prediction of response and therefore the Applicant´s approach (not to conduct specific studies on pharmacodynamics) can be accepted.

The applicant has conducted **concentration-QTc modelling** on the basis of PK data from a subset of patients in phase 3 study 2019-013-GLOB1. The PK and ECG sampling schedule is considered sufficient to capture the Cmax of fruquintinib and M11 metabolite at steady state. Taken together, the possibility of a 10 ms QTc prolongation can be excluded in normal clinical use.

It has not been possible to capture the PK and ECG at multiples of the clinically expected maximum exposure (which is a requirement of ICH E14 R3). However, given that the upper bound of 90%CI for predicted mean QTc change is several-fold lower than 10ms at the expected clinical exposures, and given that the nonclinical hERG IC50 was more than hundred-fold higher than the clinically expected unbound Cmax, the lack of clinically relevant QTc prolongation potential of fruquintinib and M11 metabolite can be ruled out. The PI states that no QTc prolongation was observed at the recommended dose, and that concentration-QTc analyses found no evidence of an association between fruquintinib plasma concentrations and changes in QTc interval from baseline, and this is acceptable.

The **efficacy E-R analyses** included patients with mCRC from Study 2019-013-GLOB1 and Cohort B of 2015-013-00US1. The exposure-efficacy analyses used AUCave and CminSS metrics of fruquintinib as predictors of OS and PFS within Cox proportional hazards models, with the data including only a single dose level of 5 mg QD 3/1. After accounting for covariate effects, fruquintinib was not a statistically significant predictor of OS, but was a significant predictor of PFS; however, the trend was one of increasing hazard with increasing exposure, i.e., the opposite of what would be expected. The statistically significant PFS exposure-response trend needs to be interpreted with caution.

The exposure-response analyses are only informed by data from one dose level, 5mg QD 3/1, and thus the exposure-response analyses are confounded by potential patient characteristics that would

simultaneously affect both exposure and response, such as the sickest patients having poor capacity to eliminate fruquintinib, which would correlate to both a short PFS and high exposures.

The applicant has conducted **exposure-safety** logistic regression modelling on the basis of PK and safety data pooled from 4 studies in patients with cancer (2019-013-GLOB1, 2009-013-00CH1, 2012-013-00CH3, and 2015-013-00US1). In univariate analyses, several exposure-safety associations were found at $p<0.05$ statistical significance: Any grade dermatological toxicity, grade ≥3 dermatological toxicity, any grade hemorrhage, grade ≥3 abnormal hepatic function, any grade proteinuria and grade ≥3 proteinuria. However, after inclusion of other covariates the exposure-safety trend remained statistically significant only for grade ≥3 dermatological toxicity. Constant dosing regimen was also a predictor of increased risk for any grade hemorrhage and grade ≥3 proteinuria. It can be concluded that 3 weeks on, 1 week off dosing scheme is associated with lower AE probability than constant dosing regimen, whereas the association between AE risk and exposure is unclear; the data are not sufficient to prove or disprove an exposure-safety relationship.

The exposure-safety analyses support the use of 3 weeks on, 1 week off dosing.

Clinical pharmacology studies conducted to date, including DDIs, food effect, and moderate hepatic or RI, did not demonstrate meaningful increases in fruquintinib or M11 exposure. Coadministration of fruquintinib with rifampin, a strong CYP3A inducer, is the only situation in which an increase in M11 Cmax by approximately 2.3-fold was observed. Therefore, fruquintinib is not expected to cause clinically significant **QT prolongation** in patients under a variety of clinical scenarios.

3.6.7. Conclusions on clinical pharmacology

Overall, the clinical pharmacology data submitted with this application is sufficient to support the marketing authorisation of fruquintinib.

3.6.8. Clinical efficacy

Table 9: An overview of clinical studies for the efficacy claims for fruquintinib monotherapy in mCRC:

Study ID **No. of study centres/locations**	**Design** **Type of control** **Enrolment status (goal); Timelines**	**Test product, dose, regimen, route**	**Study Objective(s)** **Primary & secondary endpoints**	**Number of Subjects; M/F; Median age (Range)**	**Duration of therapy**	**Diagnosis** **Incl. criteria**	**Study Status; Type of Report**
2012-013-00CH3 2 China	Phase 1b Open label Randomised comparison 1:1 A vs B-> expansion (B) uncontrolled; Completed (60 patients planned) 1st patient ICF+ 26-12-2012 DCO 24-4-2014	4 mg QD continuous (A) & 5 mg QD 3 weeks on/1 week off (B) PO	Safety, tolerance, PFS, ORR, DCR, DOR, OS, PK	62 enrolled and treated 28/12; 60 (21-69) (A), 55 (39-70) (B) years->25/17; 55.5 (33-70) (expansion with 20 patients from the randomised comparison)	28 day cycles until PD, intolerable toxicity, or withdrawal of informed consent	Advanced CRC, failed 2nd or later line chemotherapy	Completed; CSR
2012-013-00CH1 8 China	Phase 2 Double blind Placebo controlled 2:1 Completed (approx. 70 patients planned) 1st patient enrolled 01-04-2014 1st DCO 11-2-2015	5 mg QD 3 weeks on/1 week off vs placebo PO	PFS, ORR, DCR, OS, safety, tolerability	93 recruited, 71 patients randomised & treated; 52/19; 50 (25-69) (F)/54 (38-70) (pl.) years	28 day cycles until PD, death, intolerable AE, withdrawal of ICF, other meeting EOT criteria	Advanced CRC, PD or intolerable toxicity with at least 2 lines of standard chemotherapies (including 5 F U , oxaliplatin, and irinotecan)	Completed; CSR
2015-013-00US1 9 USA	Phase 1/1b Dose escalation and expansion Open label Uncontrolled Completed (128 planned)	3 & 5 mg QD 3 weeks on/1 week off PO	Dose escalation: DLT, MTD, safety, PK, ORR, DCR, DOR, PFS, percentage change in tumor size, OS Dose expansion: PFS rates, ORR,	138 patients enrolled, 101 treated; 52/49 58.72 (33.9-77.3) years	28 day cycles until PD, unacceptable toxicity, other antitumor treatment, withdrawal of consent, discontinuation by investigator	Escalation: Advanced solid tumours, PD on approved systemic therapy, no effective therapy or SOC exists. Expansion: A) advanced solid tumour, as above.	Completed; CSR

Study ID No. of study centres/locations	Design Type of control Enrolment status (goal); Timelines	Test product, dose, regimen, route	Study Objective(s) Primary & secondary endpoints	Number of Subjects; M/F; Median age (Range)	Duration of therapy	Diagnosis Incl. criteria	Study Status; Type of Report
	1st patient enrolled 11-12-2017 DCO 14-11-2012		DCR, DOR, PFS, percentage change in tumor size, OS, PK, safety			B) refractory mCRC, PD or intolerability to at least 1 FDA approved 3rd line therapy, C) refractory mCRC, PD or intolerability to at least 2 lines of SOC, no TAS102 or regorafenib D) HR+ mBC, E) TNBC.	
2013-013-00CH1 FRESCO 28 China	Phase 3 double blind Placebo controlled 2:1 Completed (around 400 patients planned) 1st patient ICF+ 8-12-2014 DCO 17-01-2017	5 mg QD 3 weeks on/1 week off vs placebo PO	OS, PFS, ORR, DCR, DOR, SD duration, safety	519 signed ICF; 416 randomised; 278/138 treated; 255/161 55 (23-75) (F)/57 (24-74) (pl.) years	28 day cycles until PD, death, intolerance to toxicity, withdrawal of ICF, termination by investigator, or other criteria for termination met.	Advanced CRC, received at least 2nd line standard chemotherapy and failed (PD or intolerance to toxicity). Standard treatment must include 5FU, oxaliplatin & irinotecan.	Completed; CSR
FRESCO-2 (2019-013-GLOB1) 132 screened at least 1, 124 randomised at least 1 USA, Europe, Japan, Australia	Phase 3 double blind Placebo controlled 2:1 Completed (687 patients planned) 14-08-2020 1st patient enrolled DCO 24-06-2022	5 mg QD 3 weeks on/1 week off vs placebo PO	OS, PFS, ORR, $ORR_{unconfirmed}$, DOR, DCR, PROs (QLQ-C30, EQ-5D-5L), health resource utilization, safety (exploratory: CEA levels, ctDNA)	934 signed ICF; 691 randomised; 686 treated 385/306 64 (56-70) years	28 day cycles until PD, unacceptable toxicity, withdrawal of consent, or discontinuation by the investigator, or other[1)]	Refractory mCRC, previously treated with 5FU-, oxaliplatin-, & irinotecan-based chemotherapy; anti-VEGF therapy; &, if RASwt, anti-EGFR therapy. Patients must also have had progression on or been intolerant to TAS-102, regorafenib, or both.	Completed; CSR

[1)] See Chapter Overview for 2019-013-GLOB1 (FRESCO-2), below

3.6.8.1. Dose response studies

The recommended dose of fruquintinib is 5 mg QD PO 3/1.

The optimal dose and dose schedule of fruquintinib were determined in 2 Phase 1 studies, 2009-013-00CH1 and 2012-013-00CH3, and confirmed in a randomised, double-blind, placebo-controlled Phase 2 study (Study 2012-013-00CH1), conducted in China, as well as in Study 2015-013-00US1, conducted in Western patients.

Study 2009-013-00CH1 investigated continuous daily doses of fruquintinib at 1, 2, 4, 5, and 6 mg QD. Fruquintinib doses of 5 and 6 mg QD were studied on a regimen of 3 weeks of continuous dosing followed by a 1-week break (3 weeks on/1 week off or 3/1) on a 28-day treatment cycle. Based on the results of this study (data not shown), the maximum tolerated dose (MTD)/RP2D was 4 mg QD continuous or 5 mg QD 3/1.

In Study 2012-013-00CH3, the safety and tolerability of these 2 dosing regimens (4 mg QD continuously vs 5 mg QD 3/1) were compared in patients with mCRC. The safety profile showed that fruquintinib was better tolerated in the 5 mg QD 3/1 group than in the 4 mg QD continuous group. In addition, there was an accumulation of drug over time in the 4 mg QD continuous group. Thus, the 5 mg QD 3/1 regimen was selected as the RP2D and the dosing regimen to be used in subsequent clinical development in China.

The RP2D dosing regimen was further evaluated in the randomised, double-blind, placebo-controlled Phase 2 study (Study 2012-013-00CH1). The 2012-013-00CH1 study confirmed that the dosing regimen of 5 mg QD 3/1 on a 28-day cycle was safe and effective in patients with refractory mCRC and established the standard dose and dosing regimen in all other studies in patients with advanced cancer, including mCRC.

The dose-escalation phase of Study 2015-013-00US1 investigated 2 doses of fruquintinib at 3 and 5 mg QD 3/1. PK data indicated comparable fruquintinib PK exposure between Chinese and Western populations, therefore confirming 5 mg QD 3/1 on a 28-day cycle as the RP2D dosing regimen (approved dose in China) for the global Phase 3 study FRESCO-2.

The observed clinical exposure at steady-state following fruquintinib 5 mg QD 3/1 was well within the concentration of 176 ng/mL associated with tumour growth inhibition in mouse xenograft models (data not shown). The efficacy E-R analysis indicated no significant relationship between OS and PK when analysed by quartiles of exposure, suggesting variability of exposure (including dose interruptions and dose reductions) in the 5 mg QD 3/1 dose did not impact efficacy. The median relative dose intensity for fruquintinib was approximately 92% in FRESCO-2 and 100% in FRESCO, indicating most patients were able to receive the intended dose of fruquintinib over their treatment duration.

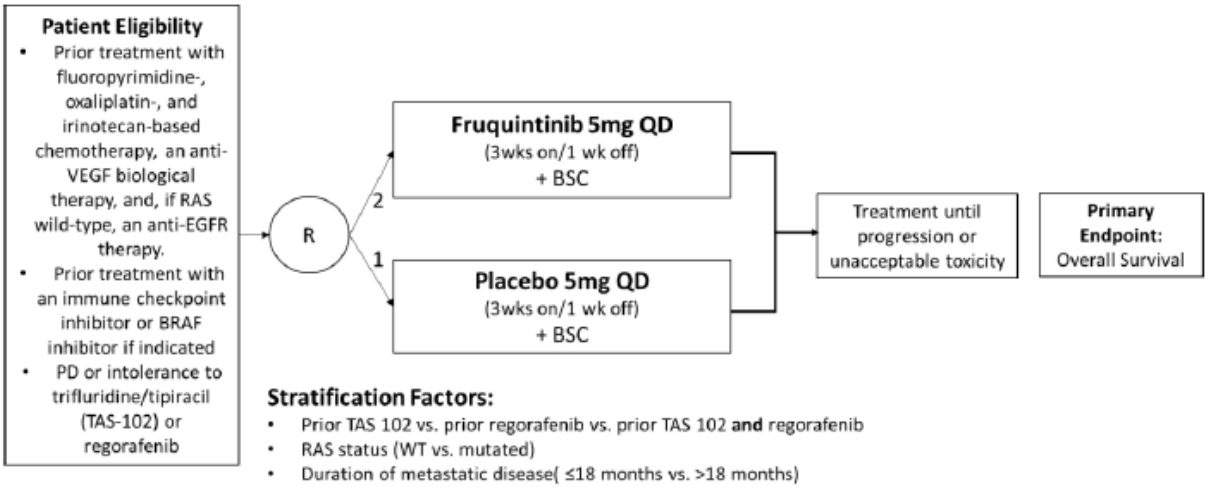
Based on safety data pooled from 3 placebo-controlled trials of fruquintinib in mCRC, a higher percentage of patients (15.9%) in the fruquintinib 5 mg 3/1 group had dose reduction due to an AE compared with the placebo arm (1.5%), and most of them were related to dermatological toxicity. The safety E-R analysis suggested that higher fruquintinib Cmax was statistically associated with higher probability of Grade $\geq$ 3 dermatological toxicity. Therefore, dose modification as currently implemented in the Phase 3 clinical studies can be used to manage AEs/toxicities associated with fruquintinib.

3.6.8.2. Main study

FRESCO-2 (2019-013-GLOB1): A Global Multicenter Randomized Placebo-Controlled Phase 3 Trial To Compare The Efficacy And Safety Of Fruquintinib Plus Best Supportive Care To Placebo Plus Best Supportive Care In Patients With Refractory Metastatic Colorectal Cancer

Methods

FRESCO-2 is an ongoing global, multicenter, double-blind, randomised 2-cohort, Phase 3 study, which evaluates the efficacy and safety of fruquintinib monotherapy in refractory mCRC. An overview of study design is shown in the Figure below.



Abbreviations: BRAF = serine/threonine protein kinase B-Raf; BSC = best supportive care; EGFR = epidermal growth factor receptor; PD = progressive disease; PO = oral(ly); QD = once daily; R = randomization; *RAS* = Rat sarcoma; VEGF = vascular endothelial growth factor; WT = wild-type.
Notes: Fruquintinib group: fruquintinib 5 mg PO, QD, plus BSC, 3 weeks on/1 week off, every 4-week cycle. Control group: matching placebo 5 mg PO, QD, plus BSC, 3 weeks on/1 week off, every 4-week cycle.

Figure 6: Study design of FRESCO-2:

Study and reporting period:

Date first subject enrolled: 14-08-2020
Date last subject enrolled: 02-12-2021
For an interim non-binding futility analysis, a DCO date of 24-09-2021 was applied.
Date of data cutoff for final analysis: 24-06-2022
Date of database lock: 29-07-2022
Unblinding occurred at the time of the DBL.
Date of release of CSR: 03-02-2023

- **Study Participants**

Key inclusion criteria

1. Histologically and/or cytologically documented metastatic colorectal adenocarcinoma;
2. Subjects must have progressed on or been intolerant to treatment with either trifluridine/tipiracil (TAS-102) or regorafenib if approved and available in the subject's country. Subjects are considered intolerant to TAS-102 or regorafenib if they have

received at least 1 dose of either agent and were discontinued from therapy for reasons other than disease progression. Subjects who have been treated with both TAS-102 and regorafenib are permitted. Subjects must also have been previously treated with standard approved therapies: fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and, if RAS wild-type, an anti-EGFR therapy;

3. Subjects with microsatellite-high (MSI-H) or mismatch repair deficient (dMMR) tumours must have been treated with immune checkpoint inhibitors if approved and available in the subject's country and if deemed appropriate;
4. Subjects who received oxaliplatin in the adjuvant setting must have progressed within 6 months of completion of adjuvant therapy;
5. Body weight ≥40kg;
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1;
7. Have measurable disease according to RECIST Version1.1 (RECIST v1.1), assessed locally. Tumours that were treated with radiotherapy are not measurable per RECIST v1.1, unless there has been documented progression of those lesions;
8. Expected survival >12 weeks;
9. For female subjects of childbearing potential and male subjects with partners of childbearing potential, agreement to use a highly effective form(s) of contraception, starting during the screening period, continuing throughout the entire study period, and for 90 days after taking the last dose of study drug.
10. Patients with BRAF-mutant tumors who were treated with a serine/threonine protein kinase B-Raf (BRAF) inhibitor if approved and available in the patient's country, unless the patient was ineligible for treatment with a BRAF inhibitor.

Key exclusion criteria

1. Serum total bilirubin >1.5 × the upper limit of normal (ULN). Subjects with Gilbert syndrome, bilirubin <2 X ULN, and normal aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) are eligible;
2. ALT or AST >2.5 × ULN in subjects without hepatic metastases; ALT or AST >5 × ULN in subjects with hepatic metastases;
3. Serum creatinine >1.5 × ULN or creatinine clearance <60 mL/min. Creatinine clearance can either be measured in a 24-hour urine collection or estimated by the Cockcroft-Gault equation;
4. Urine dipstick protein ≥2+ or 24-hour urine protein ≥1.0 g/24-h. Subjects with greater than 1+ proteinuria on urinalysis must undergo a 24-hour urine collection. For conversions between quantitative and qualitative results, please see Appendix 8;
5. Uncontrolled hypertension, defined as: systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mm Hg despite optimal medical management;
6. History of, or active gastric/duodenal ulcer or ulcerative colitis, active haemorrhage of an unresected gastrointestinal tumour, history of perforation or fistulas; or any other condition that could, in the investigator's judgment, result in gastrointestinal haemorrhage or perforation; within the 6 months prior to screening;
7. History or presence of haemorrhage from any other site (e.g., haemoptysis or hematemesis) within 2 months prior to screening;
8. History of a thromboembolic event, including deep vein thrombosis (DVT), pulmonary embolism (PE), or arterial embolism within 6 months prior to screening;
9. Stroke and/or transient ischemic attack within 12 months prior to screening;
10. Clinically significant cardiovascular disease, including but not limited to acute myocardial infarction or coronary artery bypass surgery within 6 months prior to enrolment, severe or unstable angina pectoris, New York Heart Association Class III/IV congestive heart failure,

ventricular arrhythmias requiring treatment, or left ventricular ejection fraction (LVEF) <50% by echocardiogram;

- **Treatments**

Fruquintinib 5 mg or matching placebo was administered PO, QD, on a 3 weeks on/1 week off schedule. One treatment cycle was 4 weeks. Study drug was given either in the fasting state or after meals, around the same time each day. If dose adjustment was required, 1 mg fruquintinib or matching placebo capsules were used. If vomiting occurred after dosing, study drug doses were not replaced. If a dose was missed, the missed dose could have been taken within a 12-hour window of time during which the patient typically took the dose. A double dose was not administered to make up for missed individual doses.

Dose modification in case of general hematologic and non-hematologic toxicity recommended a decrease from 5 mg QD 3 weeks on / 1 week off to 4 mg QD 3 weeks on / 1 week off (dose level -1) then to 3 mg QD 3 weeks on / 1 week off (dose level -2). The longest pause allowed was 14 days, after which the treatment should be discontinued, unless later continuation was approved by the sponsor.

Study drugs were to be continued until PD, withdrawal of consent, intolerable toxicity or AEs that warrant withdrawal of study treatment as determined by the PI, poor subject compliance, use of other antitumor treatment during the study, pregnancy, subject is lost to F-U, the investigator or sponsor determines it is in the best interest of the subject, study is terminated by the sponsor, death, or end of the study. As per amendment 1, the patients could continue to receive treatment following PD, if experiencing a treatment benefit in the opinion of the investigator.

- **Objectives**

The objectives of FRESCO-2 study are described in the section 'Outcomes/endpoints' below.

- **Outcomes/endpoints**

The primary objective of FRESCO-2 was to show superiority of fruquintinib over placebo in OS.

PFS was the key secondary endpoint. This was set to evaluate PFS of patients treated with fruquintinib compared to those treated with placebo.

Table 10: Study objectives and corresponding endpoints in FRESCO-2

Tier	Objectives	Endpoints
Primary	To evaluate the OS of fruquintinib plus BSC compared with placebo plus BSC in patients with refractory mCRC	OS
Secondary	To evaluate the PFS of fruquintinib plus BSC compared with placebo plus BSC	PFS
	To evaluate the ORR, DCR, and DoR	• ORR • DCR • DoR
	To assess the safety and tolerability of fruquintinib plus BSC compared with placebo plus BSC	Safety, including TEAEs, serious TEAEs, deaths, ECGs, and clinical laboratory abnormalities
	To characterize the PK exposure of fruquintinib and metabolite M11 in patients with refractory mCRC	Observed plasma concentrations, estimated population PK, and exposure parameters of fruquintinib and M11
	To evaluate the effect of fruquintinib on cardiac repolarization, as detected by changes in ECG QTc intervals, and the potential relationship with fruquintinib and M11 plasma concentrations	QTc interval and plasma concentrations of fruquintinib and M11 at specified time points
	To evaluate the relationship between fruquintinib exposure and endpoints for efficacy and safety	Parameters describing exposure-response with efficacy (eg, OS) and safety (eg, AEs) endpoints
	To evaluate QoL as assessed using QLQ-C30: cancer-specific; and EQ-5D-5L questionnaires	Changes in health status (QLQ-C30: cancer-specific; and EQ-5D-5L)
	To assess resource utilization (eg, hospitalizations and concomitant medications)	Resource utilization, including all concomitant medications and days in hospital
Exploratory	To assess potential predictive biomarkers of response to fruquintinib	• Change from baseline in ctDNA • Change from baseline in tumor markers (ie, CEA) • Pharmacogenomics

Abbreviations: AE = adverse event; BSC = best supportive care; CEA = carcinoembryonic antigen; ctDNA = circulating tumor DNA; DCR = disease control rate; DoR = duration of response; ECG = electrocardiogram; EQ-5D-5L = EuroQol Group 5-dimension 5-level; mCRC = metastatic colorectal cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic(s); QLQ-C30 = Quality of Life Core Questionnaire; QoL = quality of life; QTc = corrected QT interval; TEAE = treatment-emergent adverse event.

The primary efficacy endpoint OS was defined as the time (months) from date of randomisation to death from any cause. Patients without report of death at the time of analysis were censored at the date last known alive. Patients lacking data beyond the date of randomisation had their survival time censored at the date of randomisation. OS was not censored at the date of initiating the subsequent anticancer treatments if a patient received subsequent anticancer treatments after discontinuation of study treatment.

The key secondary efficacy endpoint PFS was defined as the time (months) from randomisation until the first radiographic documentation of objective progression, as assessed by the investigator using RECIST v1.1, or death from any cause. More specifically, PFS was determined using all the assessment data until the last evaluable visit prior to or on the date of (1) PD as defined by RECIST v1.1 or death, (2) withdrawal of consent or lost to follow-up, or (3) receiving subsequent anticancer therapy, whichever was earlier. Patients without report of PD or death from any cause at the time of analysis were censored according to the rules described in the Table below.

Table 11: Censoring rules for PFS in FRESCO-2

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

- **Sample size**

The study was originally planned to enrol 522 patients based on statistical power of 80%. Per amendment 2, power was raised to 90% for a better detection of treatment effect. This led to the planned number of patients being increased to 687. In this a HR of 0.73 (fruquintinib vs placebo) was assumed. If the true median OS for the placebo arm is 5 months, then the HR of 0.73 corresponds to median OS of 6.8 months in the fruquintinib arm (median OS improvement of 1.8 months).

- **Randomisation and Blinding (masking)**

Randomisation was performed centrally using an IWRS according to a randomisation schedule generated by an unblinded statistician.

Randomisation was stratified by the following:

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

- **Statistical methods**

Interim analyses:

One interim nonbinding futility analysis was performed based on 160 OS events (i.e., 1/3 of the total number of OS events). A DCO date of **24 September 2021** was applied. All patients' data collected through the DCO were locked and included in the analysis. These analyses included the interim PFS/OS analyses, interim safety analyses, and interim tumour response analyses. The IDMC reviewed the unblinded data on 18 January 2022 and recommended continuation of the study as planned to the final analysis. Although there were no plans to stop the study early for efficacy based on OS data at the interim analysis, to protect the integrity of the study and to preserve the type I error, a fraction of α (.0001) was spent at the interim analysis based on an O'Brien-Fleming stopping boundary.

Final analysis:

The final analysis was to be conducted after having observed at least 480 OS events. A DCO on **24 June 2022** was applied, and the database was locked on **29 July 2022** to perform the analyses. All study data collected up through DCO were to be summarised. Unblinding occurred at the time of the DBL. Some patients were still on treatment or in the survival follow-up phase of the study at the time of DCO.

Populations

Screened population included all patients who signed the ICF.

The ITT population included all randomised patients.

The safety population included all randomised patients who received at least 1 dose of study drug.

The PP population included only those patients in the ITT population who received the treatment to which they were randomised and had no major protocol deviations that precluded the assessment of efficacy and/or data integrity.

Statistical hypothesis

The study was designed to demonstrate superiority of fruquintinib plus BSC (fruquintinib arm) over placebo plus BSC (placebo arm) in prolonging OS for subjects with refractory mCRC. The study was designed to test the null hypothesis H0: $\lambda=1.0$ versus the alternative hypothesis Ha: $\lambda < 1.0$, where λ is the hazard ratio (treatment arm/placebo arm).

This study compared the fruquintinib group with the placebo group on the primary and key secondary efficacy endpoints. A fixed-sequence (hierarchical) testing procedure was used to control the overall type I error rate at 0.05. If the resulting 2-sided *p* value from the analysis of primary endpoint OS was ≤ 0.05, then a superiority test for PFS was conducted at the 2-sided significance level of 0.05. Multiplicity-adjusted *p* values for both comparisons were reported. The adjusted *p* value for OS is its raw *p* value, and the adjusted *p* value for PFS is the maximum value between the *p* values produced for the OS and PFS.

Statistical methods

For time-to-event variables, the Kaplan-Meier method was used to estimate its within-group median value and 25% and 75% percentile values. A 1-sided log-rank test, stratified by randomisation factors, was used for the comparison of OS of the fruquintinib with placebo group at a significance level of 0.025. The HR between the 2 treatment groups (fruquintinib vs placebo), together with its 95% CI,

was be calculated from a stratified Cox proportional hazards model stratified by the randomization stratification factors.

The estimates of DCR and ORR in each treatment group and their 2-sided 95% Cis were presented. Comparison of DCR and ORR between treatment groups was performed using stratified Cochran-Mantel-Haenszel (CMH) test. The CI of difference in DCR and ORR between treatment groups was calculated using the approximate normal distribution method of binomial distribution. The SAP further specified that if the number of objective responses is not sufficient to utilize the CMH test, a stratified exact CMH test is performed instead.

All statistical analyses were conducted using SAS, release 9.4 or higher (SAS Institute, Cary, North Carolina, USA).

Subgroup analyses:

According to SAP, "Subgroup analyses will be conducted based on the unstratified Cox proportional hazard model in which the applicable randomisation schedule stratification factors and treatment group are included in the model as covariates. It should be noted that the study was not designed to detect treatment differences with high statistical power within subgroups. For OS and PFS subgroup analysis, if a subgroup is too small, it may be pooled with others. If the number of events in a subgroup was not sufficient, analysis was not performed.".

See 'Ancillary analyses' section below.

The values of stratification factors used for subgroup analysis were the actual values of strata collected through eCRF. All the sensitivity and the subgroup analysis for both OS and PFS were considered exploratory and could only be supportive of the primary analysis of OS and PFS.

Health-related quality of life

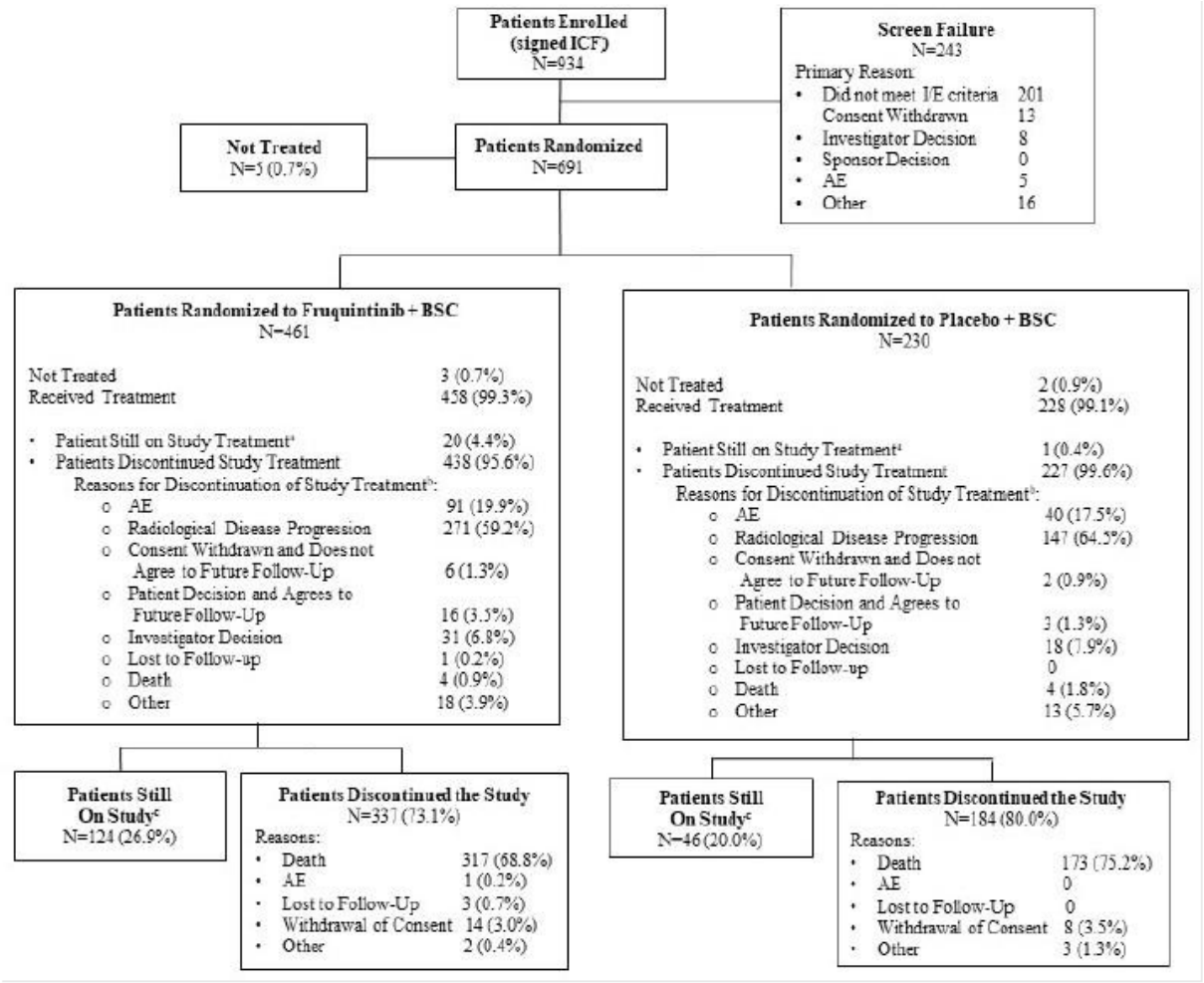
Longitudinal change from study baseline to each cycle for each Patient Reported Outcome (PRO) score was analysed by mixed-model repeated measures (MMRM) analysis. The MMRM model included treatment group, visit (i.e., cycle), treatment group by visit interaction, baseline value of scale, and randomisation schedule stratification factors as fixed effects, and reported in terms of LSMeans and LSM difference between treatment groups. Only data from the cycle with at least 20 patients remaining with observed data were included.

For each PRO score, the proportion of responder status of patients (i.e., improved, stable, or deteriorated from study baseline to each cycle) was summarized by treatment group. Responder status (improved or deteriorated) for each patient was determined based on comparing change scores to the published thresholds. When the change was not meeting the criterion of improvement or deterioration, the status of "stable" was assigned.

For each PRO score, time to deterioration (TTD) was defined as the time from date of randomisation to the date of PRO deterioration or death, whichever comes first, and summarised using Kaplan-Meier method. Estimates for TTD were tabulated by treatment group using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% CIs. In addition, the 2-sided P value was obtained from the stratified log-rank test to account for the stratification factors. The HRs between the 2 treatment groups was calculated from a stratified Cox proportional hazards model in which treatment and baseline value of scale were included as fixed effects.

Results

- **Participant flow**



Abbreviations: AE = adverse event; BSC = best supportive care; ICF = informed consent form; I/E = inclusion/exclusion.
Note: Percentages were based on the number of patients who are randomized in each treatment group unless otherwise specified.
[a] Patients who received study drug but had missing end-of-treatment information were considered to be still on treatment.
[b] Percentages were based on the number of patients who received study drug.
[c] Patients with missing end-of-study information were considered to be still on study.

Figure 7: Disposition of patients in FRESCO-2 (DCO 24 June 2022)

At DCO, 3% of patients were still receiving study treatment. At DCO, 490 patients had died, i.e., 70.9% of the patients enrolled, and 87.6% of the patients had died or had PD.

- **Recruitment**

The date of the 1st subject enrolment is 14-08-2020 and the date of the last subject enrolment 02-12-2021. The date of DCO is 24-06-2022 and the date of DBL 29-07-2022. At the time of final analysis, the median duration of follow-up was 11.3 months (95% CI, 10.6-12.4) in the fruquintinib group and 11.2 months (95% CI, 9.9-12.0) in the placebo group.

132 study sites screened at least 1 patient in the US, Europe, Japan, and Australia; 124 study sites randomised at least 1 patient. In Europe the sites were located in Austria, Belgium, Czech Republic, Estonia, France, Germany, Hungary, Italy, Poland, Spain, and UK. 495 patients were enrolled in Europe, 124 in the USA, 56 in Japan, and 16 in Australia.

- **Conduct of the study**

Protocol version 1 is dated 27-02-2020. There were four global amendments. Additionally, 8 addendum amendments restricted to Japan, 2 to US/EU, and 1 to Australia were made. The US/EU addendums were associated with COVID-19: changes to collection of assessments (PK sampling, Holter monitor QTc evaluations, and ctDNA sample collection).

The most significant change in the amendments was the increase in the study population (amendment 2), which also increased the number of sites and the duration of the study (amendments 2 and 4). Partly the changes reflect the evolution of care in mCRC (e.g., diagnosing BRAF mutations (amendments 1 and 2), use of prior BRAF inhibitor (amendment 2) and cumulative understanding regarding the use of fruquintinib (e.g., instructions for dose adjustments or discontinuations (amendments 1 and 2)). Also changes related to dose modification requirements based on AEs (amendment 2), PK (amendments 2 and 3), and safety assessment schedules (amendments 1, 2, 3 and 4), as well as clarifications concerning inclusion and exclusion criteria (amendments 1, 2, 3 and 4) and statistical methodology (amendments 2 and 3) were implemented. Partly the changes reflect requests from regulatory bodies or HAs and changes due to COVID-19.

During the study the protocol evolved to illustrate an even more heavily pre-treated patient population: at the onset prior treatment with standard approved therapies was required (fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and, if RASwt, an anti-EGFR therapy) and if MSI-H/dMMR, also prior ICI. The original protocol also stated that the patients must have progressed or been intolerant to treatment with either trifluridine/tipiracil (TAS-102) or regorafenib if approved and available in the subject's country. Receipt of both was permitted. As per amendment 1, the part "if approved and available in the subject's country" was deleted. As per global amendment 2, also prior BRAF inhibitor was required for BRAFmt (if approved and available in the subject's country unless patient ineligible).

In the original protocol to qualify for SD, its duration should last at least 6 weeks. As per amendment 2, the required duration was at least 7 weeks.

GCP

A serious GCP breach was detected in FRESCO-2 for ctDNA collection. ctDNA samples were collected from approximately 181 subjects from Austria, Germany, Spain, France, Italy, Hungary, UK, and the US, without the subjects´ explicit written consent. All samples were destroyed, and all applicable HAs/ECs were notified of the serious breach. This had no impact on the scientific validity of the study. Change from baseline in ctDNA was an exploratory endpoint.

Two GCP inspections occurred during the conduct of FRESCO-2. In Q4/21, Pyhrn-Eisenwurzen Hospital Steyr in Austria was inspected by BASG and the inspection concluded that the study at the site was not performed in accordance with the Arzneimittelgesetz (AMG) and ICH-GCP. Two critical findings were reported concerning postdating and backdating signatures. Major findings were reported concerning missing ISF documents, ICF completion, PI transition documentation, timely IRB/EC submissions, and access to electronic systems, source data discrepancies, and management of shipment and temperature records. Per the final inspection report, the inspector indicated that "the measures described in the statement, in particular those for the serious deficiencies and the critical deficiency, are considered sufficient overall to continue the study and to prevent recurrence of the deficiencies in future or other ongoing clinical studies". This site screened and enrolled 2 patients.

In Q1 2022, University Hospital-Essen in Germany was inspected by the Health Department of the State Capital of Düsseldorf. Three major and nine minor findings were identified during the inspection. Major findings were reported concerning noncompliance with the randomization procedure, timely PI acknowledgement of SUSARs, and incorrect sample storage. Per the final inspection report, "the study

site complies with fundamental GCP requirements and that the clinical trial was performed in compliance with GCP, apart from the deficiencies listed". This site screened 5 and enrolled 4 patients.

A bioresearch monitoring (BIMO) inspection was conducted by the US FDA of site ID 17090 (Istituto Oncologico Veneto, the site with highest number of enrolled patients). The inspection found that the primary efficacy endpoint data was verifiable. There were no overreporting or underreporting of AEs, SAEs, and deviations were reported according to the protocol. An FDA Form 483 Inspectional Observations was not issued. There was one verbal observation: seven subjects that met exclusion criteria were enrolled in the study. No refusals were encountered during the inspection. No samples were collected. According to preliminary information also sites CI Hochester (NJ) and CI Dasari (TX) have been inspected by the FDA, with the outcomes of "no action indicated".

FDA inspections of the contract research organization (CRO) Syneos Health have also been carried out for FRESCO-2. The 1st was classified by the CDER as NAI, no action indicated. For the 2nd, no form FDA-483 was issued and the inspection and exhibits have been forwarded to CDER for further review and final classification.

PMDA has performed GCP inspections in Osaka University Hospital, Aichi Cancer Center and Syneos Health in Japan. The outcome was NAI, no action indicated.

- **Baseline data**

Baseline demographics

Table 12: Summary of Demographics and Baseline Characteristics (ITT Population) in FRESCO-2

Category	Fruquintinib + BSC (N = 461)	Placebo + BSC (N = 230)	Total (N = 691)
Age, years[a]			
Mean (Std Dev)	62.2 (10.41)	62.4 (9.67)	62.2 (10.16)
Median (Q1, Q3)	64.0 (56.0, 70.0)	64.0 (56.0, 69.0)	64.0 (56.0, 70.0)
Min, max	25, 82	30, 86	25, 86

Category	Fruquintinib + BSC (N = 461)	Placebo + BSC (N = 230)	Total (N = 691)
Age Categories, n (%)			
< 65 years	247 (53.6)	119 (51.7)	366 (53.0)
≥ 65 years	214 (46.4)	111 (48.3)	325 (47.0)
Sex, n (%)			
Female	216 (46.9)	90 (39.1)	306 (44.3)
Male	245 (53.1)	140 (60.9)	385 (55.7)
Race, n (%)			
American Indian or Alaska Native	0	1 (0.4)	1 (0.1)
Asian	43 (9.3)	18 (7.8)	61 (8.8)
Black or African American	13 (2.8)	7 (3.0)	20 (2.9)
Native Hawaiian or Other Pacific Islander	3 (0.7)	2 (0.9)	5 (0.7)
White	367 (79.6)	192 (83.5)	559 (80.9)
Other	5 (1.1)	2 (0.9)	7 (1.0)
Multiple races[b]	2 (0.4)	0	2 (0.3)
Not reported/unknown	28 (6.1)	8 (3.5)	36 (5.2)
Ethnicity, n (%)			
Hispanic or Latino	20 (4.3)	14 (6.1)	34 (4.9)
Not Hispanic or Latino	405 (87.9)	202 (87.8)	607 (87.8)
Not reported/unknown	36 (7.8)	14 (6.1)	50 (7.2)
Region and Country, n (%)			
North America	82 (17.8)	42 (18.3)	124 (17.9)
Europe	329 (71.4)	166 (72.2)	495 (71.6)
Asia Pacific (Japan and Australia)	50 (10.8)	22 (9.6)	72 (10.4)
BMI, kg/m^2[c]			
n	450	225	675
Mean (Std Dev)	26.00 (5.159)	25.77 (5.218)	25.92 (5.176)
Median (Q1, Q3)	25.18 (22.68, 28.93)	25.10 (21.85, 28.69)	25.17 (22.48, 28.81)
Min, max	16.1, 56.7	15.7, 49.4	15.7, 56.7

Category	Fruquintinib + BSC (N = 461)	Placebo + BSC (N = 230)	Total (N = 691)
ECOG PS, n (%)			
0	196 (42.5)	102 (44.3)	298 (43.1)
1	265 (57.5)	128 (55.7)	393 (56.9)

Abbreviations: BMI = body mass index; BSC = best supportive care; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ITT = intent-to-treat; max = maximum; min = minimum; Q1 = 25th percentile; Q3 = 75th percentile; Std Dev = standard deviation.

[a] Age was calculated by sites as the number of years from date of birth up to date of informed consent.

[b] A patient with multiple races was summarized in the multiple race category.

[c] Baseline BMI was calculated as baseline weight (kg)/baseline height $(m)^2$.

Baseline disease characteristics

Table 13: Baseline Disease Characteristics and Disease History (ITT population) in FRESCO-2

Category	Fruquintinib + BSC (N = 461)	Placebo + BSC (N = 230)	Total (N = 691)
Time Since First Diagnosis of CRC, months[a]			
Mean (Std Dev)	52.74 (30.406)	56.02 (28.846)	53.83 (29.914)
Median (Q1, Q3)	47.18 (30.62, 67.38)	49.38 (33.35, 74.81)	47.93 (31.51, 70.01)
Min, Max	6.0, 242.4	7.1, 154.4	6.0, 242.4
Stage of CRC at First Diagnosis, n (%)			
Stage I	20 (4.3)	6 (2.6)	26 (3.8)
Stage II	32 (6.9)	17 (7.4)	49 (7.1)
Stage III	139 (30.2)	84 (36.5)	223 (32.3)
Stage IV	264 (57.3)	119 (51.7)	383 (55.4)
Missing	6 (1.3)	4 (1.7)	10 (1.4)

Category	Fruquintinib + BSC (N = 461)	Placebo + BSC (N = 230)	Total (N = 691)
Primary Tumor Location at First Diagnosis, n (%)			
Colon	279 (60.5)	137 (59.6)	416 (60.2)
Right (cecum, ascending colon, and hepatic flexure)	92 (20.0)	46 (20.0)	138 (20.0)
Left (splenic flexure, descending colon, transverse colon, sigmoid colon)	162 (35.1)	79 (34.3)	241 (34.9)
Right and left	3 (0.7)	2 (0.9)	5 (0.7)
Unknown	22 (4.8)	10 (4.3)	32 (4.6)
Rectum	143 (31.0)	70 (30.4)	213 (30.8)
Colon and rectum	39 (8.5)	23 (10.0)	62 (9.0)
Colon−right (cecum, ascending colon, and hepatic flexure)	5 (1.1)	7 (3.0)	12 (1.7)
Colon−left (splenic flexure, descending colon, transverse colon, sigmoid colon)	30 (6.5)	13 (5.7)	43 (6.2)
Colon−right and left	1 (0.2)	0	1 (0.1)
Colon−unknown	3 (0.7)	3 (1.3)	6 (0.9)
Duration of Metastatic Disease, months[b]			
Mean (Std Dev)	44.01 (23.978)	46.65 (24.607)	44.89 (24.204)
Median (Q1, Q3)	37.88 (26.12, 56.84)	40.97 (28.02, 59.86)	39.03 (27.01, 58.25)
Min, Max	6.0, 192.8	7.1, 147.1	6.0, 192.8
Categories			
≤ 18 months	37 (8.0)	13 (5.7)	50 (7.2)
> 18 months	424 (92.0)	217 (94.3)	641 (92.8)
Number of Metastatic Sites, n (%)			
Single	61 (13.2)	41 (17.8)	102 (14.8)
Multiple	400 (86.8)	189 (82.2)	589 (85.2)
***RAS* Status, n (%)**			
Wild-type	170 (36.9)	85 (37.0)	255 (36.9)
Mutant	291 (63.1)	145 (63.0)	436 (63.1)

Category	Fruquintinib + BSC (N = 461)	Placebo + BSC (N = 230)	Total (N = 691)
***BRAF* Status, n (%)**			
Wild-type	401 (87.0)	198 (86.1)	599 (86.7)
V600E mutation	7 (1.5)	10 (4.3)	17 (2.5)
Other	53 (11.5)	22 (9.6)	75 (10.9)
Microsatellite/Mismatch Repair Status, n (%)			
MSS and/or pMMR	427 (92.6)	215 (93.5)	642 (92.9)
MSI-H and/or dMMR	5 (1.1)	4 (1.7)	9 (1.3)
Unknown	29 (6.3)	11 (4.8)	40 (5.8)

Abbreviations: *BRAF* = B-Raf proto-oncogene; BSC = best supportive care; CRC = colorectal cancer; dMMR = deficient mismatch repair; ITT = intent-to-treat; max = maximum; min = minimum; MSI-H = microsatellite instability-high; MSS = microsatellite stable; pMMR = proficient mismatch repair; Q1 = 25th percentile; Q3 = 75th percentile; *RAS* = rat sarcoma; Std Dev = standard deviation.
Note: Percentages were based on the number of patients in each treatment group unless otherwise specified.
[a] Time since first diagnosis of CRC: (date of randomization – date of first diagnosis of CRC)/30.4375.
[b] Duration of metastatic disease: (date of randomization – date of diagnosis of metastasis disease)/30.4375.

Prior cancer-related therapies

Table 14: Summary of Prior Cancer-Related Therapies (ITT Population) in FRESCO-2

Category	Fruquintinib + BSC (N = 461)	Placebo + BSC (N = 230)	Total (N = 691)
Prior Oncology Treatments, n (%)[a]			
Prior anticancer medication	461 (100)	230 (100)	691 (100)
Prior anticancer radiotherapy	150 (32.5)	73 (31.7)	223 (32.3)
Prior anticancer procedures	373 (80.9)	193 (83.9)	566 (81.9)
Patients With at Least 1 Prior Anticancer Medication, n (%)[b]	461 (100) [6345]	230 (100) [3202]	691 (100) [9547]
Prior Treatment Lines[c]			
n	461	230	691
Mean (Std Dev)	5.1 (1.84)	5.2 (1.94)	5.1 (1.87)
Median (Q1, Q3)	5.0 (4.0, 6.0)	5.0 (4.0, 6.0)	5.0 (4.0, 6.0)
Min, Max	2, 16	2, 12	2, 16
Number of Prior Treatment Lines, n (%)			
0	0	0	0
1	0	0	0
2	2 (0.4)	3 (1.3)	5 (0.7)
3	75 (16.3)	41 (17.8)	116 (16.8)
> 3	384 (83.3)	186 (80.9)	570 (82.5)
Number of Prior Treatment Lines for Metastatic Disease, n (%)			
≤ 3	125 (27.1)	64 (27.8)	189 (27.4)
> 3	336 (72.9)	166 (72.2)	502 (72.6)
Prior Anticancer Therapy With Fluoropyrimidine, Oxaliplatin, and Irinotecan, n (%)			
Fluoropyrimidine	460 (99.8)	230 (100)	690 (99.9)
Oxaliplatin	460 (99.8)	228 (99.1)	688 (99.6)
Irinotecan	459 (99.6)	229 (99.6)	688 (99.6)

Category	Fruquintinib + BSC (N = 461)	Placebo + BSC (N = 230)	Total (N = 691)
Prior Therapy With TAS-102 and/or Regorafenib, n (%)			
TAS-102	240 (52.1)	121 (52.6)	361 (52.2)
Regorafenib	40 (8.7)	18 (7.8)	58 (8.4)
TAS-102 and regorafenib	181 (39.3)	91 (39.6)	272 (39.4)
Prior Treatment With VEGF Inhibitors,[d] n (%)			
Yes	445 (96.5)	221 (96.1)	666 (96.4)
No	16 (3.5)	9 (3.9)	25 (3.6)
Prior Treatment With EGFR Inhibitors, n (%)			
Yes	88 (38.3)	180 (39.0)	268 (38.8)
No	142 (61.7)	281 (61.0)	423 (61.2)
Prior Treatment With EGFR/VEGF Inhibitors, n (%)			
No anti-VEGF and no anti-EGFR	4 (0.9)	5 (2.2)	9 (1.3)
Anti-VEGF, or anti-EGFR, or both	457 (99.1)	225 (97.8)	682 (98.7)
Anti-VEGF and no anti-EGFR	277 (60.1)	137 (59.6)	414 (59.9)
No anti-VEGF and anti-EGFR	12 (2.6)	4 (1.7)	16 (2.3)
Both anti-VEGF and anti-EGFR	168 (36.4)	84 (36.5)	252 (36.5)

Abbreviations: BSC = best supportive care; EGFR = epidermal growth factor receptor; ITT = intent-to-treat; max = maximum; min = minimum; Q1 = 25th percentile; Q3 = 75th percentile; Std Dev = standard deviation; TAS-102 = trifluridine/tipiracil; VEGF = vascular endothelial growth factor.

[a] Patients with multiple prior oncology treatments in the same category were summarized only once within the particular category.

[b] Total number of anticancer medications was included in the bracket.

[c] Prior treatment lines were the distinct number of regimens started prior to the first administration of study drug.

[d] VEGF inhibitors included bevacizumab, ramucirumab, and aflibercept.

Table 15: Summary of Prior Anti-cancer Medication for Metastatic Disease (ITT population) in FRESCO-2

	Placebo + BSC (N=230)	Fruquintinib + BSC (N=461)	Total (N=691)
Subjects with at Least 1 Prior Anti-cancer Medication for Metastatic Disease, n (%) [a]	230 (100)	461 (100)	691 (100)
Prior treatment lines for metastatic disease [b]			
n	230	461	691
Mean (SD)	4.7 (1.88)	4.7 (1.81)	4.7 (1.83)
Median (Q1, Q3)	4.0 (3.0,6.0)	4.0 (3.0,6.0)	4.0 (3.0,6.0)
Min, Max	2,12	2,16	2,16
Category of prior treatment lines for metastatic disease			
0	0	0	0
1	0	0	0
2	11 (4.8)	19 (4.1)	30 (4.3)
3	53 (23.0)	106 (23.0)	159 (23.0)
4	59 (25.7)	122 (26.5)	181 (26.2)
5	47 (20.4)	93 (20.2)	140 (20.3)
6	21 (9.1)	54 (11.7)	75 (10.9)
>6	39 (17.0)	67 (14.5)	106 (15.3)

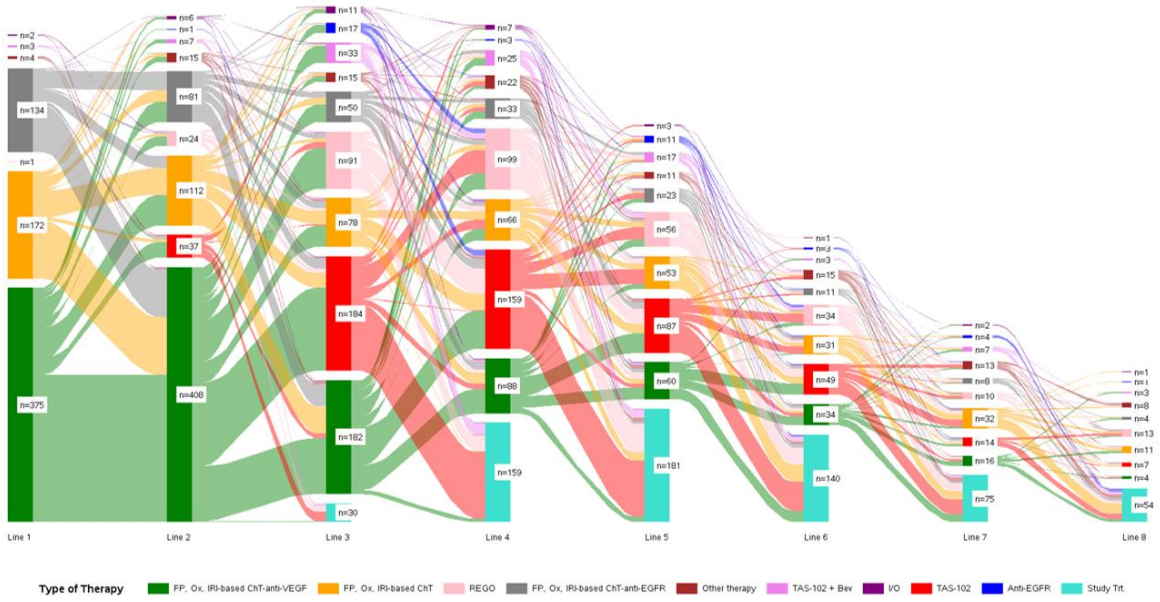
[a] Total number of anti-cancer medications is included in the bracket.
[b] Prior treatment lines are the distinct number of regimens started prior to the first administration of study medication.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; Max=Maximum; Min=Minimum; Q1=25% percentile; Q3=75% percentile; SD=Standard deviation.
Source: Listing 16.2.4.5.2.1.
Program Name: T-14-01-04-02-02-02.SAS Data cut date: 24JUN2022

Table 16: Additional information for prior treatment for metastatic disease (ITT population) in FRESCO-2

History of Colorectal Cancer
(Intent-to-Treat Population)

	Placebo + BSC (N=230)	Fruquintinib + BSC (N=461)	Total (N=691)
Prior treatment with EGFR/VEGF Inhibitors, n (%)			
No anti-VEGF and no anti-EGFR	5 (2.2)	4 (0.9)	9 (1.3)
Anti-VEGF, or anti-EGFR, or both	225 (97.8)	457 (99.1)	682 (98.7)
Anti-VEGF and no anti-EGFR	137 (59.6)	277 (60.1)	414 (59.9)
No anti-VEGF and anti-EGFR	4 (1.7)	12 (2.6)	16 (2.3)
Both anti-VEGF and anti-EGFR	84 (36.5)	168 (36.4)	252 (36.5)
Prior Treatment with Immune Checkpoint Inhibitors for MSI-H/dMMR, n (%)			
Yes	11 (4.8)	21 (4.6)	32 (4.6)
No	219 (95.2)	440 (95.4)	659 (95.4)
Prior Treatment with BRAF Inhibitors for BRAF V600E Mutation, n (%)			
Yes	7 (3.0)	9 (2.0)	16 (2.3)
No	223 (97.0)	452 (98.0)	675 (97.7)
Liver Metastases at Baseline, n (%)			
Yes	156 (67.8)	339 (73.5)	495 (71.6)
No	74 (32.2)	122 (26.5)	196 (28.4)
Number of Metastatic Sites, n (%)			
Single	41 (17.8)	61 (13.2)	102 (14.8)
Multiple	189 (82.2)	400 (86.8)	589 (85.2)

[a] Time since diagnosis of colorectal cancer: (date of randomization - date of first diagnosis of colorectal cancer)/30.4375
[b] Duration of metastatic disease: (date of randomization - date of diagnosis of metastatic disease)/30.4375.
[c] Subjects with multiple prior oncology treatment in the same category will be summarized only once within the particular category.
[d] This is due to patient 17120-002 who only had RECTUM.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BRAF=B-Raf proto-oncogene; BSC=Best supportive care; dMMR=Deficient mismatch repair; EGFR=Epidermal growth factor receptor; Max=Maximum; Min=Minimum; nMSI-H=Microsatellite instability-high; MSS=Microsatellite stable; pMMR=Proficient mismatch repair; Q1=25% percentile; Q3=75% percentile; nRAS=Rat sarcoma; SD=Standard deviation; TAS-102=Trifluridine/Tipiracil; VEGF=Vascular endothelial growth factor.
Source: Listing 16.2.4.5.1.
Program Name: T-14-01-03-02.SAS Data cut date: 24JUN2022 Table Generation: 01SEP2022 06:56



Source: FRESCO-2 Ad hoc Figure 23.1.1.4.
EGFR: epidermal growth factor receptor; FP: fluoropyrimidine; FRESCO-2: Study 2019-013-GLOB1; I/O: immunotherapy; ITT: intent-to-treat; IRI-based ChT: irinotecan-based chemotherapy; Ox: oxaliplatin; REGO: regorafenib; VEGF: vascular endothelial growth factor; Trt: treatment.

Figure 8: Patient journey in FRESCO-2 (ITT population)

- **Numbers analysed**

Table 17: Analysis populations (all enrolled patients) in FRESCO-2

Category	Number of Patients, n (%)		
	Fruquintinib + BSC (N = 461)	Placebo + BSC (N = 230)	Total (N = 691)
ITT Population	**461**	**230**	**691**
Safety Population[a]	**456**	**230**	**686**
Reason for exclusion			
No dose of study treatment received	3	2	5
PK Population[a]	**329**	**2**	**331**
Reason for exclusion			
No postdose PK sample collected and analyzed	127	228	355
No single dose of study treatment received	3	2	5
PP Population	**444**	**225**[b]	**669**
Reason for exclusion			
Major protocol deviation	17	5[b]	22
Inclusion or exclusion criteria	12	3[b]	15
Incorrect IP kit given to patient	2	0	2
Randomized but not treated	3	2	5
Did not receive the treatment to which they were randomized	2	0	2

Abbreviations: BSC = best supportive care; DBL = database lock; IP = investigational product; ITT = intent-to-treat; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic(s); PP = per protocol; VEGF = vascular endothelial growth factor.
Note: Percentages were based on the number of patients in each treatment group unless otherwise specified.
[a] Two patients who were assigned to the fruquintinib group received placebo during the study. Refer to Section 10.2.
[b] One randomized patient did not receive either regorafenib or anti-VEGF listed in prior anticancer medication; hence, the patient should not have been randomized into the study and should have been excluded from the PP population. However, this patient was only identified after DBL, and post hoc analyses were conducted for both OS and PFS with the updated PP population.

Protocol compliance:

Table 18: Summary of Protocol Deviations (ITT Population) in FRESCO-2

Category	Number of Patients, n (%)		
	Fruquintinib + BSC (N = 461)	Placebo + BSC (N = 230)	Total (N = 691)
Number of Patients With Any Protocol Deviations	450 (97.6)	225 (97.8)	675 (97.7)
Type of protocol deviation			
Major	417 (90.5)	196 (85.2)	613 (88.7)
Minor	427 (92.6)	214 (93.0)	641 (92.8)
Category of Criteria for Major Protocol Deviations			
Concomitant medication/administration of prohibited medication	45 (9.8)	25 (10.9)	70 (10.1)
Inclusion or exclusion criteria	168 (36.4)[a]	80 (34.8)[b]	248 (35.9)[a,b]
ICF not signed or signed late	7 (1.5)	5 (2.2)	12 (1.7)
ICF/other	6 (1.3)	1 (0.4)	7 (1.0)
Incorrect IP kit given to patient	4 (0.9)	1 (0.4)	5 (0.7)
IP dosing	233 (50.5)	93 (40.4)	326 (47.2)
IP/other	9 (2.0)	5 (2.2)	14 (2.0)
Met withdrawal criteria but was not withdrawn	9 (2.0)	2 (0.9)	11 (1.6)
Patient privacy/other	1 (0.2)	0	1 (0.1)
Randomization/other	0	2 (0.9)	2 (0.3)
Randomized not treated	3 (0.7)	2 (0.9)	5 (0.7)
SAE not reported or reported late	24 (5.2)	21 (9.1)	45 (6.5)

Category	Number of Patients, n (%)		
	Fruquintinib + BSC (N = 461)	Placebo + BSC (N = 230)	Total (N = 691)
Missed study procedure	246 (53.4)	101 (43.9)	347 (50.2)
Study procedure/other	151 (32.8)	63 (27.4)	214 (31.0)
Study procedure/site staff authorization, delegation, training	0	1 (0.4)	1 (0.1)
Study procedure/visit missing	63 (13.7)	44 (19.1)	107 (15.5)
Visit window	69 (15.0)	26 (11.3)	95 (13.7)
Category of Criteria for Minor Protocol Deviations			
Inclusion or exclusion criteria	0	1 (0.4)	1 (0.1)
ICF not signed or signed late	5 (1.1)	2 (0.9)	7 (1.0)
ICF/other	7 (1.5)	2 (0.9)	9 (1.3)
Incorrect IP kit given to patient	1 (0.2)	0	1 (0.1)
IP dosing	116 (25.2)	39 (17.0)	155 (22.4)
IP/other	18 (3.9)	14 (6.1)	32 (4.6)
Met withdrawal criteria but was not withdrawn	0	1 (0.4)	1 (0.1)
SAE not reported or reported late	1 (0.2)	0	1 (0.1)
Study procedure/missed procedure	392 (85.0)	187 (81.3)	579 (83.8)
Study procedure/other	243 (52.7)	107 (46.5)	350 (50.7)
Study procedure/visit missing	22 (4.8)	13 (5.7)	35 (5.1)
Visit window	210 (45.6)	76 (33.0)	286 (41.4)

Abbreviations: BSC = best supportive care; DBL = database lock; ICF = informed consent form; IP = investigational product; ITT = intent-to-treat; SAE = serious adverse event.
Notes: Percentages were based on the number of patients in each treatment group unless otherwise specified.
Patients with multiple major and/or minor protocol deviations in the same category were summarized only once within the particular category.
[a] There was 1 additional patient with a major protocol deviation under the category "Inclusion or exclusion criteria" noted after DBL.
[b] There was 1 additional patient with a major protocol deviation under the category "Inclusion or exclusion criteria" noted after DBL. The details are provided in Table 12.

Table 19: Summary of patients with major protocol deviations excluded from the PP population in FRESCO-2

Major Protocol Deviation	Number of Patients	
	Fruquintinib + BSC (N = 461)	Placebo + BSC (N = 230)
Number of patients excluded from PP population	17	5
Reasons for exclusion		
Randomized not treated	3	2
Inclusion or exclusion criteria	12	3
Incorrect IP kit given to patient	2	0

Abbreviations: BSC = best supportive care; DBL = database lock; IP = investigational product; PP = per protocol.
Note: There was 1 additional patient with a major protocol deviation noted after the DBL that led to the patient being excluded from the PP population. This also led to the post hoc analysis described in Section 9.7.4.14.

- **Outcomes and estimation**

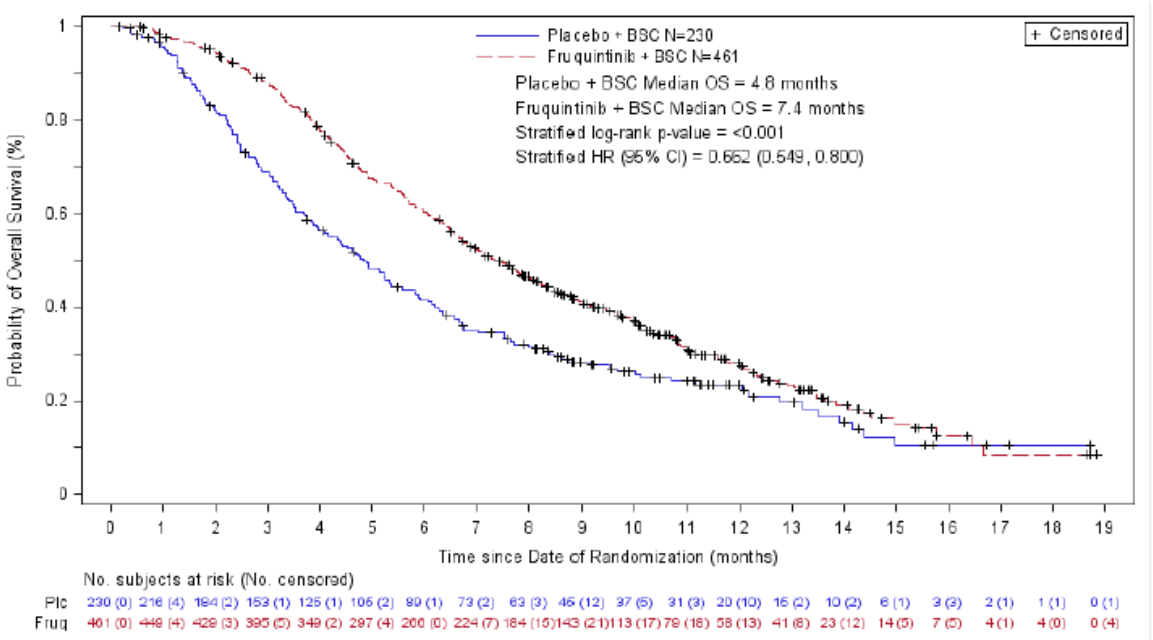
OS

Table 20: Summary of OS (ITT population) in FRESCO-2

Statistics	Fruquintinib + BSC (N = 461)	Placebo + BSC (N = 230)
Number of Patients Who Died, n (%)	317 (68.8)	173 (75.2)
Number of Patients Censored, n (%)	144 (31.2)	57 (24.8)
Censoring Reasons, n (%)		
Alive[a]	127 (88.2)	49 (86.0)
Lost to follow-up[a]	3 (2.1)	0
Withdrawal of consent[a]	14 (9.7)	8 (14.0)
OS (months)[b]		
25% percentile (95% CI)	4.3 (3.9, 4.6)	2.5 (2.2, 2.9)
Median (95% CI)	7.4 (6.7, 8.2)	4.8 (4.0, 5.8)
75% percentile (95% CI)	12.4 (11.2, 13.6)	10.1 (8.1, 13.5)
Min, max	0.2,[c] 18.9[c]	0.2, 18.7[c]
Probability (%) of Being Alive at (95% CI)[d]		
3 months	88.1 (85.1, 91.1)	68.8 (62.8, 74.9)
6 months	60.4 (55.9, 64.9)	41.5 (35.0, 48.0)
9 months	41.1 (36.4, 45.8)	28.2 (22.1, 34.3)
12 months	27.8 (23.0, 32.6)	23.2 (17.1, 29.2)
18 months	8.3 (2.3, 14.2)	10.3 (3.9, 16.8)

Statistics	Fruquintinib + BSC (N = 461)	Placebo + BSC (N = 230)
Duration (Months) to Follow-up[b,e]		
25% percentile (95% CI)	9.0 (8.5, 9.5)	8.7 (8.1, 9.6)
Median (95% CI)	11.3 (10.6, 12.4)	11.2 (9.9, 12.0)
75% percentile (95% CI)	14.2 (13.2, 15.4)	15.5 (12.1, 16.7)
Min, max	0.2, 18.9	0.2,[c] 18.7
Comparison (Fruquintinib vs Placebo)		
Stratified HR (SE)[f]	0.662 (0.096)	
95% CI[f]	(0.549, 0.800)	
2-sided *P* value[g]	< .001	

Abbreviations: BSC = best supportive care; CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; max = maximum; min = minimum; OS = overall survival; SE = standard error.
Notes: Percentages were based on the number of patients in each treatment group unless otherwise specified.
OS was defined as the time (months) from date of randomization to death from any cause and calculated as (date of death or last known alive – date of randomization + 1)/30.4375.
[a] Percentage was based on the number of censored patients.
[b] The median, 25% and 75% percentiles were calculated using the Kaplan-Meier method, and the corresponding 95% CIs are calculated from a log-log transformation based on the Brookmeyer-Crowley method.
[c] Censored value.
[d] The survival probabilities and corresponding 95% CIs were calculated using a linear transformation based on the Brookmeyer-Crowley method at the selected landmarks.
[e] Duration (months) to follow-up refers to the time interval between date of randomization and last date known to be alive for patients who had not yet been reported to have died by the time of analysis. Patients who were reported to have died would be censored at death date.
[f] The stratified HR and its 95% CI are estimated using stratified Cox proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group was the only covariate in the model.
[g] *P* value to test the treatment effect was calculated using the stratified log-rank test to account for the randomization schedule stratification factors.



Abbreviations: BSC = best supportive care; CI = confidence interval; Fruq = fruquintinib; HR = hazard ratio; ITT = intent-to-treat; OS = overall survival; Plc = placebo.

Figure 9: Kaplan-Meier curve for OS by treatment group (ITT population) in FRESCO-2

To address the concern about possible bias caused by gender-imbalance between the treatment arms, the Applicant delivered the requested analysis of OS with gender as a covariate. The results of this analysis were consistent with the primary analysis (HR=0.667, 95% CI 0.552, 0.805, p<0.001) (data not shown).

Of note, the Applicant performed an OS sensitivity analysis, adjusted for key prognostic factors (on ITT population). In this analysis, the randomisation schedule stratification factors and treatment group are covariates in the model and additional adjustments for key prognostic factors are selected using stepwise selection process with level of entry and removal at alpha=0.15 (data not shown). In this the HR for OS is 0.562, 2-sided *P* <0.001.

PFS

Table 21: Summary of PFS (ITT Population) in FRESCO-2

Statistics	Fruquintinib + BSC (N = 461)	Placebo + BSC (N = 230)
Number of Patients Who Died or Had PD, n (%)	392 (85.0)	213 (92.6)
Number of patients who had PD, n (%)	301 (65.3)	167 (72.6)
Number of patients who died, n (%)	91 (19.7)	46 (20.0)
Number of Patients Censored, n (%)	69 (15.0)	17 (7.4)
Censoring Reasons, n (%)		
No baseline or postbaseline assessment[a]	17 (24.6)	7 (41.2)
Lost to follow-up without death or PD[a]	1 (1.4)	0
Withdrawal of consent without death or PD[a]	4 (5.8)	1 (5.9)
New antitumor therapy started prior to death or PD[a]	10 (14.5)	3 (17.6)
Death or PD occurred after ≥ 2 consecutive missed assessments[a]	0	0
No death or PD by the time of data cutoff for final analysis[a]	37 (53.6)	6 (35.3)
PFS (months)[b]		
25% percentile (95% CI)	1.9 (1.9, 1.9)	1.6 (1.3, 1.7)
Median (95% CI)	3.7 (3.5, 3.8)	1.8 (1.8, 1.9)
75% percentile (95% CI)	5.8 (5.6, 6.3)	2.1 (1.9, 2.6)
Min, max	0.0,[c] 18.9[c]	0.0,[c] 11.6
Probability (%) of Being Alive at (95% CI)[d]		
3 months	59.6 (55.0, 64.2)	17.9 (12.7, 23.0)
6 months	23.8 (19.7, 28.0)	1.1 (0.0, 2.6)
9 months	11.3 (8.1, 14.6)	0.5 (0.0, 1.6)

Statistics	Fruquintinib + BSC (N = 461)	Placebo + BSC (N = 230)
12 months	3.8 (1.6, 5.9)	0
18 months	2.1 (0.4, 3.8)	0
Comparison (Fruquintinib vs Placebo)		
Stratified HR (SE)[e]	0.321 (0.094)	
95% CI[e]	0.267, 0.386	
2-sided *P* value[f]	< .001	

Abbreviations: BSC = best supportive care; CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; max = maximum; min = minimum; PD = progressive disease; PFS = progression-free survival; SE = standard error.
Notes: PFS was defined as the time (months) from randomization until the first PD or death from any cause and calculated as (date of death or PD or last assessment – date of randomization + 1)/30.4375.
Percentages were based on the number of patients in each treatment group unless otherwise specified.
[a] Percentage was based on the number of censored patients.
[b] The median and 25% and 75% percentiles were calculated using the Kaplan-Meier method, and the corresponding 95% CIs were calculated from a log-log transformation based on the Brookmeyer-Crowley method.
[c] Censored value.
[d] The survival probabilities and corresponding 95% CIs were calculated using a linear transformation based on the Brookmeyer-Crowley method at the selected landmarks.
[e] The stratified HR and its 95% CI were estimated using stratified Cox proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group was the only covariate in the model.
[f] *P* value was calculated using the stratified log-rank test.

Of note, above the probability of being alive is a misleading expression, as this includes patients, who are alive and without progression at these timepoints.

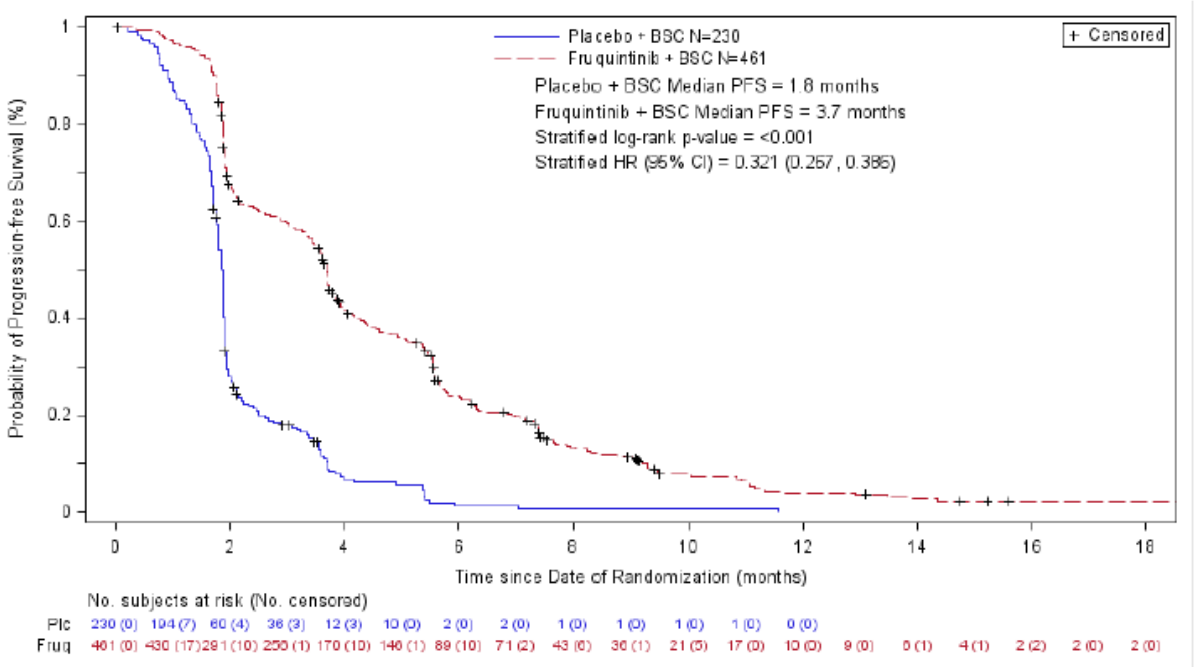


Figure 10: Kaplan-Meier curve for PFS by treatment group (ITT population) in FRESCO-2

Some of the disease progressions may have been masked by the switch to other anticancer treatment (OATr) before PD. In the main analysis of PFS, 13 patients were censored for this reason. A sensitivity

analysis was conducted where PFS events were considered regardless of switch to subsequent anticancer therapy and led into consistent results (data not shown).

BOR, ORR, and DCR per Investigator

Table 22: Summary of BOR, ORR, and DCR per Investigator (ITT population) in FRESCO-2

	Fruquintinib + BSC (N = 461)	Placebo + BSC (N = 230)
BOR		
CR	0	0
PR	7 (1.5)	0
SD	249 (54.0)	37 (16.1)
$CR_{Unconfirmed}$	0	0
$PR_{Unconfirmed}$	5 (1.1)	0
PD	139 (30.2)	143 (62.2)
NE	6 (1.3)	1 (0.4)

	Fruquintinib + BSC (N = 461)	Placebo + BSC (N = 230)
NA	60 (13.0)	49 (21.3)
ORR: CR + PR, n (%)	7 (1.5)	0
2-sided 95% CI[a]	0.6, 3.1	0.0, 1.6
Adjusted difference (fruquintinib – placebo) (SE)[b]	1.5 (0.006)	
95% CI[b]	0.4, 2.7	
2-sided *P* value[c]	.059	
DCR: CR + PR + SD for at least 7 weeks, n (%)	256 (55.5)	37 (16.1)
2-sided 95% CI[a]	50.9, 60.1	11.6, 21.5
Adjusted difference (fruquintinib – placebo) (SE)[b]	39.4 (0.034)	
95% CI[b]	32.8, 46.0	
2-sided *P* value[c]	<.001	
ORR (regardless of confirmation): ORR: any CR + any PR), n (%)	12 (2.6)	0
2-sided 95% CI[a]	1.4, 4.5	0.0, 1.6
Adjusted difference (fruquintinib – placebo) (SE)[b]	2.6 (0.007)	
95% CI[b]	1.2, 4.1	
2-sided *P* value[c]	.014	

Abbreviations: BOR = best overall response; BSC = best supportive care; CI = confidence interval; CR = complete response; DCR = disease control rate; ITT = intent-to-treat; NA = not applicable; NE = not evaluable; ORR = objective response rate; PD = progressive disease; PR = partial response; SD = stable disease; SE = standard error.

Note: Percentages were based on the number of patients in each treatment group unless otherwise specified.

[a] 95% CI of ORR or DCR was calculated using the Clopper-Pearson exact method.

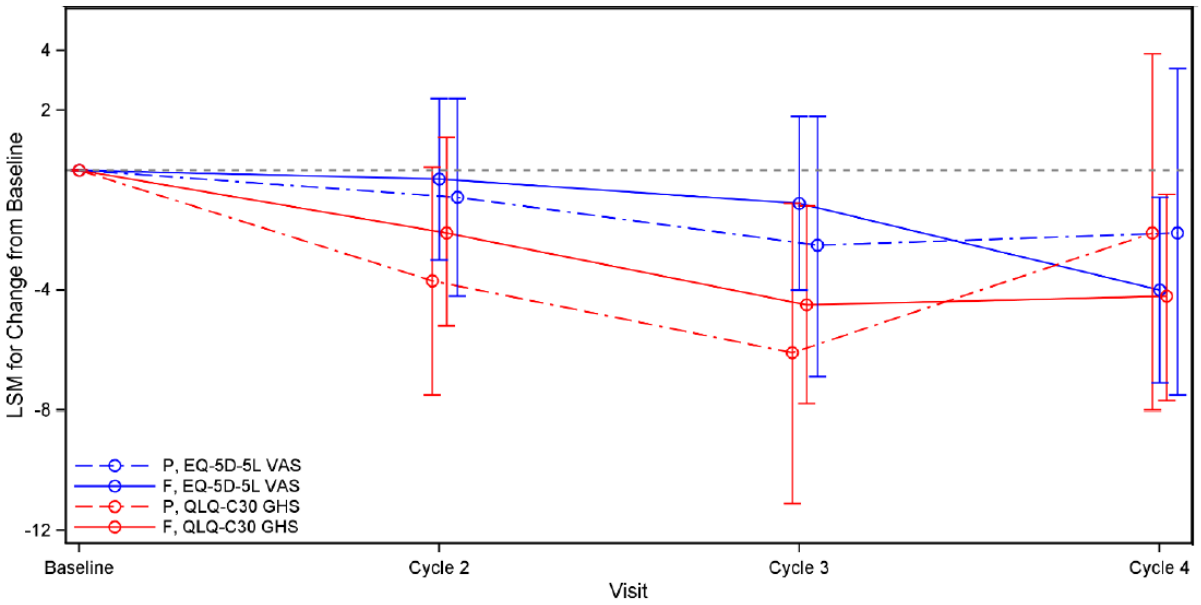
[b] The adjusted difference and its 95% CI were calculated using the Wald method to account for the randomization schedule stratification factors.

[c] *P* value was calculated from a stratified Cochran-Mantel Haenszel test accounting for the randomization schedule stratification factors.

Health related quality of life (HR QoL)

HRQoL data were evaluated based on the EORTC QLQ-C30 and EQ-5D-5L questionnaires.

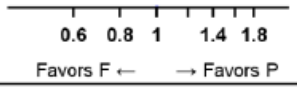
LSM difference between fruquintinib and placebo for LSM change from baseline results for Cycle 2 and Cycle 3 for the QLQ-C30 Global Health Status and EQ-5D-5L VAS score showed a trend indicating benefit in patients treated with fruquintinib compared to those treated with placebo (figure not included).



Abbreviations: F = fruquintinib; GHS = global health status; LSM = least squares mean; P = placebo.
Note: A higher score for each scale indicated a better overall condition for a patient.

Figure 11: Least Square Mean Change from Baseline: QLQ-C30 Global Health Status and EQ-5D-5L VAS (ITT Population) in FRESCO-2

Scale	Median (Months) F	Median (Months) P	Hazard Ratio (95% CI)
EQ-5D-5L VAS	2.6	1.9	0.8 (0.6, 0.9)
EQ-5D-5L Index Scores	3	1.9	0.8 (0.7, 1.0)
Global health status QLQ-C30	2.1	1.8	0.9 (0.7, 1.0)
Physical functioning	2.8	2.1	1.0 (0.8, 1.2)
Role functioning	2.5	2	1.0 (0.8, 1.1)
Emotional functioning	4.1	2.8	0.8 (0.7, 1.0)
Cognitive functioning	3	2.6	1.0 (0.8, 1.2)
Social functioning	3.2	2.3	0.9 (0.8, 1.1)
Fatigue	1.9	1.8	0.8 (0.7, 1.0)
Nausea and vomiting	4.5	3.1	0.8 (0.7, 1.0)
Pain	2.2	2	1.0 (0.8, 1.2)
Dyspnoea	4.3	2.2	0.7 (0.6, 0.9)
Insomnia	3.9	2.2	0.8 (0.7, 0.9)
Appetite loss	3.4	2.5	0.9 (0.8, 1.1)
Constipation	4.6	3.1	0.8 (0.7, 1.0)
Diarrhoea	4.3	3.7	1.0 (0.8, 1.2)
Financial difficulty	5.4	3.3	0.8 (0.6, 0.9)



Abbreviations: CI = confidence interval; F = fruquintinib; P = placebo; HR = hazard ration; TTD = time to deterioration.
Note: Median TTD (months) was calculated using the Kaplan-Meier method. Stratified HR and its 95% CI were estimated using Cox hazard model (accounting for the randomization schedule stratification factors), in which treatment and baseline value of scale was included as fixed effects.

Figure 12: Forest Plot for Hazard Ratio (Fruquintinib vs Placebo) of Time to Deterioration for QLQ-C30 Global Health, QLQ-C30 Subscales and EQ-5D-5L (ITT Population) in FRESCO-2

Health Resource Utilization

The primary reasons for visits and types of resources used were similar between the fruquintinib and placebo groups. The median duration of visits was 1.0 day in both treatment groups, with a range of 1 to 99 days for the fruquintinib group and 1 to 59 days for the placebo group; the median number of visits was 2.0 in both groups (1-24 and 1-18, respectively). In addition, the median number of prescribed concomitant medications was 1.0 in both treatment groups (range, 1-18 and 1−9, respectively). Thus, there were no relevant differences in health resource utilization between patients treated with fruquintinib or patients treated with placebo.

Exploratory endpoints

Exploratory endpoints were used to assess predictive biomarkers of response to fruquintinib. These included:

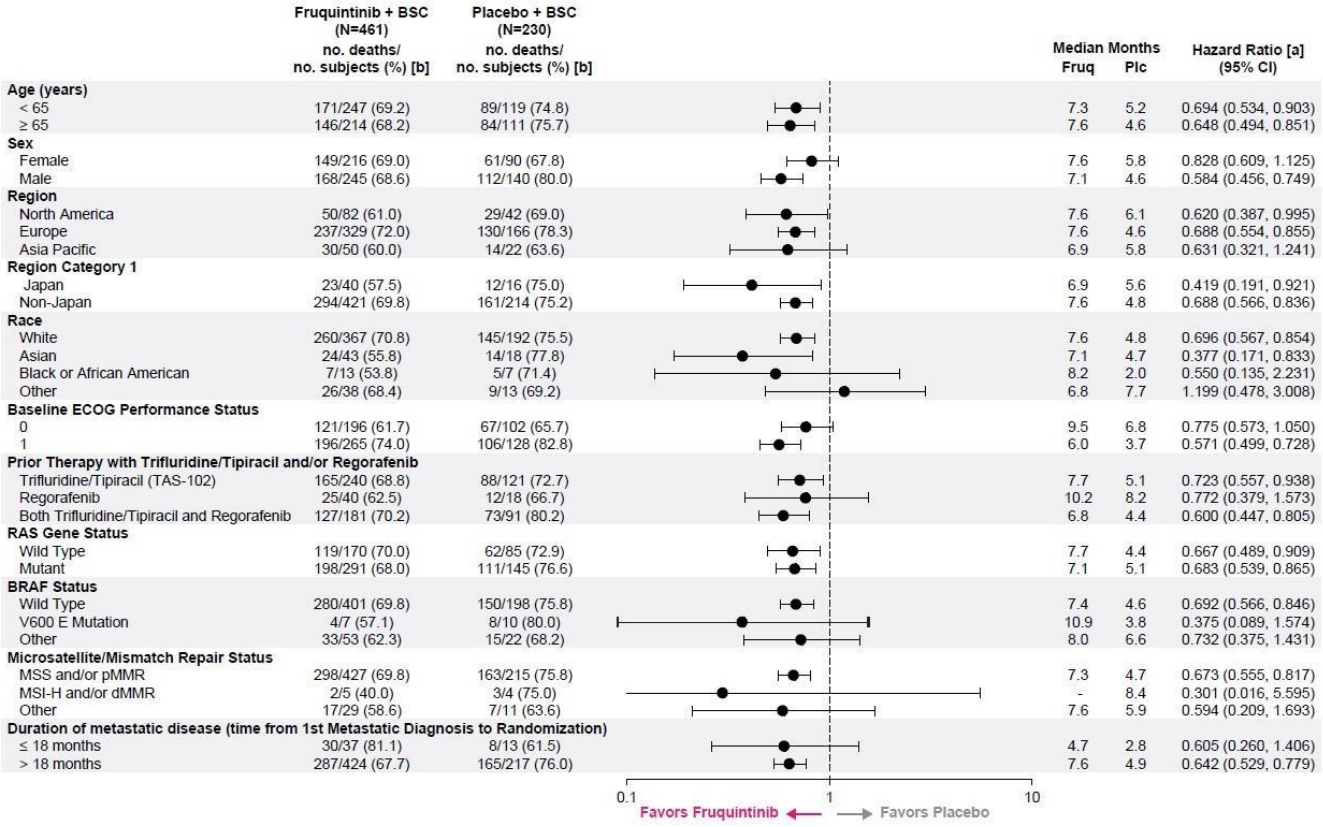
- change from baseline in serum CEA;
- change from baseline in ctDNA;
- pharmacogenomics.

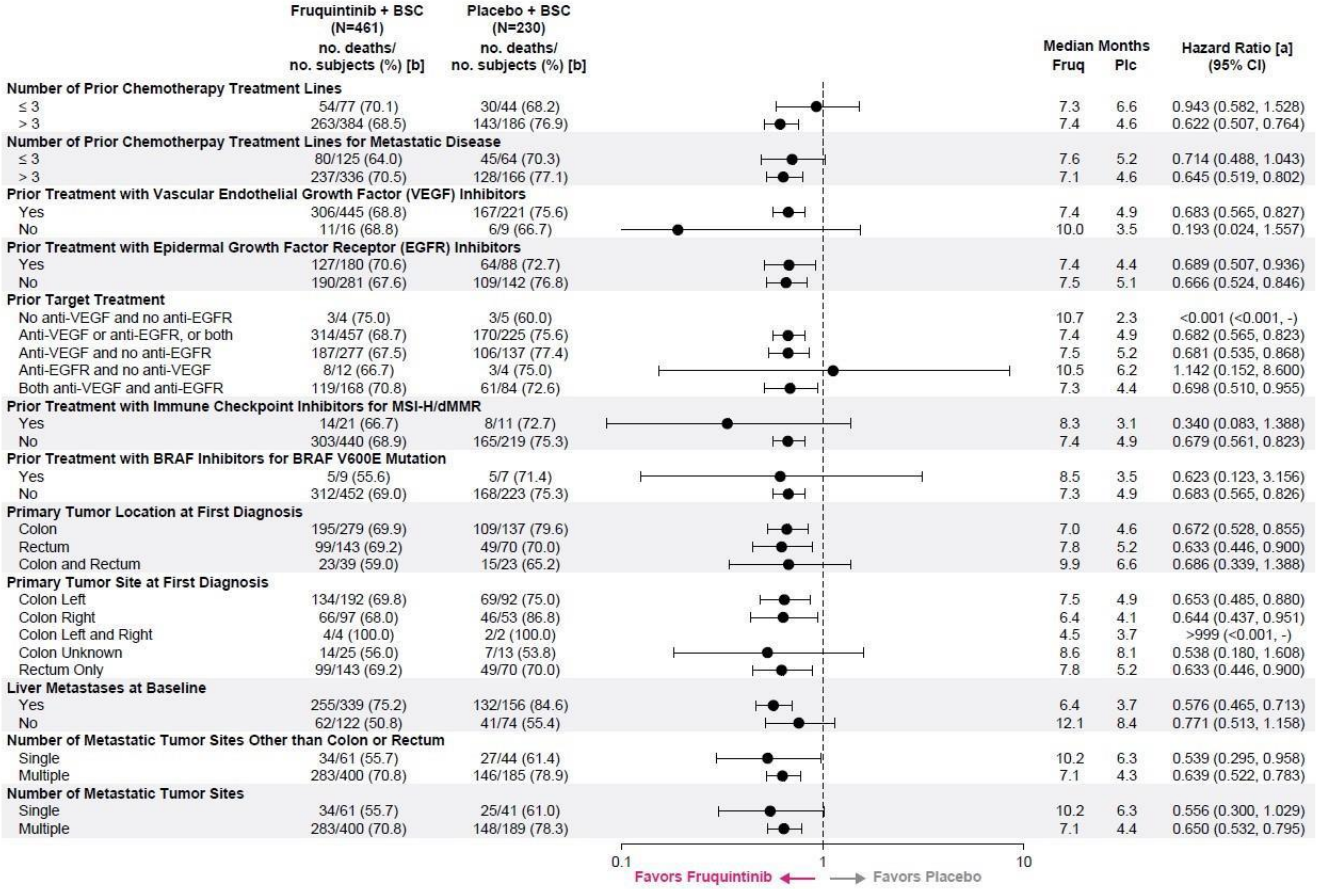
The results for changes in CEA were summarised in table format (data not shown). The median in CEA at baseline was 127 in the fruquintinib group and 169 in the placebo group.

- **Ancillary analyses**

Subgroup analyses

OS subgroup analysis





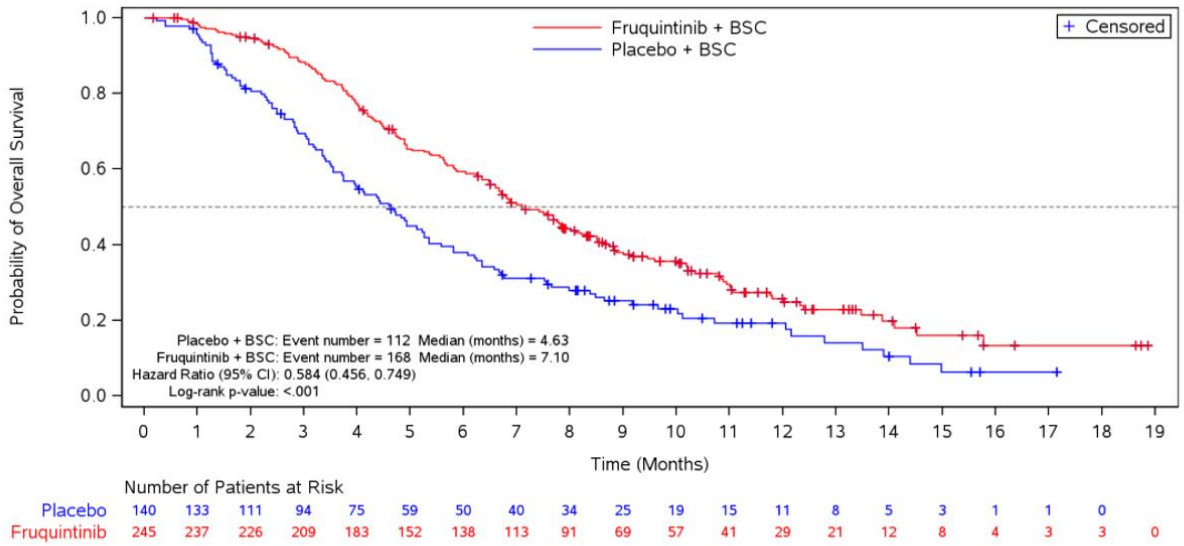
Abbreviations: *BRAF* = B-Raf proto-oncogene; BSC = best supportive care; CI = confidence interval; dMMR = deficient mismatch repair; ECOG = Eastern Cooperative Oncology Group; Fruq = fruquintinib; HR = hazard ratio; ITT = intent-to-treat; MSI-H = microsatellite instability-high; MSS = microsatellite stable; OS = overall survival; Plc = placebo; pMMR = proficient mismatch repair; *RAS* = Rat sarcoma.

[a] The unstratified Cox proportional hazards model in which the applicable randomization schedule stratification factors and treatment group are included in the model as covariates.

[b] Percentage is based on the number of patients in the subgroup.

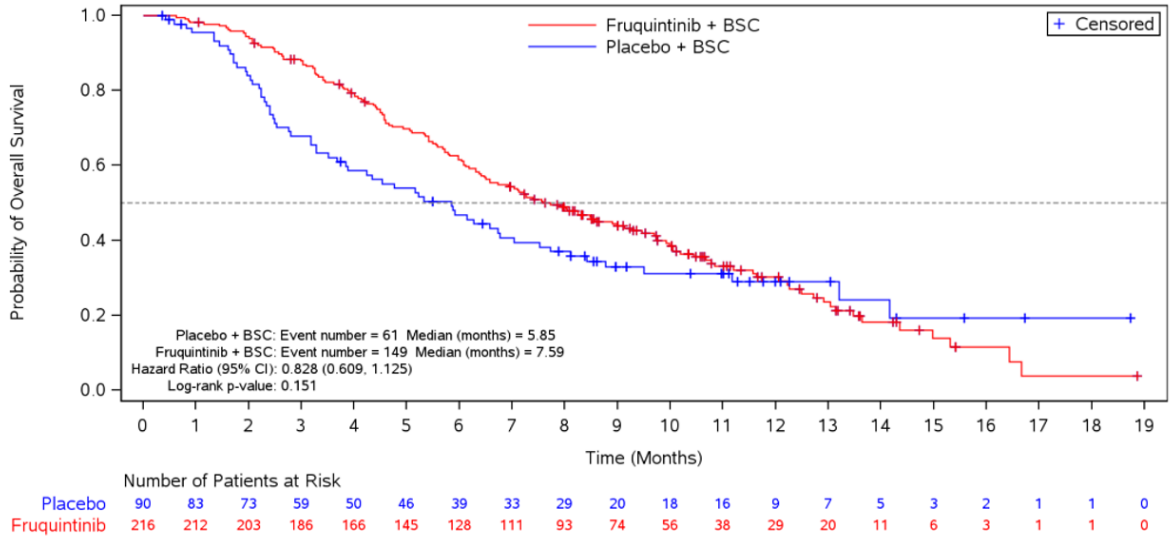
Figure 13: Forest Plot for Hazard Ratio and 95% CI for unstratified OS by Subgroups (ITT Population) in FRESCO-2

Note that the subgroups based on number of prior treatment lines are mislabelled as containing chemotherapies only; in fact, all prior anticancer treatment lines were included.



Source: Day 120 Efficacy Analysis Figure 35.1.1.1.1C.
BSC: best supportive care; FRESCO-2: Study 2019-013-GLOB1; ITT: intent-to-treat.

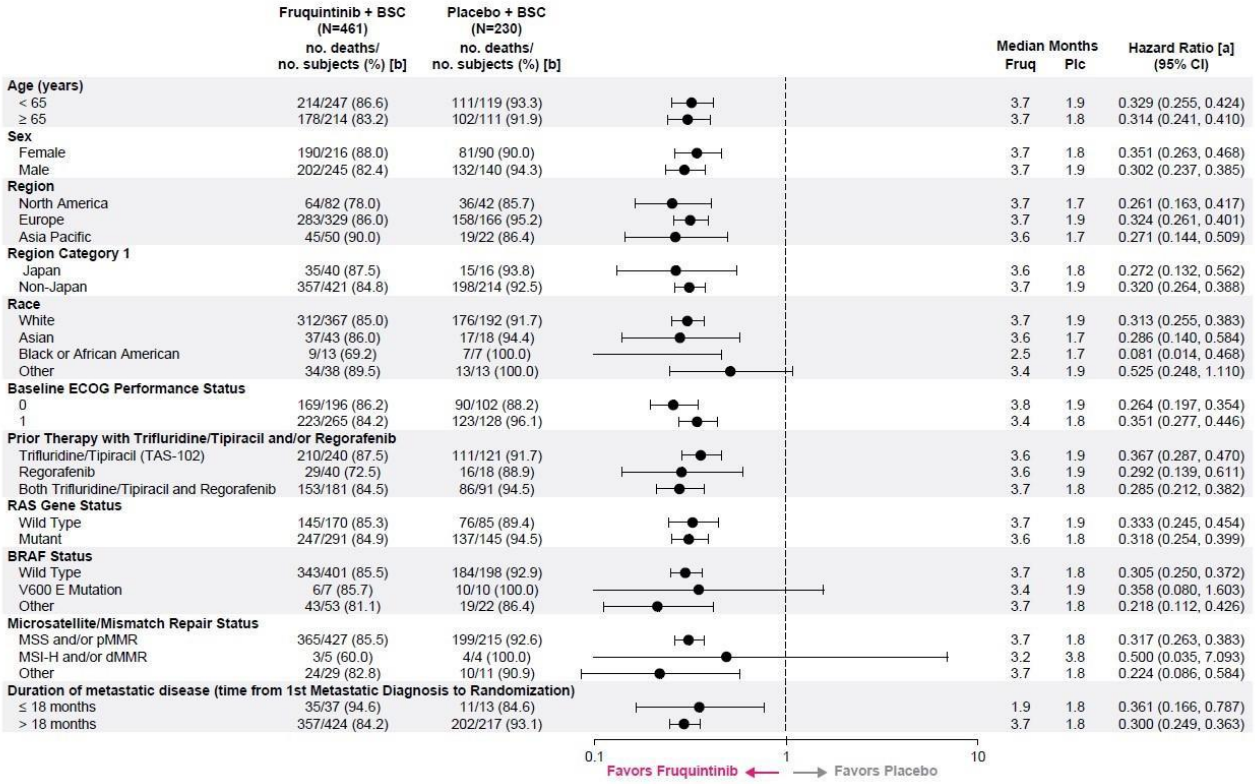
Figure 14: Kaplan-Meier curve for OS by gender – male (ITT population of FRESCO-2)



Source: Day 120 Efficacy Analysis Figure 35.1.1.1.1C.
BSC: best supportive care; FRESCO-2: Study 2019-013-GLOB1; ITT: intent-to-treat.

Figure 15: Kaplan-Meier curve for OS by gender – female (ITT population of FRESCO-2)

PFS subgroup analysis



	Fruquintinib + BSC (N=461) no. deaths/ no. subjects (%) [b]	Placebo + BSC (N=230) no. deaths/ no. subjects (%) [b]	Median Months Fruq	Median Months Plc	Hazard Ratio [a] (95% CI)
Age (years)					
< 65	214/247 (86.6)	111/119 (93.3)	3.7	1.9	0.329 (0.255, 0.424)
≥ 65	178/214 (83.2)	102/111 (91.9)	3.7	1.8	0.314 (0.241, 0.410)
Sex					
Female	190/216 (88.0)	81/90 (90.0)	3.7	1.8	0.351 (0.263, 0.468)
Male	202/245 (82.4)	132/140 (94.3)	3.7	1.9	0.302 (0.237, 0.385)
Region					
North America	64/82 (78.0)	36/42 (85.7)	3.7	1.7	0.261 (0.163, 0.417)
Europe	283/329 (86.0)	158/166 (95.2)	3.7	1.9	0.324 (0.261, 0.401)
Asia Pacific	45/50 (90.0)	19/22 (86.4)	3.6	1.7	0.271 (0.144, 0.509)
Region Category 1					
Japan	35/40 (87.5)	15/16 (93.8)	3.6	1.8	0.272 (0.132, 0.562)
Non-Japan	357/421 (84.8)	198/214 (92.5)	3.7	1.9	0.320 (0.264, 0.388)
Race					
White	312/367 (85.0)	176/192 (91.7)	3.7	1.9	0.313 (0.255, 0.383)
Asian	37/43 (86.0)	17/18 (94.4)	3.6	1.7	0.286 (0.140, 0.584)
Black or African American	9/13 (69.2)	7/7 (100.0)	2.5	1.7	0.081 (0.014, 0.468)
Other	34/38 (89.5)	13/13 (100.0)	3.4	1.9	0.525 (0.248, 1.110)
Baseline ECOG Performance Status					
0	169/196 (86.2)	90/102 (88.2)	3.8	1.9	0.264 (0.197, 0.354)
1	223/265 (84.2)	123/128 (96.1)	3.4	1.8	0.351 (0.277, 0.446)
Prior Therapy with Trifluridine/Tipiracil and/or Regorafenib					
Trifluridine/Tipiracil (TAS-102)	210/240 (87.5)	111/121 (91.7)	3.6	1.9	0.367 (0.287, 0.470)
Regorafenib	29/40 (72.5)	16/18 (88.9)	3.6	1.9	0.292 (0.139, 0.611)
Both Trifluridine/Tipiracil and Regorafenib	153/181 (84.5)	86/91 (94.5)	3.7	1.8	0.285 (0.212, 0.382)
RAS Gene Status					
Wild Type	145/170 (85.3)	76/85 (89.4)	3.7	1.9	0.333 (0.245, 0.454)
Mutant	247/291 (84.9)	137/145 (94.5)	3.6	1.8	0.318 (0.254, 0.399)
BRAF Status					
Wild Type	343/401 (85.5)	184/198 (92.9)	3.7	1.8	0.305 (0.250, 0.372)
V600 E Mutation	6/7 (85.7)	10/10 (100.0)	3.4	1.9	0.358 (0.080, 1.603)
Other	43/53 (81.1)	19/22 (86.4)	3.7	1.8	0.218 (0.112, 0.426)
Microsatellite/Mismatch Repair Status					
MSS and/or pMMR	365/427 (85.5)	199/215 (92.6)	3.7	1.8	0.317 (0.263, 0.383)
MSI-H and/or dMMR	3/5 (60.0)	4/4 (100.0)	3.2	3.8	0.500 (0.035, 7.093)
Other	24/29 (82.8)	10/11 (90.9)	3.7	1.8	0.224 (0.086, 0.584)
Duration of metastatic disease (time from 1st Metastatic Diagnosis to Randomization)					
≤ 18 months	35/37 (94.6)	11/13 (84.6)	1.9	1.8	0.361 (0.166, 0.787)
> 18 months	357/424 (84.2)	202/217 (93.1)	3.7	1.8	0.300 (0.249, 0.363)

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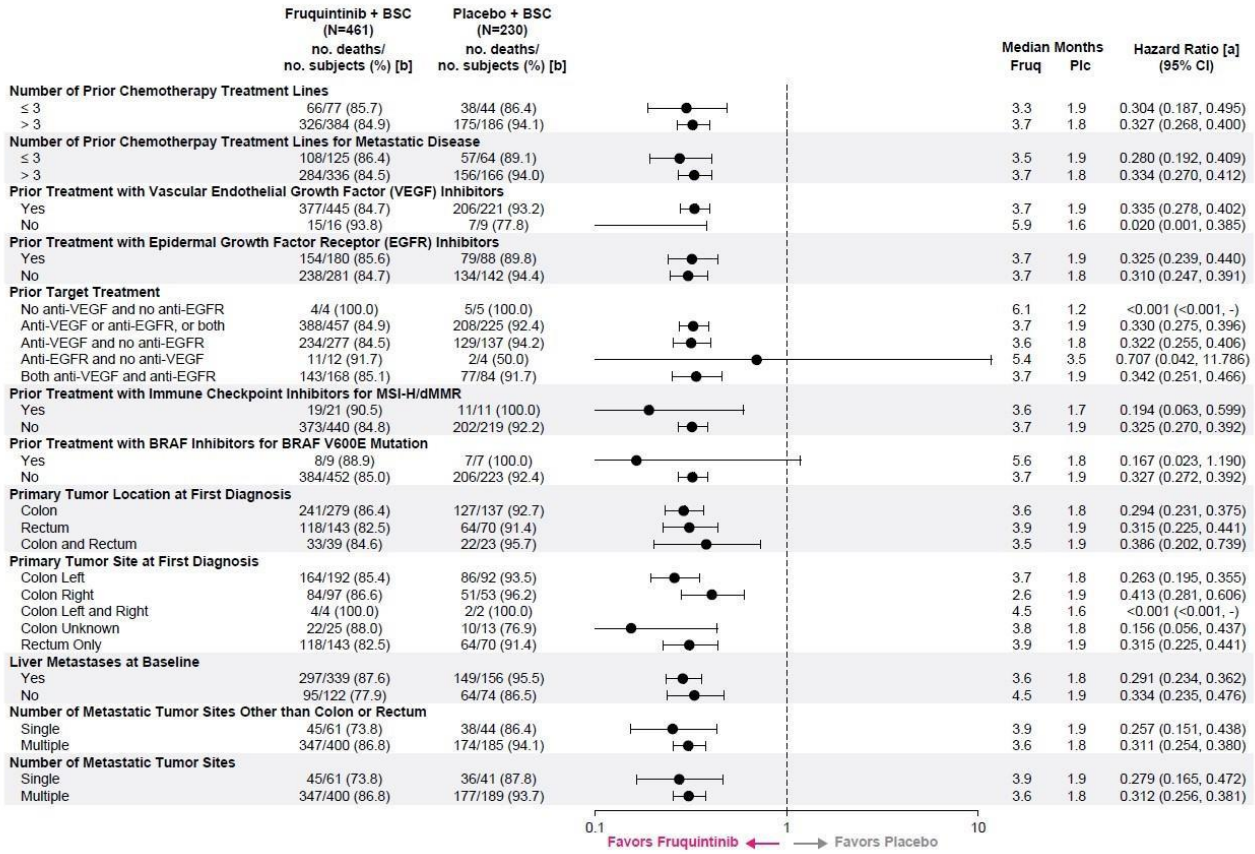
Favors Fruquintinib ← → Favors Placebo



	Fruquintinib + BSC (N=461) no. deaths/ no. subjects (%) [b]	Placebo + BSC (N=230) no. deaths/ no. subjects (%) [b]	Median Months Fruq	Median Months Plc	Hazard Ratio [a] (95% CI)
Number of Prior Chemotherapy Treatment Lines					
≤ 3	66/77 (85.7)	38/44 (86.4)	3.3	1.9	0.304 (0.187, 0.495)
> 3	326/384 (84.9)	175/186 (94.1)	3.7	1.8	0.327 (0.268, 0.400)
Number of Prior Chemotherpay Treatment Lines for Metastatic Disease					
≤ 3	108/125 (86.4)	57/64 (89.1)	3.5	1.9	0.280 (0.192, 0.409)
> 3	284/336 (84.5)	156/166 (94.0)	3.7	1.8	0.334 (0.270, 0.412)
Prior Treatment with Vascular Endothelial Growth Factor (VEGF) Inhibitors					
Yes	377/445 (84.7)	206/221 (93.2)	3.7	1.9	0.335 (0.278, 0.402)
No	15/16 (93.8)	7/9 (77.8)	5.9	1.6	0.020 (0.001, 0.385)
Prior Treatment with Epidermal Growth Factor Receptor (EGFR) Inhibitors					
Yes	154/180 (85.6)	79/88 (89.8)	3.7	1.9	0.325 (0.239, 0.440)
No	238/281 (84.7)	134/142 (94.4)	3.7	1.8	0.310 (0.247, 0.391)
Prior Target Treatment					
No anti-VEGF and no anti-EGFR	4/4 (100.0)	5/5 (100.0)	6.1	1.2	<0.001 (<0.001, -)
Anti-VEGF or anti-EGFR, or both	388/457 (84.9)	208/225 (92.4)	3.7	1.9	0.330 (0.275, 0.396)
Anti-VEGF and no anti-EGFR	234/277 (84.5)	129/137 (94.2)	3.6	1.8	0.322 (0.255, 0.406)
Anti-EGFR and no anti-VEGF	11/12 (91.7)	2/4 (50.0)	5.4	3.5	0.707 (0.042, 11.786)
Both anti-VEGF and anti-EGFR	143/168 (85.1)	77/84 (91.7)	3.7	1.9	0.342 (0.251, 0.466)
Prior Treatment with Immune Checkpoint Inhibitors for MSI-H/dMMR					
Yes	19/21 (90.5)	11/11 (100.0)	3.6	1.7	0.194 (0.063, 0.599)
No	373/440 (84.8)	202/219 (92.2)	3.7	1.9	0.325 (0.270, 0.392)
Prior Treatment with BRAF Inhibitors for BRAF V600E Mutation					
Yes	8/9 (88.9)	7/7 (100.0)	5.6	1.8	0.167 (0.023, 1.190)
No	384/452 (85.0)	206/223 (92.4)	3.7	1.9	0.327 (0.272, 0.392)
Primary Tumor Location at First Diagnosis					
Colon	241/279 (86.4)	127/137 (92.7)	3.6	1.8	0.294 (0.231, 0.375)
Rectum	118/143 (82.5)	64/70 (91.4)	3.9	1.9	0.315 (0.225, 0.441)
Colon and Rectum	33/39 (84.6)	22/23 (95.7)	3.5	1.9	0.386 (0.202, 0.739)
Primary Tumor Site at First Diagnosis					
Colon Left	164/192 (85.4)	86/92 (93.5)	3.7	1.8	0.263 (0.195, 0.355)
Colon Right	84/97 (86.6)	51/53 (96.2)	2.6	1.9	0.413 (0.281, 0.606)
Colon Left and Right	4/4 (100.0)	2/2 (100.0)	4.5	1.6	<0.001 (<0.001, -)
Colon Unknown	22/25 (88.0)	10/13 (76.9)	3.8	1.8	0.156 (0.056, 0.437)
Rectum Only	118/143 (82.5)	64/70 (91.4)	3.9	1.9	0.315 (0.225, 0.441)
Liver Metastases at Baseline					
Yes	297/339 (87.6)	149/156 (95.5)	3.6	1.8	0.291 (0.234, 0.362)
No	95/122 (77.9)	64/74 (86.5)	4.5	1.9	0.334 (0.235, 0.476)
Number of Metastatic Tumor Sites Other than Colon or Rectum					
Single	45/61 (73.8)	38/44 (86.4)	3.9	1.9	0.257 (0.151, 0.438)
Multiple	347/400 (86.8)	174/185 (94.1)	3.6	1.8	0.311 (0.254, 0.380)
Number of Metastatic Tumor Sites					
Single	45/61 (73.8)	36/41 (87.8)	3.9	1.9	0.279 (0.165, 0.472)
Multiple	347/400 (86.8)	177/189 (93.7)	3.6	1.8	0.312 (0.256, 0.381)

0.1 1 10
Favors Fruquintinib ← → Favors Placebo

Abbreviations: *BRAF* = B-Raf proto-oncogene; BSC = best supportive care; CI = confidence interval; dMMR = deficient mismatch repair; ECOG = Eastern Cooperative Oncology Group; Fruq = fruquintinib; HR = hazard ratio; ITT = intent-to-treat; MSI-H = microsatellite instability-high; MSS = microsatellite stable; no. = number; PFS = progression-free survival; Plc = placebo; pMMR = proficient mismatch repair; *RAS* = Rat sarcoma.
[a] The unstratified Cox proportional hazards model in which the applicable randomization schedule stratification factprs and treatment group are included in the model as covariates.
[b] Percentage is based on the number of patients in the subgroup.

Figure 16: Forest Plot for Hazard Ratio and 95% CI for PFS by Subgroups (ITT Population) in FRESCO-2

Note that subgroups based on number of prior treatment lines are mislabelled as containing chemotherapies only; in fact, all prior anticancer treatment lines were included.

Table 23: FRESCO-2: OS and PFS by Number of Prior Treatment Lines for Metastatic Disease (Intent-to-Treat Population)

Number of Prior Treatments	Fruquintinib + BSC		Placebo + BSC		Adjusted HR (SE) [b]
	n	Median (95% CI) [a]	n	Median (95% CI)	
OS					
3	106	7.56 (5.72, 9.59)	53	5.22 (3.22, 8.64)	0.692 (0.212)
4	122	7.43 (6.31, 8.84)	59	4.70 (3.84, 6.21)	0.661 (0.192)
5	93	8.05 (5.98, 10.35)	47	3.35 (2.53, 5.26)	0.310 (0.226)
6	54	6.82 (5.39, 8.84)	21	6.51 (4.11, NE)	1.202 (0.329)
>6	67	6.67 (5.06, 8.87)	39	4.83 (3.06, 7.03)	0.693 (0.239)
PFS					
3	106	3.38 (2.17, 3.68)	53	1.87 (1.81, 1.91)	0.311 (0.213)
4	122	3.65 (2.40, 4.21)	59	1.81 (1.64, 1.87)	0.322 (0.184)
5	93	3.88 (3.65, 5.39)	47	1.87 (1.71, 1.91)	0.245 (0.217)
6	54	3.68 (2.04, 4.01)	21	1.91 (1.68, 2.89)	0.440 (0.301)
>6	67	3.71 (3.02, 4.93)	39	1.77 (1.61, 1.87)	0.289 (0.253)

Source: Adapted from Day 120 Efficacy Analysis Table 23.1.2.1.10 and Table 23.1.2.2.10.
BSC: best supportive care; FRESCO-2: Study 2019-013-GLOB1;HR: hazard ratio; NE: not estimable; OS: overall survival; PFS: progression-free survival; SE: standard error.
OS was defined as the time (months) from date of randomization to death from any cause and calculated as (date of death or last known alive - date of randomization + 1)/30.4375.
PFS was defined as the time (months) from date of randomization until the first progressive disease or death from any cause and calculated as (date of last progressive disease or last assessment – date of randomization +1)/30.4375.
[a] The median was calculated using the Kaplan-Meier method and the corresponding 95% CIs were calculated from a log-log transformation based on the Brookmeyer-Crowley method.
[b] The adjusted HR and its 95% CI were estimated using Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates in the model.

Post hoc analyses

Several post hoc analyses were performed.

A post hoc sensitivity analysis for PFS ignored the subsequent anticancer therapy, i.e., events observed after subsequent anticancer therapy were also considered to be valid PFS events. The median PFS for fruquintinib was 3.7 months vs. 1.9 months for placebo.

The fruquintinib group compared with the placebo group had a significantly delayed time to first occurrence of ECOG PS ≥ 2 or death within 37 days after last dose date (stratified HR, 0.551; 95% CI, 0.436-0.697; stratified log-rank test P < .001). The absolute delay in the median time to worsening of ECOG PS was 3.7 months in favour of the fruquintinib group, with a median in the fruquintinib group of 6.6 months (95% CI, 5.5-7.9) and a median in the placebo group of 2.9 months (95% CI, 2.5-3.7).

When all the deaths observed during the study were included in the analysis irrespective of when they occurred, the fruquintinib group compared with the placebo group demonstrated significantly delayed time to ECOG PS ≥ 2 or death (stratified HR, 0.637; 95% CI, 0.528-0.767; stratified log-rank test P < .001). The absolute delay in the median time to worsening of ECOG PS was 2.4 months favouring the fruquintinib group, with a median in the fruquintinib group of 5.3 months (95% CI, 4.5-5.8) and a median in the placebo group of 2.9 months (95% CI, 2.5-3.5).

The relevance of post hoc analyses is minor for the B/R assessment of fruquintinib. E.g., enrolment was restricted to ECOG 0-1 at baseline. The delay in development of ECOG 2 is longer in fruquintinib arm than in placebo arm. This is a logical finding, as delay in progression delays also the deterioration of performance score.

- **Summary of main efficacy results**

The following table summarises the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 24: Summary of efficacy for trial FRESCO-2 (2019-013-GLOB1)

Title: A Phase 3, randomised, double blind, placebo-controlled, global study that compared fruquintinib plus BSC with placebo plus BSC in patients with mCRC		
Study identifier	Protocol No: 2019-013-GLOB1 ClinicalTrials.gov Identifier: NCT04322539 EudraCT Number: 2020-000158-88 First Patient Enrolled (ICF Signed): 14 August 2020 Date of Data Cut-off for the Analysis: 24 June 2022	
Design	This study is a global, randomised, double-blind, placebo-controlled Phase 3 study that compared fruquintinib with placebo in adult patients with refractory mCRC.	
	Duration of main phase:	1 treatment cycle = 4 weeks, treatment continued until progressive disease (PD), death, intolerable toxicity, withdrawal of informed consent, noncompliance, discontinuation by the physician and/or Sponsor, use of other anticancer treatment, pregnancy, or lost to follow-up.
	Duration of Run-in phase:	Not applicable
	Duration of Extension phase:	Not applicable
Hypothesis	Superiority	

Treatments groups	Fruquintinib 5 mg/day		Fruquintinib 5 mg once daily (QD) + best supportive care (BSC) for 3 weeks of continuous dosing followed by a 1-week break (3 weeks on/1 week off). Each cycle length was 28 days. Cycles continued until disease progression or unacceptable toxicity, via oral administration (n=461)	
	Placebo		Placebo 5 mg once daily (QD) + best supportive care (BSC) for 3 weeks of continuous dosing followed by a 1-week break (3 weeks on/1 week off). Each cycle length was 28 days. Cycles continued until disease progression or unacceptable toxicity, via oral administration (n=230)	
Endpoints and definitions	Primary endpoint	OS	Overall Survival (OS) defined as the time (months) from date of randomisation to death from any cause.	
	Secondary endpoint	PFS	Progression-free survival (PFS) defined as the time (months) from randomisation until the first radiographic documentation of objective progression, as assessed by the investigator using RECIST v1.1, or death from any cause.	
	Other secondary endpoint	ORR	Objective Response Rate (ORR) was calculated using a strict interpretation of RECIST v1.1 Objective Response Rate UNCONFIRMED was calculated using all responses regardless of confirmation.	
	Other secondary endpoint	DCR	Disease Control Rate (DCR) was defined as the proportion of patients with a best overall response (BOR) of confirmed complete response (CR), confirmed partial response (PR), or stable disease (SD) for 7 weeks.	
	Other secondary endpoint	DoR	Duration of Response (DoR) defined as the time (months) from the first occurrence of PR or CR by RECIST v1.1, until the first date that PD was documented by RECIST v1.1 or death, whichever came first.	
Database lock	29 July 2022.			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	ITT (intention to treat)			
Descriptive statistics and estimate variability	**Treatment group**	**Fruquintinib 5 mg/day**	**Placebo**	
	Number of subjects	461	230	
	OS median (months)[a]	7.4	4.8	
	Confidence Interval 95% CI (months)	6.7-8.2	4.0-5.8	
Effect estimate per comparison	OS	**Comparison groups**	**Fruquintinib 5 mg/day**	**Placebo**
		Stratified HR (95% CI)[c]	0.662 (0.549, 0.800)	N/A

		Log-rank *P* value (2-sided)[d]	< 0.001	N/A
		Probability (%) of being alive (95% CI)[b] 3 months 6 months 9 months 12 months 18 months	 88.1 (85.1, 91.1) 60.4 (55.9, 64.9) 41.1 (36.4, 45.8) 27.8 (23.0, 32.6) 8.3 (2.3, 14.2)	 68.8 (62.8, 74.9) 41.5 (35.0, 48.0) 28.2 (22.1, 34.3) 23.2 (17.1, 29.2) 10.3 (3.9, 16.8)
		Duration (months) of follow-up[a,c], median (95% CI)	11.3 (10.6, 12.4)	11.2 (9.9, 12.0)
Analysis description	**Secondary analysis**			
Analysis population and time point description	ITT based on Investigator Assessments			
Effect estimate per comparison	PFS	**Comparison groups**	**Fruquintinib 5 mg/day**	**Placebo**
		PFS (months), median (95% CI)	3.7 (3.5, 3.8)	1.8 (1.8, 1.9)
		Stratified HR (95% CI)[c]	0.321 (0.267, 0.386)	N/A
		Log-rank *P* value (2-sided)[d]	< 0.001	N/A
		Probability (%) of PFS (95% CI) 3 months 6 months 9 months 12 months 18 months	 59.6 (55.0, 64.2) 23.8 (19.7, 28.0) 11.3 (8.1, 14.6) 3.8 (1.6, 5.9) 2.1 (0.4, 3.8)	 17.9 (12.7, 23.0) 1.1 (0.0, 2.6) 0.5 (0.0, 1.6) 0 0
	ORR	Confirmed ORR: CR + PR, n (%)	7 (1.5)	0
		2-sided 95% CI[d]	0.6, 3.1	0.0, 1.6
		Adjusted difference (fruquintinib – placebo) (SE)	1.5 (0.006)	
		95% CI[e]	0.4, 2.7	
		2-sided *P* value[f]	0.059	
	DCR	DCR: CR + PR + SD for at least 7 weeks, n (%)	256 (55.5)	37 (16.1)
		2-sided 95% CI[d]	50.9, 60.1	11.6, 21.5
		Adjusted difference (fruquintinib – placebo) (SE)[e]	39.4 (0.034)	
		95% CI[e]	32.8, 46.0	

		2-sided *P* value[f]	<.001	
	DoR	Median DoR	10.7 months (95% CI: 3.9)	N/A

[a] The median, 25%, and 75% percentiles were calculated using the Kaplan-Meier method, and the corresponding 95% Cis are calculated from a log-log transformation based on the Brookmeyer-Crowley method.

[b] The survival probabilities and corresponding 95% Cis were calculated using a linear transformation based on the Brookmeyer-Crowley method at the selected landmarks.

[c] P value to test the treatment effect was calculated using the stratified log-rank test to account for the randomization schedule stratification factors.

[d] 95% CI of ORR or DCR was calculated using the Clopper-Pearson exact method.

[e] The adjusted difference and its 95% CI were calculated using the Wald method to account for the randomisation schedule stratification factors.

[f] P value was calculated from a stratified Cochran-Mantel Haenszel test accounting for the randomisation schedule stratification factors.

3.6.8.3. Clinical studies in special populations

No separate clinical efficacy studies have been performed in paediatric population or in patients with renal or hepatic impairment.

Table 25: Clinical efficacy in elderly population

	Total Number of Subjects (N = 1413)		
Study	**Age 65-74 n (% of total)**	**Age 75-84 n (% of total)**	**Age ≥85 n (% of total)**
Controlled studies	358 (25.3)	67 (4.7)	1 (0.1)
Noncontrolled studies	53 (3.8)	4 (0.3)	0

3.6.8.4. In vitro biomarker test for patient selection for efficacy

Currently there are no *in vitro* biomarker tests for patient selection for efficacy. FRESCO-2 had exploratory endpoints to assess potential predictive biomarkers of response to fruquintinib (change from baseline in ctDNA, change from baseline in tumour markers (i.e., CEA), and pharmacogenomics, see section 'Exploratory endpoints').

3.6.8.5. Analysis performed across trials (pooled analyses and meta-analysis)

FRESCO-2 was a Phase 3, global, randomised, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of fruquintinib monotherapy + BSC vs. placebo + BSC in patients with refractory mCRC. FRESCO was a Phase 3, randomized, double-blind, placebo-controlled, multicenter study conducted in China to assess the efficacy and safety of fruquintinib monotherapy in patients with refractory mCRC. The 2015-013-00US1, 2012-013-00CH1, and 2012-013-00CH3 studies also enrolled patients with mCRC. Efficacy data were not pooled by the Applicant across studies for the purpose of efficacy evaluation due to differences in study design, specifically as they related to differences in prior treatments.

Comparison of patient demographics across FRESCO-2, FRESCO and the phase 1/1b study 2015-013-00US1 showed that median age was higher in FRESCO-2 than in the other two studies. All patients were Asian in FRESCO unlike in FRESCO-2 and in 2015-013-00US1, in which patients were mainly White. More patients had a BMI ≥24 kg/m^2 in FRESCO-2 and 2015-013-00US1 than in FRESCO in

which the majority had a BMI ≥18.5 and <24 kg/m^2. More patients were ECOG 0 in FRESCO-2 than in FRESCO. Similar finding but to a lesser extent was seen in 2015-013-00US1.

Mirroring inclusion criteria, prior treatment lines were different, and no patient received trifluridine-tipiracil or regorafenib in FRESCO and cohort C of 2015-013-00US1. In addition, fewer patients received prior VEGF inhibitor and EGFR inhibitor in FRESCO, reflecting enrolment criteria (VEGF and EGFR inhibitors were allowed but not mandatory).

Median OS in both treatment arms was longer in FRESCO and in cohort C of 2015-013-00US1 compared to FRESCO-2 and to cohort B of 2015-013-00US1, which may be attributed to the earlier treatment line. Nevertheless, median OS in cohort B of 2015-013-00US1 was 1 month longer than in FRESCO-2, although the low number of patients in cohort B of 2015-013-00US1 may explain a variability. Lack of control arm hampers the evaluation of a time-to-endpoint.

Median PFS was similar in FRESCO-2 and FRESCO in both treatment groups. However, median PFS was substantially longer in 2015-013-00US1, in which PFS as investigator assessed in an open-label study could explain the difference.

ORR was consistent across studies with an activity seen mainly as SD.

3.6.8.6. Supportive study(ies)

Table 26: Clinical studies supporting clinical efficacy for fruquintinib

Monotherapy, Phase 3, pivotal	2013-013-00CH1 (FRESCO)	5.3.5.1	Efficacy and safety	Randomized, double-blind, placebo-controlled, multicenter	Fruquintinib/placebo 5 mg QD 3/1; oral	Fruquintinib/placebo: 278/138	Patients with advanced CRC who had progressed after 2nd-line and above standard chemotherapy	Patients continued treatment until PD, death, unacceptable toxicity, investigator/ patient decision	Completed, Full CSR
Monotherapy; Phase 1/1b	2015-013-00US1	5.3.3.2	Safety, PK, and preliminary efficacy	Multi-center, open-label	Fruquintinib; 3 or 5 mg QD 3 weeks on/1 week off; oral	Dose Escalation (3 mg QD) cohort: 7; Dose Escalation (5 mg QD) + Cohort A: 13; Cohort B: 41; Cohort C: 40; Cohort D: 14; Cohort E: 12	Dose Escalation: patients with advanced solid tumors Expansion: patients with advanced solid tumors (Cohort A), with refractory mCRC (Cohorts B and C), and with metastatic breast cancer (Cohorts D and E).	Patients continued treatment until PD, death, unacceptable toxicity, investigator/ patient decision.	Completed; CSR for Dose Escalation cohorts and Expansion Cohorts A through C, CSR addendum for Expansion Cohorts D and E.
Monotherapy, Phase 2	2012-013-00CH1	5.3.5.1	Efficacy and safety	Randomized, double-blind, placebo-controlled, multicenter	Fruquintinib/placebo 5 mg QD 3/1; oral	Fruquintinib/placebo: 47/24	Patients with advanced CRC who had progressed with 2 or more lines of standard chemotherapy	Patients continued treatment until PD, death, unacceptable toxicity, investigator/ patient decision	Completed, Full CSR
Monotherapy, Phase 1b	2012-013-00CH3	5.3.5.1	Safety, PK, and preliminary efficacy	Randomized, open-label, 2 center	Fruquintinib:4 mg QD continuous dosing group or 5 mg QD 3/1; oral	62	Patients with advanced CRC who had failed 2 lines or more of standard chemotherapy	Patients continued treatment until PD, death, unacceptable toxicity, investigator/ patient decision	Completed, Full CSR

FRESCO (2013-013-00CH1)

FRESCO was a randomised, double-blind, multicenter and placebo-controlled Phase III trial conducted in China to evaluate the efficacy and safety of treatment with fruquintinib in advanced CRC subjects who have failed second-line or above standard chemotherapy.

Objective: To evaluate the efficacy and safety of treatment with fruquintinib in advanced CRC subject who have failed second-line or above standard chemotherapy.

Location and number of study sites: China, 28

Study dates: ICF signed by 1st patient 08-12-2014; the date of last patient enrolled not known; DCO 17-01-2017

Method: The trial planned to enrol and randomise around 400 subjects. A total of 519 subjects (signed the ICF) were screened, and 416 subjects were randomised in the trial (with fruquintinib and placebo at a ratio of 2:1) into the following treatment arms:

- 5 mg of fruquintinib, once a day (QD), via oral administration, combined with BSC
- Placebo combined with BSC
- Treatment regimen of 3 weeks on/1 week off, with 4 weeks as 1 cycle.

The study enrolled subjects who had received at least 2nd line standard chemotherapy and had failed. These standard treatment regimens must have included fluorouracil, oxaliplatin and irinotecan. Treatment failure was defined as PD or intolerance to toxic side effects during treatment or within 3 months after the last treatment. Prior anti-tumor treatment regimens that use chemotherapy combined with targeted drugs such as cetuximab, panitumumab or other epidermal growth factor receptor (EGFR) inhibitors or VEGF inhibitors were allowed. The tumour condition of the subjects was evaluated once every 8 weeks using imaging methods until disease progression.

Treatment regimen was 3 weeks on/1 week off, with 4 weeks as 1 cycle. Double-blind drug administration was adopted. Subjects continued to take the investigational drug until the occurrence of PD, death, intolerance to toxicity, withdrawal of ICF, until termination of treatment is deemed by the principal investigator to be in the patient's best interest, or other criteria for termination of treatment are met.

Primary Efficacy Endpoint:

• Overall survival (OS)

Secondary Efficacy Endpoints:

• Progression-free survival (PFS) (according to RECIST Version 1.1)

• Objective response rate (ORR), disease control rate (DCR), duration of response (DOR) and duration of stable disease (SD)

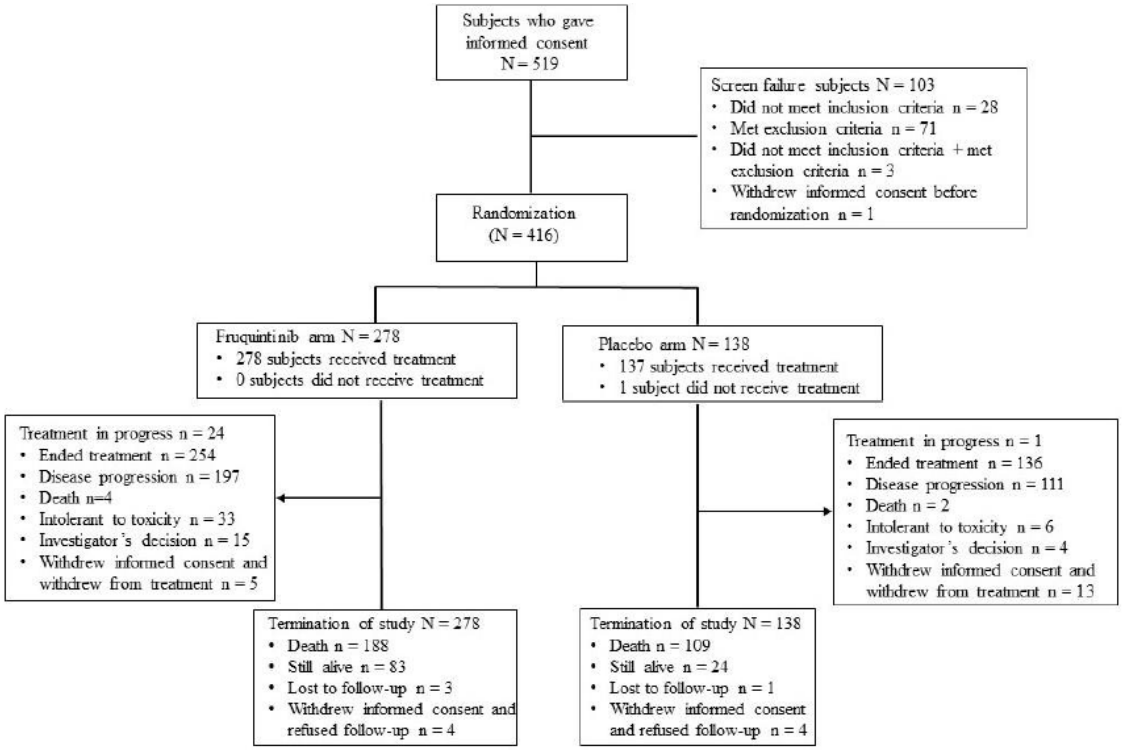


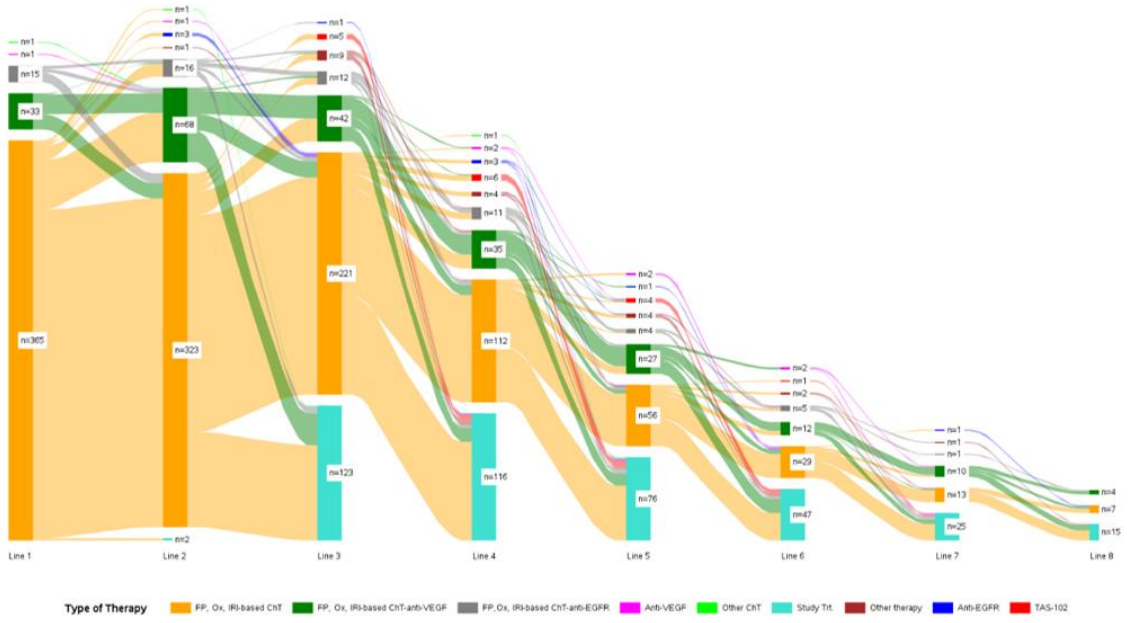
Figure 17: Subject distribution flow chart (FRESCO)

Key demographic data: In the intention-to-treat analysis set, all subjects were of Asian descent (Chinese). The median age of patients in the fruquintinib arm was 55 years and in the placebo arm 57 years. The male-to-female ratio in the fruquintinib arm was 56.8%:43.2%; the male-to-female ratio in the placebo arm was 70.3%:29.7%. The median time to 1st diagnosis of metastasis and randomisation was 16.03 months in the fruquintinib arm and 17.22 months in the placebo arm. 56.5% of patients in the fruquintinib arm and 53.6% in the placebo arm were KRASwt.

All subjects in the 2 arms had received prior treatment with fluorouracil, oxaliplatin and irinotecan. 68.3% and 71.0% of the subjects in the fruquintinib arm and placebo arm, respectively, received second-line or third-line systematic chemotherapy. The percentage of subjects in the fruquintinib arm and the placebo arm who previously received VEGF inhibitor was 30.2% vs 29.7% and EGFR inhibitor was 14.4% vs 13.8%, respectively.

The median number of cycles received by the subjects was 4 in the fruquintinib arm and 2 in the placebo arm.

Below a patient journey graph illustrates prior treatments and the lines when study treatments were used.

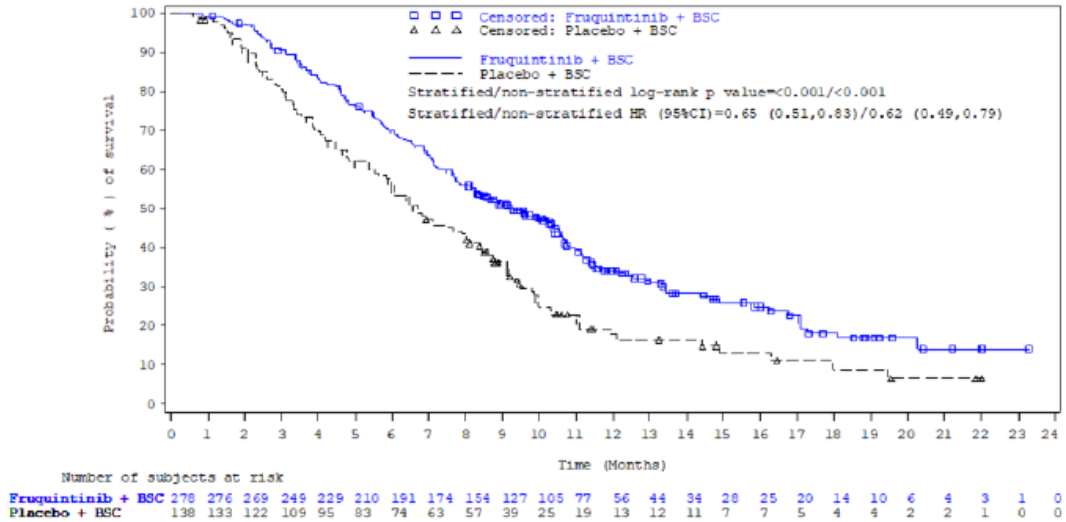


Source: FRESCO Ad hoc Figure 23.2.1.4.
EGFR: epidermal growth factor receptor; FP: fluoropyrimidine; FRESCO: Study 2013-013-00CH1; ITT: intent-to-treat; IRI-based ChT: irinotecan-based chemotherapy; Ox: oxaliplatin; REGO: regorafenib; VEGF: vascular endothelial growth factor; Trt: treatment.

Figure 18: FRESCO patient journey (ITT population)

Key efficacy results:

OS: As of the data cutoff date, 297 subjects died (fruquintinib arm vs placebo arm: 188 vs 109). As compared to the placebo arm, the OS of fruquintinib arm was extended from 6.6 months (95% CI: 5.9, 8.1) in the placebo arm to 9.3 months in the fruquintinib arm (95% CI: 8.2, 10.5); stratified HR was 0.65 (95% CI: 0.51, 0.83; stratified log-rank test p < 0.001), indicating that the risk of death of subjects in the fruquintinib arm reduced by 35% as compared to the placebo arm (see figure below).

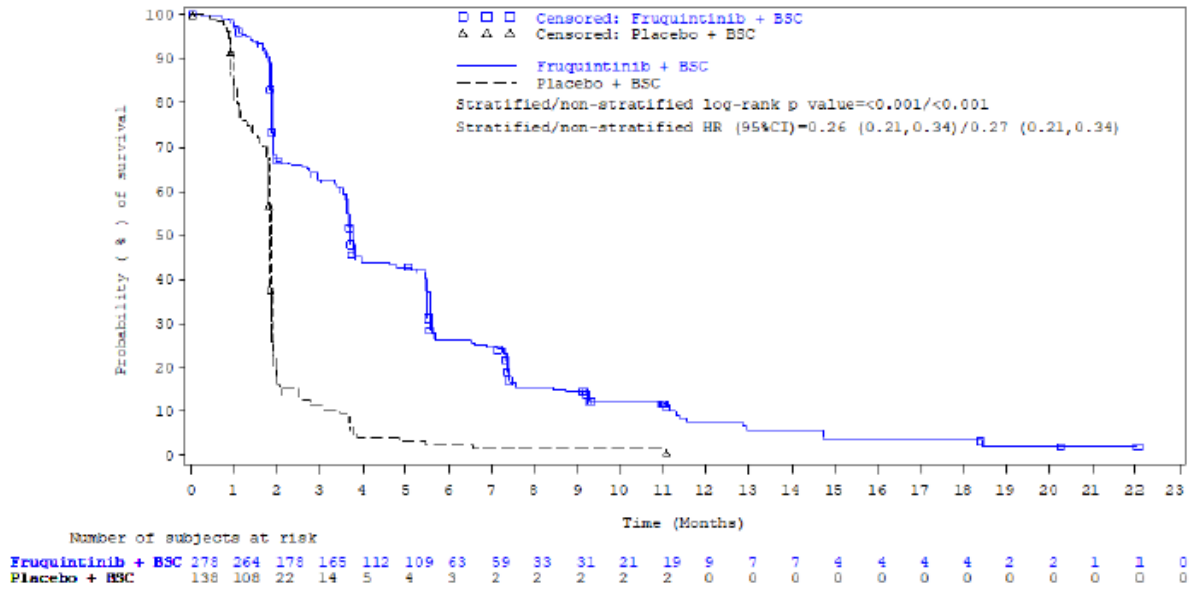


Abbreviations: BSC = best supportive care; CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat.

Figure 19: FRESCO: Kaplan-Meier Curve of Overall Survival (ITT Population)

PFS: As of the data cutoff date, 360 subjects experienced PD (fruquintinib arm vs placebo arm: 235 subjects vs 125 subjects). In comparison to the placebo arm, the PFS in the fruquintinib arm was extended from 1.8 months (95% CI: 1.81, 1.84) to 3.7 months (95% CI: 3.7, 4.6); stratified HR was

0.26 (95% CI: 0.21, 0.34). The *p* value of the stratified log-rank test was < 0.001, indicating that the risk of occurrence of disease progression in the fruquintinib arm decreased by 74% as compared to the placebo arm (see figure below).



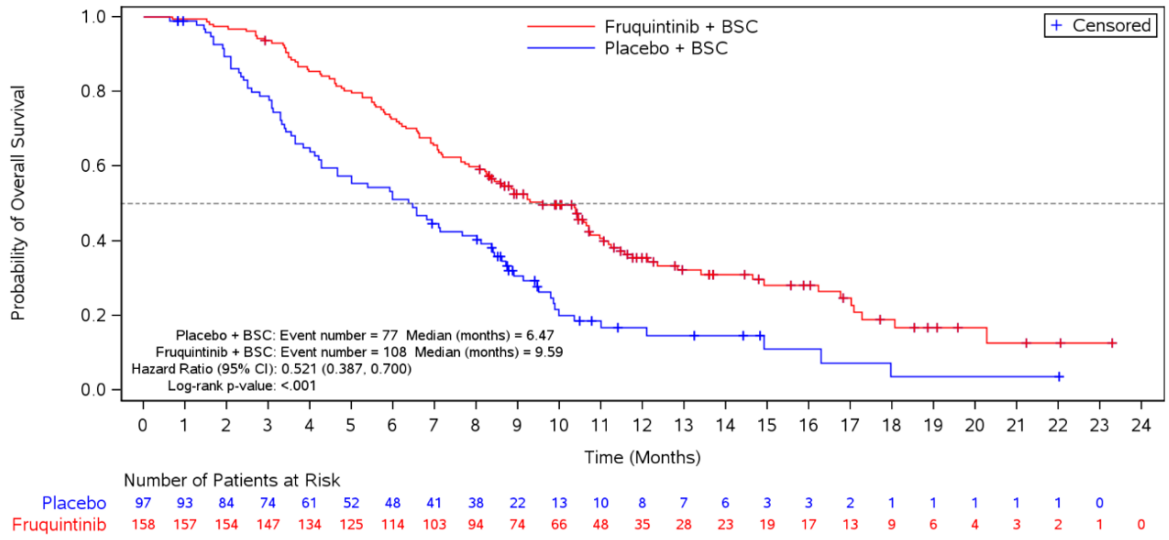
Abbreviations: BSC = best supportive care; CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat.

Figure 20: FRESCO: Kaplan-Meier Curve of Progression-Free Survival (ITT Population)

ORR: The ORR of subjects in the fruquintinib arm was 4.7% (13 subjects) and no subjects in the placebo arm achieved objective response.

DCR: The DCR of subjects in the fruquintinib arm was 62.2% (173 subjects), and the DCR of the placebo arm was 12.3% (17 subjects).

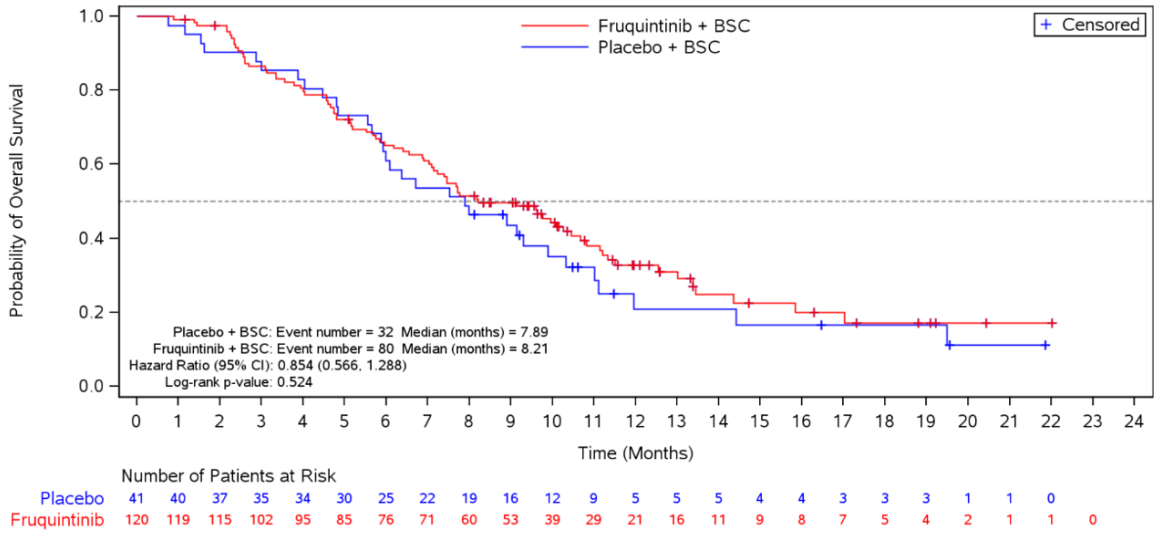
Further, the Applicant provided Kaplan-Meier curves (see figures below) and a detailed output of OS analysis, for females and males separately using the database of the initial submission. In addition, the Applicant was asked to provide the same set of outputs using updated data. The latter request was declined by the Applicant as of the opinion that the dataset is mature for OS. The applicant was also asked to evaluate whether apparently diluted OS effect in females, as seen in the submission outputs, might be associated with the higher rates of TEAEs leading to dose reduction and of grade ≥3 treatment emergent AESIs in. No association could be verified (for details, see Safety section).



Source: Day 120 Efficacy Analysis Figure 35.1.2.1.1C.
BSC: best supportive care; FRESCO: Study 2013-013-00CH1; ITT: intent-to-treat.

Figure 21: Kaplan-Meier curve for OS by gender – male (ITT population in FRESCO)

Source:



Source: Day 120 Efficacy Analysis Figure 35.1.2.1.1C.
BSC: best supportive care; FRESCO: Study 2013-013-00CH1; ITT: intent-to-treat.

Figure 22: Kaplan-Meier curve for OS by gender – female (ITT population in FRESCO)

2015-013-00US1 (bridging study)

2015-013-00US1 is a multicenter, open-label, Phase 1/1b clinical study to evaluate the safety, tolerability, pharmacokinetics and anticancer activity of fruquintinib in patients with advanced solid tumors of any type (Cohort A), refractory mCRC (Cohorts B and C), or metastatic breast cancer (mBC) (Cohort D and E). It is a dose-confirmatory, bridging study to confirm the RP2D (approved dose in China) of fruquintinib in US cancer patients and to evaluate the preliminary efficacy and safety of fruquintinib in a Western mCRC patient population.

Objective:

Dose-Escalation Phase: to evaluate the safety and tolerability of fruquintinib in patients with advanced solid tumors and to determine the RP2D.

Dose-Expansion Phase: To evaluate the anticancer activity of fruquintinib at the RP2D from the Dose-Escalation Phase, in patients with advanced solid tumors.

Locations of study sites: US

Study dates: ICF signed by 1st patient 11-12-2017, DCO 14-01-2022

Methods: Approximately 128 patients were planned to be enrolled in this study with 12 patients to be enrolled in the Dose-Escalation Phase, and 116 additional patients (6 with advanced solid tumors of any type, 40 with refractory mCRC who progressed on all standard therapies including TAS-102 and/or regorafenib, 40 with mCRC who had progressed on all standard therapies but had not received TAS-102 or regorafenib, 15 with refractory HR+/HER2- mBC, and 15 with advanced, refractory triple negative breast cancer) to be enrolled in the Dose-Expansion Phase.

A total of 138 patients were enrolled (signed the ICF), and, of this number, a total of 101 patients were treated and analyzed for safety and efficacy (cohorts D and E not covered in CSR and will be provided by the Applicant as an addendum to the CSR).

The dose levels investigated in the Dose-Escalation Phase were 3 mg and 5 mg once daily, 3 weeks on/1 week off. Based on the cumulative safety data, the RP2D was determined to be 5 mg orally QD, 3 weeks on, 1 week off, on a 28-day cycle.

Treatment was to be continued until disease progression (according to RECIST version 1.1) unless there was reasonable evidence of clinical benefit to justify continuation on the study treatment, death, end of study, withdrawal of consent, intolerable toxicity, poor patient compliance, use of other antitumor treatment during the study, pregnancy occurred during the study treatment period, patient was lost to follow up, treatment discontinuation was in the best interest of the patient based on the assessment of the Investigator and the Sponsor.

Primary endpoint:

Dose-escalation phase: incidence of DLT

Dose-expansion: PFS rates

Secondary endpoints:

Dose-escalation phase: PK, ORR, DCR (CR+PR+SD for 7 weeks), DOR, PFS, percentage change in tumor size according to RECIST version 1.1, OS

Dose-expansion phase: ORR, DCR, DOR, PFS, OS, percentage of change in tumor size according to RECIST version 1.1, PK, safety

Key demographic data: As of DCO 101 patients were exposed to at least 1 dose of study drug. Of this total, 7 patients were in the fruquintinib 3 mg Cohort, 13 patients in the fruquintinib 5 mg DE Cohort + Cohort A, 41 patients in Cohort B, and 40 patients in Cohort C. Thus, 81 patients were enrolled into the mCRC cohorts.

Across all cohorts, most patients were male (51.5%), white (84.2%), with a median age of 58.72 years (33.9 to 77.3 years), and a baseline ECOG PS of 1 (64.4%). The median times from 1st metastasis diagnosis was 36.7 months in Cohort B and 30 months in Cohort C. In Cohort B, 85.4% were reported with >3 prior treatment lines, in Cohort C 50% with > 3 prior treatment lines.

Key efficacy results:

• For the fruquintinib 3 mg Cohort: 1 patient (16.7%) was reported with a confirmed PR for an ORR of 16.7% (95% CI: 0.42, 64.12). An additional 3 patients (50.0%) were reported with a BOR of SD, for a DCR of 66.7% (95% CI: 22.28, 95.67).

• For the fruquintinib 5 mg DE Cohort + Cohort A (advanced solid tumors): 1 patient (7.7%) was reported with a confirmed PR for an ORR of 7.7% (95% CI: 0.19, 36.03). An additional 8 patients (61.5%) were reported with a BOR of SD, for a DCR of 69.2% (95% CI: 38.57, 90.91).

• For Cohort B (mCRC, prior treatment with trifluridine-tipiracil or regorafenib): 1 patient (2.4%) was reported with a confirmed PR for an ORR of 2.4% (95% CI: 0.06, 12.86). An additional 27 patients (65.9%) were reported with a BOR of SD, for a DCR of 68.3% (95% CI: 51.91, 81.92).

• For Cohort C (mCRC, no prior trifluridine-tipiracil or regorafenib): 2 patients (5.1%) were reported with a confirmed PR for an ORR of 5.1% (95% CI: 0.63, 17.32). An additional 21 patients (53.8%) were reported with a BOR of SD, for a DCR of 59.0% (95% CI: 42.10, 74.43).

Thus, across different cohorts the results from 2015-013-00US1 showed ORRs of 2.4%-16.7%. These consisted of PRs as there were no CRs. DCRs varied between 59% and 69.2%.

2012-013-00CH3

A randomised, open-label, phase Ib 2-center clinical study of fruquintinib administered based on "4 mg, once daily" versus "5 mg, once daily for 3 weeks/withdrawal of 1 week" as third-line or above treatment in patients with advanced colorectal tumours who have failed to respond to standard treatment regimen. The study was conducted in China.

Objective: To compare the safety and tolerability of two different regimens of fruquintinib ("4 mg qd continuous dosing" vs. "5 mg qd 3 weeks on treatment and 1 week off") in treatment of advanced colorectal cancer in patients who had failed standard therapy, and to further observe and evaluate the safety and efficacy (progression-free survival, or PFS) of fruquintinib under the dosing regimen of "5 mg qd 3 weeks on treatment and 1 week off" ("3 weeks on/1 week off") in treatment of advanced colorectal cancer in patients who had failed standard therapy in the expansion stage.

Locations of study sites: China

Study dates: ICF signed by 1st patient 26-12-2012, DCO 24-04-2014

Methods: About 60 subjects were planned to be enrolled. Sixty-two subjects were actually enrolled with 40 subjects enrolled in the randomized comparison stage and 22 subjects enrolled in the expansion stage.

The study consisted of a randomized comparison stage and an expansion stage. The subjects were randomized into fruquintinib "4 mg qd continuous dosing" group or "5 mg qd 3 weeks on/1 week off" group in the randomized comparison stage.

The expansion stage was to expand the sample size by including about 20 subjects to further evaluate the safety and efficacy based on the recommended dose determined in the randomized comparison stage. The dosing regimen of "5 mg qd 3 weeks on/1 week off" was used for the expansion stage based on the results from randomized comparison stage.

The drug administration was continued until progression of disease, intolerable toxicity, or withdrawal of informed consent.

Patients: ≥ 18 years of age with advanced CRC who had failed 2 or more lines of standard therapy, defined as fluoropyrimidine-, oxaliplatin-, or irinotecan-containing regimens. Prior anti-VEGF inhibitors, such as bevacizumab or aflibercept, were allowed but not required. Patients who received prior treatment with VEGFR inhibitors (e.g., small molecule TKIs available at the time the study was conducted) were excluded.

Primary objectives and endpoints: To compare the safety and tolerability of two different regimens of fruquintinib ("4 mg qd continuous dosing" vs. "5 mg qd 3 weeks on treatment and 1 week off") in treatment of advanced colorectal cancer in patients who had failed standard therapy, and to further observe and evaluate the safety and efficacy (progression-free survival, or PFS) of fruquintinib under the dosing regimen of "5 mg qd 3 weeks on treatment and 1 week off" ("3 weeks on/1 week off") in treatment of advanced colorectal cancer in patients who had failed standard therapy in the expansion stage. The primary safety endpoints include overall incidence of adverse events, incidence of G3/4 adverse events and serious adverse events.

Secondary objectives and endpoints: 1) To compare the objective response rate (ORR), disease control rate (DCR), duration of response (according to the RECIST 1.1 criteria), progression-free survival (PFS), and overall survival (OS) between two different regimens of fruquintinib in treatment of advanced colorectal cancer in patients who had failed standard therapy; and to further evaluate the disease control rate (DCR), objective response rate (ORR), and overall survival (OS) with the dosing regimen of "5 mg qd 3 weeks on/1 week off" in treatment of advanced colorectal cancer in patients who had failed standard therapy during the expansion stage. Expansion trial: The primary efficacy endpoint is 16-week progression-free survival. The secondary efficacy endpoints are DCR, ORR and OS.

2) To explore the pharmacokinetic profiles of two different regimens of fruquintinib in treatment of advanced colorectal cancer in patients who had failed standard therapy.

Key demographic data:

Randomised comparison stage: All of the 28 males and 12 females enrolled were Asian and Han in ethnicity. The median age was 60 and 55 in the two treatment groups. 5 subjects had received bevacizumab-containing chemotherapy and 28 subjects had received more than 3 chemotherapy regimens.

Expansion stage: All 25 males and 17 females were Asian and Han with the median age at 55.5 years. 10 subjects had received bevacizumab-containing chemotherapy and 37 subjects had received more than 3 chemotherapy regimens.

Efficacy results:

1. Results from randomised comparison stage: One (2.9%) subject achieved the best response of partial response (PR) and 27 (77.1%) achieved SD among the 35 evaluable subjects during the treatment. Group A had 1 PR and 12 SDs with 5.9% ORR and 76.5% DCR. Group B had no complete response (CR) or PR but 15 SDs with 0% ORR and 83.3% DCR. The ORR and DCR were not significantly different between Groups A and B.

2. Results from expansion stage: The best responses of 4 subjects (10.26%) among the 39 efficacy-evaluable subjects were all PR during treatment. However, they were not confirmed after 4 weeks. Two of the 4 subjects were withdrawn from the trial due to adverse events and the other 2 subjects had not been confirmed by the time of data cutoff). Twenty-eight (71.8%) subjects were evaluated to have SD with the ORR at 10.26% and DCR at 82.05%.

2012-013-00CH1

2012-013-00CH1 is a randomised, double-blind, placebo-controlled, multicenter phase II study comparing fruquintinib plus BSC and placebo plus BSC in patients with advanced colorectal cancer who have failed to respond to second-line and above standard chemotherapy and must not have received a prior treatment with a VEGFR inhibitor. The study was conducted in China.

Objective: To compare the Progression-free Survival (PFS) of fruquintinib combined with best supportive care (BSC) versus placebo combined with BSC in patients with advanced colorectal cancer (CRC) who failed to respond to second-line and above standard chemotherapy.

Locations of study sites: China

Study dates: ICF signed by 1st patient 01-04-2014, DCO 11-02-2015

Methods: About 70 patients were planned to be enrolled in the study; 93 patients were actually recruited; 71 patients were randomized. After subjects were evaluated as meeting screening eligibility criteria, patients were randomized into either the fruquintinib combined with BSC group (treatment group) or the placebo combined with BSC group (control group) at a ratio of 2:1.

Test group: Subjects received fruquintinib 5 mg/dose orally, quaque die (QD), for 3 weeks on/1 week off plus BSC.

Control group: Subjects received placebo 5 mg/dose orally, QD, for 3 weeks on/1 week off plus BSC.

All the subjects received the treatment for 3 weeks on/1 week off with 4 weeks as one treatment cycle until the occurrence of PD, death, intolerable AE or withdrawal of ICF or other conditions that met the End of Treatment (EOT) criteria.

Patients: Adult patients who had been histologically or cytologically diagnosed with advanced CRC and failed at least 2 prior lines of standard chemotherapy (including fluoropyrimidine-, oxaliplatin, and irinotecan).

Primary Efficacy Endpoint:

PFS (According to Response Evaluation Criteria In Solid Tumors [RECIST] Version 1.1)

Secondary Efficacy Endpoint:

ORR, DCR (of which, SD for at least 8 weeks), and OS

Key demographic data:

47 and 24 were randomized into the fruquintinib group and the placebo control group, respectively. Subjects were all Asian and of ethnic origin Han. Mean age of subjects in the fruquintinib group (± Standard Deviation [Std]) was 49.6 years (± 10.86) and 54.1 years (± 9.40) in the placebo group. The distribution of males and females between the two groups was similar with male subjects in the majority (74.5% in the fruquintinib group, 70.8% in the placebo group). Most chemotherapy regimens were ≥ third line (74.5% in the fruquintinib group, 70.8% in the placebo group).

Key efficacy data:

Median PFS in the fruquintinib group was significantly longer than that of the placebo group: The placebo group was 0.986 months, while the fruquintinib group was prolonged to 4.731 months. The DCR in the fruquintinib group and the placebo group were 68.1% (32 subjects) and 20.8% (5 subjects), respectively. The number of cases obtaining objective response was 1 (2.1%) in the fruquintinib group. No patients achieved CR. There were no cases of obtaining objective response in the placebo group. OS was prolonged in the fruquintinib group: Placebo group was 5.520 months and the fruquintinib group was prolonged to 7.721 months.

3.6.9. Discussion on clinical efficacy

Dose response studies

Based on the collective nonclinical information and clinical safety, efficacy, and E-R results, fruquintinib 5 mg QD 3/1 provided improved safety compared to the continuous daily regimens, while also maintaining concentrations above the nonclinical threshold in the majority of patients and providing efficacious exposure with similar efficacy on OS across the exposure range that is superior to placebo. The choice of final dosing regimen consisting of 5 mg QD 3 weeks on, 1 week off is mainly based on tolerability, and is based on 2 studies conducted in China (a double-blind placebo-controlled phase 2 study and an open-label phase 1b study) and one phase 1/1b, open-label, dose-confirmatory bridging study in US. The phase 3 studies have been conducted with the dose for which the MA is being applied.

As a results, 5 mg QD 3/1 was selected as the posology for fruquintinib. This is reflected in section 4.2 of the SmPC.

Design and conduct of clinical studies

The central evidence for the MAA comes from FRESCO-2, a global, multi-center, double-blind, phase 3 trial in mCRC comparing fruquintinib and BSC to placebo and BSC, which randomised 691 patients. The applicant also considered FRESCO (a multi-center, double-blind, phase 3 trial comparing fruquintinib to placebo, which randomised 416 patients in China) as a pivotal study to support the efficacy claims. However, after assessment FRESCO was considered to be a supportive study for the current MAA, its main emphasis for the safety data. As the CHMP considered FRESCO-2 the single pivotal study for the current MAA, the main focus in the following discussion is on it.

Pivotal FRESCO-2 Study

Study design: A randomised, double-blind, phase 3 study with experimental therapy against placebo is a valid approach to evaluate efficacy and adequate for the purpose of the MAA. It also follows current guidelines from EMA for trials with anticancer therapies. FRESCO-2 did not include a cross-over option for patients progressing on placebo, which is a strength. Overall, the design of FRESCO-2 is considered appropriate with regards to the objectives.

I/E criteria: At the onset the enrolment criteria in FRESCO-2 defined patients with advanced CRC, having failed available standard therapies. The criteria were further tightened during the trial. The patients were highly selected (ECOG 0-1, able to undergo required prior therapies and to fulfil all enrolment criteria). A tight selection of patients hampers the direct applicability of the results to everyday clinical praxis. ECOG 0-1 may not reflect use in a last line setting in real life conditions and the representativeness of the population was considered. According to RWD from US and Europe, 10-17% of mCRC patients treated in various later lines could have ECOG ≥2, thus differing from FRESCO-2 patients. The future target population is likely to contain a higher proportion of ECOG 2, due to the late line setting and burden of comorbidities. Differences with trial population vs. real life patients and resulting uncertainties is a regrettable issue with clinical trials. Main exclusion criteria, including ECOG ≥2, were added to SmPC, along with the minimum body weight for enrolment (40 kg).

While the protocol advised for use of oxaliplatin in adjuvant setting, it did not give explicit advice regarding the use of neoadjuvant therapy (a treatment alternative in rectal cancer) and progression during or within 6 months of its completion. Further, intermediate risk stage II colon cancer can be treated with capecitabine monotherapy. Inclusion criteria do not explicitly differentiate between fluoropyrimidine monotherapy in adjuvant treatment or in treatment of metastatic disease. Not including HER2 amplification or NTRK fusion testing, missing from all protocol versions, is not according to current ESMO guideline.

The trial could enrol patients who progressed or were intolerant to trifluridine-tipiracil or regorafenib or both. Progression through prior therapy is often a straightforward clinical decision and in a fit patient next line therapy is typically started. However, if the patient did not tolerate the therapy but a PR or SD had been reached, some clinicians might not immediately initiate next line therapy but wait for PD.

Placebo as comparator: For these heavily pre-treated patients there were no evidence-based treatment alternatives and the placebo-control was adequate.

Selection of endpoints: OS as primary endpoint is appropriate in a trial with mCRC patients, having undergone available standard therapies and with a poor prognosis. However, OS can be confounded by subsequent anticancer therapies, which were nearly as frequent in both arms (29.4% of patients in fruquintinib arm and 34.3% of patients in placebo arm). These numbers illustrate the selected nature of the study population. PFS as the key secondary endpoint, analysed only after statistical significance in OS was seen, is acceptable and not confounded by subsequent therapies. PFS was assessed by the investigators. The trial did not incorporate blinded independent central review, which would have strengthened these results. Typical AEs from anti-VEGF(R)-therapy can have unblinded a considerable number of patients. This can have subtle influence on response assessment and treatment decisions (e.g., whether or not to continue therapy). Whether unintentional unblinding occurred and whether this had any influence on treatment decisions was not pursued further, as OS is the primary endpoint. In general, secondary endpoints are also considered appropriate and in line with current anticancer guideline (EMA/CHMP/205/95) and standard for a trial enrolling patients with an incurable cancer. Progressive disease was not explicitly required prior enrolment. Thus, SD could be due to disease characteristics, not the activity of the medicinal product. Overall, ORR, DCR, and DOR have minor relevance in the B/R assessment, as the main objectives are the time-to-event endpoints OS and PFS.

Randomisation/blinding: The selection and number of stratification factors are acceptable. Scientific advice by CHMP found the 2:1 ratio acceptable.

Interim and final analyses: The current results can be considered mature for OS and PFS.

The statistical methods used to analyse the primary endpoint OS were conventional and acceptable. This is also true for the key secondary endpoint PFS apart from the deviations from the relevant EMA guideline regarding continued data collection and censoring of PFS. The methods for analysing ORR and related quantities are conventional and appropriate if the sample size and number of responses are not small. It was planned to use stratified exact test and CI if the number of objective responses or disease control was insufficient to support Cochran-Mantel-Haenszel (CMH) test and the odds ratio. Despite observing no responses in the placebo arm, CMH test and Mantel-Haenszel CI appear to have been used. For HRQoL endpoints, MMRM and analysis of time-to-deterioration were used which are both difficult to interpret. Due to the low importance of these endpoints no OCs were raised.

Four global amendments were made during the study, of which most important was #2, increasing the sample size from 552 to 687 patients and the statistical power from 80% to 90%. The requirements for prior treatment were amended, adding BRAF inhibitor treatment for patients with BRAFmt CRC (amendment #2) and deleting the sentence "if approved and available in the subject's country" from prior use trifluridine-tipiracil and regorafenib (amendment #1). The amendments also mirror the growing understanding of fruquintinib (e.g., with evolving guidance for dose modifications) and changes due to COVID-19. In general, the amendments do not jeopardize the integrity of the study.

Two GCP inspections occurred during the conduct of FRESCO-2, one in Austria and one in Germany, with critical, major, and minor findings. Thus, despite critical and major GCP findings, the effects on study integrity are not major due to low patient numbers. However, the coverage of GCP inspections is low, while there were 124 study sites randomizing at least 1 patient. The Italian site enrolling the

highest number of patients was the target of inspection conducted by the FDA. Based on currently available information, there are no concerns on data quality, and no GCP inspection was proposed.

Efficacy data and additional analyses

Baseline characteristics: 80.9% of patients were White and 71.6% from Europe. The median duration of metastatic disease was 39 months prior enrolment. As 502 patients had ≥4 prior treatment lines for metastatic disease, fruquintinib or placebo was administered as 5th line or beyond therapy for the majority (72.6%). Overall, 95.7% of patients had received at least 3 lines to metastatic disease, thus receiving fruquintinib or placebo as 4th line and beyond therapy.

Protocol deviations: Protocol deviations were high in both treatment arms. Major deviations were more frequent in the fruquintinib arm (90.5%) than in the placebo arm (85.2%), while minor deviations were as frequent in both arms (92.6% in fruquintinib arm and 93% in placebo arm). One factor behind deviations was COVID-19 and some differences between arms were related to longer duration of treatment in the fruquintinib arm.

OS results: Patients in the fruquintinib arm lived longer with 7.4 months vs 4.8 months median survival in placebo arm, respectively, HR of 0.662 (95%: 0.549, 0.800), P < 0.001, with the reduction in risk of death by 34%. Thus, the primary goal of the trial was reached. The observed difference of 2.6 months in OS is clinically meaningful, as it concerns a very late line treatment setting, without relevant, evidence-based further therapy options.

PFS results: FRESCO-2 reached its target, with a stratified HR of 0.321 (0.267, 0.386), and raw and adjusted 2-sided *P* < 0.001, indicating a 68% reduction in risk of death or progression. With the median PFS of 3.7 months with fruquintinib and 1.8 months with placebo, the 1.9 months delay in disease progression is short but can be seen clinically meaningful when evaluated together with the OS results. The short PFS in the placebo arm illustrates the progressive nature of mCRC. As 87.6% of patients have died or had PD by the final analysis, PFS data is more mature than OS data.

In both treatment arms, but especially in the placebo arm, the Kaplan-Meier curves for PFS drop steeply from month 0. The applicant stated that early progressions were most commonly detected due to symptomatic deterioration, which could have led to an earlier tumour assessment. Early PDs were mainly detected on unscheduled visits occurring in roughly similar ratio in both treatment arms. To address the concern of possible detection biases (e.g., participants in placebo being assessed for PD earlier) in PFS sensitivity analysis events were allocated to the scheduled time of evaluation, providing mPFS estimates of 3.68 vs 1.87 months with fruquintinib and placebo, respectively (HR 0.383). When PDs were analysed as interval-censored events, the mPFS estimates with fruquintinib and placebo were 3.02 and 0.99 months, respectively (HR 0.331).

The applicant provided efficacy results for 3 mg and 4 mg dose cohorts separately. For the 121 patients treated with fruquintinib and a dose reduction from 5 mg to 4 mg the mOS was 10.78 months and mPFS 5.59 months, while the ORR was 5% and DCR 81%. The patient population treated with fruquintinib and dose reduction from 4 mg to 3 mg contained only 45 patients, with mOS as 13.86 months and mPFS 7.39 months. These populations are highly selected, of limited size and affected by confounding factors. Moreover, it is not known when these reductions took place in each patient's treatment pathway. Overall, these analyses did not suggest a decreased efficacy in patients with a dose reduction of fruquintinib.

PFS2 was defined as time from randomisation to discontinuation of next-line therapy, 2nd objective disease progression, or death of any cause, whichever occurred first. There were 342 (74%) PFS2 events in the fruquintinib arm and 189 (82%) events in the placebo arm. The median PFS2 in the fruquintinib arm was 6.41 months (95% CI: 5.82-6.90) vs. 4.14 months (3.65-4.93) in the placebo

arm. According to the Applicant, there were no carry-over effects for toxicity with subsequent anticancer therapy but data to support this statement was not provided.

Other endpoints and additional considerations: Partial unblinding of patients due to toxicity and lack of blinded independent central review decrease the significance of differences in ORR, DCR, and DOR, which would be of limited utility in the light of significant OS and PFS results. Considering the MoA of fruquintinib and the late line treatment setting, it is not unexpected that confirmed responses were rare. The main effect of fruquintinib is to delay progression (54% with SD in fruquintinib arm, 16.1% in placebo arm). Progression was not an explicit requirement for all patients for enrolment. Thus, some SD responses could be related to the characteristics of the underlying disease, also noting the SDs in the placebo arm. The number of progressors is higher in placebo arm (62.2% vs. 30.2%) and DCR favours fruquintinib (55.5% vs. 16.1%). While the adjusted difference (fruquintinib-placebo) for ORR (CR+PR) was not statistically different, the adjusted difference (fruquintinib-placebo) for DCR (CR+PR+SD) was statistically different. The duration of response concerns only 7 patients, all with a PR as no CRs were detected.

From statistical methodological perspective, the very low response rates may have led to the predetermined methods for estimating SE, confidence intervals and p-values being inappropriate. Overall, the relevance of these secondary endpoints is minor as the time-to-event endpoints OS and PFS are central for the assessment.

HRQoL: HR QoL data were evaluated based on the EORTC QLQ-C30 and EQ-5D-5L questionnaires. In general, the differences in HR QoL measurements are minor, partly showing trends favouring fruquintinib over placebo. Major variability prevents firm conclusions. The applicant has not incorporated HR QoL findings in the SmPC, which is supported.

Exploratory endpoints: Albeit median CEA in the placebo group was higher, baseline disease characteristics were balanced. The median in CEA at last assessment on treatment was 119 in the fruquintinib group and 261 in the placebo group. These results are not contradictory to the other efficacy results.

Ancillary analyses

Subgroup analyses for OS favour fruquintinib in most subgroups, including patients with prior anti-VEGF (HR 0.689, 7.4 months with fruquintinib vs 4.4 months with placebo). This is relevant considering the MoA of fruquintinib. For some subgroups the findings should be interpreted with utmost care due to small sample sizes.

Females have only a weak, if any, OS benefit: 69% of the females in fruquintinib arm died vs 67.8% in the placebo arm, whereas 68.6% of males in the fruquintinib arm died vs. 80% in the placebo arm. The HR for OS (95% CI) was 0.828 (0.609-1.125) for females, despite PFS benefit appearing consistent between genders. No explanations regarding demographic and baseline characteristics nor safety were identified that could explain the smaller or lack of OS benefit. The fruquintinib-treated populations' survival curves are similar among males and females, with 25-30% surviving 12 months or longer and mOS being 7.10 and 7.59 months for males and females, respectively. The treatment difference appears homogenous between genders during the first few months since the start of study treatment. The dilutions to the treatment effect (HR) appear to be mainly related to the fact that, among the 29 female survivors originally randomised to placebo, few deaths were observed from month 8 onwards and thus the females' K-M curves cross at 12 months. Overall, the evaluation of OS effect among females is uncertain due to initially small sample and large proportion of censored data.

The treatment exposure with fruquintinib was slightly higher in males (median total duration of exposure 3.22 months while 2.79 months in females). The median number of fruquintinib cycles was

higher in males in (4 vs 3 cycles in females). The mPFS was 3.7 months for both genders, which suggests that females may have stopped treatment more often before PD.

In conclusion, some uncertainty remains about the survival benefit of fruquintinib among females. Despite the consistent positive PFS effect in females, OS benefit among females was weak and not robustly demonstrated, which may be partly from effect dilution due to use of subsequent anticancer treatment and partly due to random chance in absence of mechanistic rationale. The applicant clarified that this finding appeared not to be associated with any particular safety issue.

An attempt to analyse separately those patients with intolerance to or progressing on trifluridine-tipiracil or regorafenib was hampered by the very small number of patients with intolerance, as the majority progressed on these agents. A trend with longer OS was seen after intolerance to trifluridine-tipiracil or to regorafenib than after PD. This may suggest that evolving resistance mechanisms after prior PD decrease the efficacy of fruquintinib and could be partly related to treatment durations. For PFS, there was no difference with fruquintinib after prior treatment with regorafenib ending in PD or in intolerance. For trifluridine-tipiracil the PFS with fruquintinib was slightly longer after intolerance than after PD.

The applicant presented additional data to disentangle, whether the efficacy is similar, if the patient received trifluridine-tipiracil first, then regorafenib, followed by fruquintinib/placebo (139 patients), as if the therapy is given in a reverse order (regorafenib -> trifluridine-tipiracil -> fruquintinib/placebo, 129 patients)) (data not shown). These showed, that OS and PFS benefits favored fruquintinib over placebo irrespective of the order in prior therapies.

In the subgroup analyses for PFS, the HRs favour fruquintinib in most subgroups, excluding those with very small numbers of patients. There are no evident differences between females and males. For PFS the subgroups for prior therapies (trifluridine-tipiracil, regorafenib, or both) are consistent for a PFS benefit from fruquintinib. Some subgroups are too small for firm conclusions, resulting in wide 95% CIs.

An additional analysis was provided to evaluate a possible association of improved antitumor efficacy and development of hypertension during antiangiogenic therapy. When comparing patients treated with fruquintinib, those without hypertension occurrence had a median OS of 6.57 months, while those with hypertension occurrence had a median OS of 9.46 months, with were nearly identical mPFS times (3.58 months vs 3.91 months, respectively). Several confounding factors can affect these results.

Supportive studies

FRESCO and other clinical trials with fruquintinib in mCRC patients have several differences and limitations e.g., in inclusion/exclusion criteria and prior therapies, and sizes and designs of the trials. Therefore, their relevance for efficacy assessment in the current MAA is limited, and hence not discussed in detail. Albeit the Applicant provided several justifications to regard FRESCO as pivotal and as part of the sought indication, this was not agreed with by the CHMP. Therefore, the Applicant agreed to align the indication with FRESCO-2 population.

FRESCO

The design of FRESCO can be regarded adequate (a randomised double-blind phase 3 comparing fruquintinib to placebo). FRESCO enrolled 416 patients with mCRC in 2:1 allocation to 5 mg of fruquintinib QD 3 weeks on, 1 week off, or to corresponding placebo. Prior enrolment the patients had to have received at least 2 lines of standard chemotherapy and failed. Overall, 225 patients had 0, 1, or 2 prior lines for metastatic disease, i.e. 54% of the ITT population (151 were treated with fruquintinib and 74 with placebo). In all, 78.8% of patients had ≤3 prior treatment lines for metastatic disease and 21.2% of patients >3 prior lines.

The study was positive for the primary endpoint of OS, with a benefit of 2.7 months over placebo (9.3 months vs 6.6 months; HR=0.65; P<0.001). Median OS was longer than in FRESCO-2, possibly related to the earlier treatment line and differences in patient populations. However, the efficacy of fruquintinib was not established in patients of ≥65 years (HR for OS 0.95, 95% CI 0.55-1.63). Further, in the subgroup analyses for the OS the HR for males was 0.52 while the OS HR for females was 0.85. Thus, despite PFS benefit appearing consistent between genders the Kaplan-Meier curves for OS by gender show no OS benefit in females in FRESCO. Overall, differences in disease history between genders do not explain a lesser OS benefit with fruquintinib. The imbalance between allocation of sexes between study arms was major (120 and 41 females were randomized to fruquintinib and placebo, respectively, when 2:1 ratio was expected). The applicant provided OS analyses, adjusted for this imbalance by using gender as a covariate in Cox proportional hazards model. This analysis provided a mOS of 9.30 months with fruquintinib and 6.57 months with placebo, HR 0.653 and was thus consistent with the primary analyses (HR=0.65). The overall effect on OS is not biased by the random imbalance with respect to gender.

PFS with fruquintinib (3.7 months with fruquintinib vs 1.8 months with placebo; HR=0.26; P<0.001) was similar to that seen in FRESCO-2, even though the patients in FRESCO were treated in an earlier setting. This indicates that advanced CRCs can rapidly develop resistance irrespective of the treatment line.

The enrolled population differs from the European mCRC population. Prior diagnostics and prior treatments received are not in line with the European treatment praxis. This is clearly illustrated by the differences in patient journey graphs in 1st and 2nd line when comparing to FRESCO-2 population. Although more than half (55.5%) of the patients were KRASwt, prior use of EGFRi was low (14%), indicating undertreatment compared to European praxis. The same issue concerns the high proportion (70%) of VEGFi naïve patients. This is relevant noting the MoA of fruquintinib. Further, the use of anti-VEGF in FRESCO was scattered through treatment lines (1.9% in 1st line, 12% in 2nd line, 6.3% in 3rd line, 5.3% in 4th line and 4.6% in 5th line and beyond). There is no data for MSI-H/dMMR and the use of ICIs, nor data for BRAF mutations and the use of BRAFi. The limited use of prior therapies is illustrated by the fact that the majority of patients (57%) had less than 18 months from the 1st diagnosis of metastasis to randomisation. In FRESCO-2 the proportion of patients with ≤18 months duration of metastatic disease was 7.2%.The issue about differences in prior lines and their content is broader than comparing proportions of patients who have received specific prior treatments or comparing efficacy in subgroups of patients after specific therapies. Prior treatments and prior lines of therapy can have an impact on efficacy (responsiveness of the tumour), safety (by added / overlapping toxicities), and tolerability (due to adverse events, ECOG, and age).

The patients are younger than currently typical patients are in the Europe or seen in the FRESCO-2. FRESCO also had an upper age limit, which is contrary to current trial practice in Europe or to FRESCO-2. There were also differences in disease characteristics: The proportion of patients with a rectal primary (44%) is higher than in the FRESCO-2 trial (30.8%) and what is typically reported for European patients (i.e., a third). The proportion of patients with stage IV disease at 1st diagnosis (43%) is higher than reported in Europe (15-30%).

The applicability of results is not hampered by a single effect modifier or prognostic factor, but rather by a large number of clinically relevant differences in patient populations, baseline characteristics and prior treatments. The B/R determined for the FRESCO patient population cannot be reliably extrapolated to current European mCRC population. In all, differences and uncertainties preclude considering FRESCO suitable to support a 3rd line indication. To support a 3rd line indication the need for an active comparator was stated in the CHMP/SAWP scientific advice in 2020.

Other supportive studies

2015-013-00US1 is a dose-confirmatory, bridging study to confirm the RP2D (approved dose in China) of fruquintinib in US cancer patients and to evaluate the preliminary efficacy and safety of fruquintinib in a Western mCRC patient population. 101 patients were treated and analysed for safety and efficacy. 81 patients were enrolled into the mCRC cohorts. Across different cohorts the results showed ORRs of 2.4%-16.7%. These consisted of PRs as there were no CRs. In general, the efficacy results concerning BOR, ORR, and DCR are not discrepant from those observed in FRESCO-2. However, the numbers of patients are very limited, and the patient populations differ from FRESCO-2. In conclusion, the 2015-013-00US1 study can be considered for dose bridging, but its relevance for efficacy claims is minor.

2012-013-00CH3 is a randomised, open-label, phase Ib clinical study of fruquintinib administered as "4 mg, once daily, continuous" versus "5 mg, once daily for 3 weeks/withdrawal of 1 week" as 3rd line or above treatment in patients with advanced CRC, carried out in China. 40 subjects were enrolled in the randomized comparison stage and 22 subjects enrolled in the expansion stage. Regarding the results from the expansion stage, as there is no comparator, the PFS and OS results cannot be evaluated. In general, the response rates and DCR are not discrepant from those of FRESCO-2. However, the unconfirmed nature of responses in the expansion stage precludes conclusions. The main input from the trial was to determine the dose and dosing for the expansion stage and for the later trials.

2012-013-00CH1 is double-blind, placebo-controlled, multicenter phase 2 study comparing fruquintinib plus BSC and placebo plus BSC in patients with advanced CRC who have failed to respond to 2nd line and above standard chemotherapy, carried out in China with the dosing regimen of fruquintinib 5 mg QD for 3 weeks on, 1 week off. With the allocation ratio 2:1, 47 and 24 patients were randomised into the fruquintinib group and the placebo group. Due to the small size and differences in patient population and prior treatments the contribution of this study for efficacy assessment of fruquintinib for the applied indication is negligible. Despite the earlier treatment setting, OS and PFS results do not clearly differ from the results obtained in FRESCO-2.

Overall, these four studies provide supportive data for efficacy of fruquintinib in patients with 2 or 3 prior treatment lines with advanced CRC.

To conclude, efficacy data from FRESCO cannot be extrapolated to current European patients and treatment context. It forms supportive evidence especially for safety of fruquintinib. If fruquintinib would have been studied for 1st line treatment, the differences in patient populations would have carried less weight, as these would have been more limited (e.g. diagnostics). When fruquintinib is to be used after prior therapies, these differences cannot be overlooked. Studies 2012-013-00CH3 and 2012-013-00CH1 provided data for the proof of concept and early development, and study 2012-013-00CH3 also for determining the dose and dosing. Study 2015-013-00US1 is relevant for bridging the dose to Western patients. For the sought indication FRESCO-2 forms the central evidence.

Wording of the therapeutic indication

The initially proposed indication was "*Fruzaqla is indicated for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with or are not considered candidates for available therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and an anti-EGFR therapy*."

The indication was not considered to be approvable, as it is not in line with the patient population of FRESCO-2, and FRESCO was not considered to provide sufficient evidence to support an earlier line indication. The applicant provided additional justifications, including MAIC comparisons to trifluridine-tipiracil and regorafenib, and various subgroup analyses. The applicant also argued that fruquintinib

could have better tolerability as compared to regorafenib due to its selectivity, but there was no sufficient data to confirm this hypothesis. Although the MoA of trifluridine-tipiracil is different, no conclusions can be drawn either from its toxicity vs fruquintinib.

The initially proposed wording *"who are not considered candidates for available therapies"* was considered vague, with no clear definition in clinical practice or in relation to FRESCO-2 population. This could open loopholes for early line treatment without solid scientific evidence.

Overall, the provided argumentation and analyses failed to convincingly justify the requested indication for 3rd line (or even earlier) in mCRC. While it is acknowledged that possibly apart from prior VEGF(R) inhibitors the prior treatments are not expected to directly modify the treatment effect of fruquintinib, major differences in prior treatments and patient characteristics are expected to have an impact on efficacy, safety and tolerability of the treatment, thus hampering extrapolation of B/R. Further, multiple differences, while expected to have a smaller impact on efficacy, safety and tolerability on their own, were observed, potentially adding up bias to the results and hampering B/R extrapolation to a significant degree. Currently European patients who have failed 2 prior lines of treatment have established treatment options. This reduces the unmet medical need and the need to justify multiple uncertainties on extrapolation of B/R balance.

The applicant agreed to align the indication with FRESCO-2 study population as follows:

"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."

3.6.10. Conclusions on the clinical efficacy

Advanced CRC has a high incidence and when radical surgery is not an option, it has a dismal prognosis. Albeit there are several evidence-based systemic treatments, an unmet medical need prevails when the patient has exhausted them.

In FRESCO-2, OS as primary endpoint and PFS as key secondary endpoint were clinically and statistically significantly longer in patients treated with fruquintinib. Although modest, efficacy of fruquintinib showed a 50% increase in median OS and gain of two months in median PFS compared to placebo. Efficacy mainly reflects disease stabilisation, with few PRs and no CRs.

Overall, efficacy results in last line setting of mCRC support a relevant clinical benefit.

3.6.11. Clinical safety

The safety profile of fruquintinib has been characterized primarily based on the safety data from a single pivotal randomized placebo-controlled phase 3 study FRESCO-2 and supportive data from another phase 3 study FRESCO in Chinese study sample as well as pooled data analysis. Details on the individual studies are found in the efficacy section. No data integration was performed, across the different categories or the 2 phase 3 studies, due to differences in study samples and trial designs.

Pooled Safety Data

Safety data from 8 clinical monotherapy studies (2019-013-GLOB1 [FRESCO-2], including the Japanese safety lead-in portion, 2013-013-00CH1 [FRESCO], 2012-013-00CH1, 2009-013-00CH1,

2012-013-00CH3, 2015-013-00US1, 2014-013-00CH1, and 2015-013-00CH1 [FALUCA]) were pooled into 3 ISAS groups to increase the sensitivity to detect adverse events (AEs) and to better assess and understand the safety and tolerability profile of fruquintinib using the dosing schedule of fruquintinib 5 mg 3/1 in different clinical settings. The 3 ISAS groups for patient populations treated in the monotherapy setting, who received at least 1 dose of study drug (fruquintinib or placebo) are as described below.

1. Integrated Safety Analysis Set—Metastatic Colorectal Cancer (ISAS—mCRC). All patients from the 3 randomized, 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) were included in this analysis set.

2. Integrated Safety Analysis Set—Expanded Metastatic Colorectal Cancer (ISAS—Expanded mCRC). In addition to the patients in the ISAS—mCRC, 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-2 were included, but only mCRC patients.

3. Integrated Safety Analysis Set—Fruquintinib Overall (ISAS—Fruquintinib Overall). All patients from the 8 monotherapy studies detailed above, regardless of indication.

The focus of discussion is on the safety data from ISAS-mCRC pool where a placebo arm is present for contextualization of incidence rates.

As indicated in the efficacy assessment, under Section Statistical methods, the safety population included all randomized patients who received at least 1 dose of study drug. Patients in this population were analysed according to the treatment they actually received. This population was used for all safety analyses. For details, see Section Statistical methods above.

The pooling strategy to evaluate the safety of fruquintinib appears meaningful and justified and is in general endorsed. Overall, the safety pools seem representative of the target population for whom fruquintinib is indicated.

The FRESCO-2 study is considered the pivotal phase 3 study for this MAA. The other phase 3 study, the FRESCO study, is deemed at best supportive for an EU MAA, considering the inherent differences noted in the design of the two studies and the target populations (including ethnicity and lines of treatment) and differences were also seen in the safety results.

3.6.11.1. Patient exposure

FRESCO-2 and FRESCO studies

Study drug exposure is summarized for FRESCO and FRESCO-2 studies in Table 27.

Table 27: Summary of Study Drug Exposure in Studies 2013-013-00CH1 (FRESCO) and 2019-013-GLOB1 (FRESCO-2)

	FRESCO		FRESCO-2	
	Fruquintinib 5 mg 3/1 (N = 278)	**Placebo (N = 137)**	**Fruquintinib 5 mg 3/1 (N = 456)**	**Placebo (N = 230)**
Duration of exposure (months) [a]				
Mean (SD)	4.93 (3.969)	1.89 (1.522)	4.04 (3.120)	2.03 (1.362)
Median	3.68	1.84	3.06	1.84
Min, Max	0.1, 21.9	0.1, 11.1	0.3, 19.1	0.3, 12.0
Number of cycles received [b]				
Mean (SD)	5.5 (4.28)	2.2 (1.62)	4.34 (3.196)	2.32 (1.422)
Median (Q1, Q3)	4.0	2.0	3.0 (2.0, 6.0)	2.0 (1.0, 3.0)
Min, Max	1, 24	1, 12	1, 20	1, 13
Number of cycles received categories, n (%)				
1	23 (8.3)	39 (28.5)	58 (12.7)	59 (25.7)
2	72 (25.9)	76 (55.5)	118 (25.9)	108 (47.0)
3	19 (6.8)	4 (2.9)	57 (12.5)	29 (12.6)
4	32 (11.5)	10 (7.3)	62 (13.6)	18 (7.8)
5	16 (5.8)	4 (2.9)	23 (5.0)	8 (3.5)
6	36 (12.9)	1 (0.7)	43 (9.4)	6 (2.6)
>6	80 (28.8)	3 (2.2)	95 (20.8)	2 (0.9)

Abbreviations: min = minimum; max = maximum; SD = standard deviation. Unless otherwise specified, percentages are based on the number of patients in each group (ie N).

As FRESCO illustrates an earlier treatment setting, the median number of cycles of fruquintinib was four, while patients in FRESCO-2 were more heavily pretreated and received the median number of three cycles of fruquintinib. In both the median number of placebo-cycles received was two.

Pooled safety data

Study drug exposure is summarized for the overlapping safety pools ISAS—mCRC and ISAS—Expanded mCRC in Table 28.

Table 28: Summary of Study Drug Exposure ISAS—mCRC and ISAS—Expanded mCRC pools

	ISAS—mCRC		ISAS—Expanded mCRC
	Fruquintinib 5 mg 3/1 (N = 781)	Placebo (N = 391)	Fruquintinib 5 mg 3/1 (N = 911)
Duration of exposure (months) [a]			
Mean (SD)	4.40 (3.479)	2.00 (1.616)	4.51 (3.642)
Median (Q1, Q3)	3.65 (1.84, 5.75)	1.84 (0.92, 2.04)	3.68 (1.84, 5.91)
Min, Max	0.3, 22.1	0.2, 17.5	0.3, 23.0
Number of cycles received [b]			
Mean (SD)	4.8 (3.65)	2.3 (1.71)	4.8 (3.83)
Median (Q1, Q3)	4.0 (2.0, 6.0)	2.0 (1.0, 2.0)	4.0 (2.0, 6.0)
Min, Max	1, 24	1, 19	1, 25
Number of cycles received categories, n (%)			
1	88 (11.3)	115 (29.4)	112 (12.3)
2	197 (25.2)	186 (47.6)	214 (23.5)
3	82 (10.5)	34 (8.7)	102 (11.2)
4	100 (12.8)	29 (7.4)	111 (12.2)
5	42 (5.4)	14 (3.6)	58 (6.4)
6	88 (11.3)	7 (1.8)	92 (10.1)
7 to 10	129 (16.5)	2 (0.5)	150 (16.5)
11 to 12	25 (3.2)	2 (0.5)	33 (3.6)
> 12	30 (3.8)	2 (0.5)	39 (4.3)

ISAS = integrated safety analysis set; Max = maximum; mCRC = metastatic colorectal cancer; min = minimum; PT = preferred term; Q1 = 25% percentile; Q3 = 75% percentile; SD = standard deviation. [a]Duration of exposure is derived as (last dose date of study drug – first dose date of study drug + 8)/30.4375. [b]The number of cycles in which at least one dose of study drug is taken.
Source: Table ISS 5.2.1.1

As of the cut-off date (24 June 2022) for FRESCO-2, the total cumulative exposure for fruquintinib was 1371 patients, who have been exposed to at least 1 dose of fruquintinib 5 mg 3/1 (ISAS—Fruquintinib Overall), with 911 mCRC patients (ISAS—Expanded mCRC), which is also the population used for identification of ADRs for section 4.8. For placebo comparison, within the ISAS—mCRC, 781 mCRC patients were exposed to fruquintinib 5 mg 3/1, and 391 patients were exposed to matching placebo. In addition to this, 100 healthy subjects received fruquintinib 5 mg alone as a single dose at least once in the 5 clinical pharmacology studies in ISAS—ClinPharm (see PK section). For details of the study populations, including patient disposition, background demographics and other baseline characteristics, prior and concomitant medications, see the efficacy section.

Overall, the extent of exposure is considered sufficient to be able to identify the most common adverse events.

3.6.11.2. Adverse events

Overview of Treatment Emergent Adverse Events

FRESCO-2 and FRESCO studies

Table 29: Summary of Treatment-Emergent Adverse Events for Study 2013-013- FRESCO and 2019-013-GLOB1 (FRESCO-2), Safety Analysis Set

Adverse Event Category	FRESCO		FRESCO-2	
	Fruquintinib 5 mg 3/1 (N = 278)	Placebo (N = 137)	Fruquintinib 5 mg 3/1 (N = 456)	Placebo (N = 230)
Patients with any TEAE	274 (98.6)	121 (88.3)	451 (98.9)	213 (92.6)
Grade ≥ 3	170 (61.2)	27 (19.7)	286 (62.7)	116 (50.4)
Treatment-related	266 (95.7)	97 (70.8)	395 (86.6)	130 (56.5)
Treatment-related, Grade ≥ 3	128 (46.0)	10 (7.3)	164 (36.0)	26 (11.3)
Serious TEAE	43 (15.5)	8 (5.8)	171 (37.5)	88 (38.3)
Treatment-related, serious TEAE	17 (6.1)	2 (1.5)	43 (9.4)	8 (3.5)
Adverse event of special interest	257 (92.4)	74 (54.0)	368 (80.7)	122 (53.0)
TEAE leading to dose reduction	67 (24.1)	6 (4.4)	110 (24.1)	9 (3.9)
TEAE leading to dose interruption	98 (35.3)	14 (10.2)	213 (46.7)	61 (26.5)
TEAE leading to treatment discontinuation	42 (15.1)	8 (5.8)	93 (20.4)	49 (21.3)
TEAE leading to death	9 (3.2)	2 (1.5)	48 (10.5) [a]	45 (19.6)

TEAE = treatment-emergent adverse event. The number of patients in each category as a percentage of the total number of patients in the relevant analysis sets. If more than 1 TEAE occurred in the patients, it was counted once according to the highest severity or the strongest correlation.

Pooled safety data

An Overview of TEAEs in ISAS-mCRC population is presented in Table 30.

Table 30: Overview of Treatment-Emergent Adverse Events in ISAS—mCRC and ISAS—Expanded mCRC

Category, n (%) Parameter	ISAS—mCRC		ISAS—Expanded mCRC
	Fruquintinib 5 mg 3/1 (N = 781)	**Placebo (N = 391)**	**Fruquintinib 5 mg 3/1 (N = 911)**
Patients with Any TEAEs	**770 (98.6)**	**355 (90.8)**	**899 (98.7)**
CTCAE Grade ≥ 3	489 (62.6)	151 (38.6)	578 (63.4)
Treatment-related	705 (90.3)	243 (62.1)	828 (90.9)
Leading to Dose Reduction	190 (24.3)	15 (3.8)	225 (24.7)
Leading to Dose Interruption	327 (41.9)	80 (20.5)	386 (42.4)
Leading to Treatment Discontinuation	142 (18.2)	59 (15.1)	164 (18.0)
Treatment-related Leading to Dose Reduction	166 (21.3)	10 (2.6)	198 (21.7)
Treatment-related Leading to Dose Interruption	234 (30.0)	27 (6.9)	275 (30.2)
Treatment-related Leading to Treatment Discontinuation	73 (9.3)	9 (2.3)	85 (9.3)
Leading to Death	61 (7.8) [a]	49 (12.5)	65 (7.1) [a]
Patients with Any Serious TEAEs	**228 (29.2)** [a]	**101 (25.8)**	**274 (30.1)** [a]
CTCAE Grade ≥ 3	208 (26.6) [a]	96 (24.6)	251 (27.6) [a]
Treatment-related	67 (8.6)	13 (3.3)	82 (9.0)
Leading to Dose Reduction	13 (1.7)	3 (0.8)	20 (2.2)
Leading to Dose Interruption	75 (9.6)	26 (6.6)	90 (9.9)
Leading to Treatment Discontinuation	88 (11.3)	46 (11.8)	103 (11.3)
Treatment-related Leading to Dose Reduction	8 (1.0)	0	13 (1.4)
Treatment-related Leading to Dose Interruption	13 (1.7)	3 (0.8)	19 (2.1)
Treatment-related Leading to Treatment Discontinuation	34 (4.4)	3 (0.8)	40 (4.4)
Leading to Death	60 (7.7) a	49 (12.5)	63 (6.9)
Patients with Any Treatment-emergent AESIs	**677 (86.7)**	**228 (58.3)**	**802 (88.0)**
Serious	99 (12.7)	30 (7.7)	122 (13.4)
CTCAE Grade ≥ 3	317 (40.6)	63 (16.1)	377 (41.4)
Treatment-related	601 (77.0)	142 (36.3)	716 (78.6)
Leading to Dose Reduction	124 (15.9)	6 (1.5)	144 (15.8)

Leading to Dose Interruption	186 (23.8)	39 (10.0)	222 (24.4)
Leading to Treatment Discontinuation	69 (8.8)	19 (4.9)	82 (9.0)
Treatment-related Leading to Dose Reduction	106 (13.6)	4 (1.0)	123 (13.5)
Treatment-related Leading to Dose Interruption	138 (17.7)	11 (2.8)	165 (18.1)
Treatment-related Leading to Treatment Discontinuation	51 (6.5)	4 (1.0)	60 (6.6)
Leading to Death	17 (2.2)	5 (1.3)	19 (2.1)
Patients with Any Treatment-emergent AESIs	**677 (86.7)**	**228 (58.3)**	**802 (88.0)**
Dermatological toxicity	363 (46.5)	45 (11.5)	440 (48.3)
CTCAE Grade ≥ 3	69 (8.8)	1 (0.3)	79 (8.7)
Hypertension (SMQ)	371 (47.5)	46 (11.8)	450 (49.4)
CTCAE Grade ≥ 3	144 (18.4)	5 (1.3)	174 (19.1)
Thyroid dysfunction (SMQ)	260 (33.3)	17 (4.3)	312 (34.2)
CTCAE Grade ≥ 3	2 (0.3)	0	2 (0.2)
Proteinuria (SMQ)	257 (32.9)	59 (15.1)	326 (35.8)
CTCAE Grade ≥ 3	22 (2.8)	2 (0.5)	23 (2.5)
Hepatic function abnormal (SMQ)	284 (36.4)	92 (23.5)	343 (37.7)
CTCAE Grade ≥ 3	69 (8.8)	37 (9.5)	80 (8.8)
Haemorrhages (SMQ)	207 (26.5)	57 (14.6)	249 (27.3)
CTCAE Grade ≥ 3	16 (2.0)	4 (1.0)	21 (2.3)
Infections	183 (23.4)	52 (13.3)	222 (24.4)
CTCAE Grade ≥ 3	47 (6.0)	15 (3.8)	63 (6.9)
Embolic and thrombotic events (SMQ)	28 (3.6)	6 (1.5)	28 (3.1)
CTCAE Grade ≥ 3	17 (2.2)	3 (0.8)	17 (1.9)
Gastrointestinal perforation (SMQ)	22 (2.8)	2 (0.5)	23 (2.5)
CTCAE Grade ≥ 3	15 (1.9)	2 (0.5)	16 (1.8)
Left ventricular ejection fraction decreased (SMQ)	5 (0.6)	6 (1.5)	8 (0.9)
CTCAE Grade ≥ 3	4 (0.5)	2 (0.5)	5 (0.5)

AE = adverse event; AESI = adverse event of special interest; CTCAE = common terminology criteria for adverse event; ISAS = integrated safety analysis set; mCRC = metastatic colorectal cancer; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = Standardized MedDRA query; TEAE = treatment-emergent adverse event The term "3/1" means a dosing schedule of 3-weeks on/ 1-week off during each 28-day cycle. Unless otherwise specified, percentages are based on the number of patients in each group (i.e., N).

When interpreting the presented pooled data, it should be noted that there is a significant overlap between the pools, i.e., the ISAS-mCRC and ISAS-Expanded mCRC populations; the majority of the patients in ISAS-Expanded mCRC pool (fruquintinib 5mg 3/1 N=911) were from ISAS-mCRC (fruquintinib 5mg 3/1 N=781) pool. The subjects in ISAS-mCRC were all from placebo-controlled studies, allowing assessment of safety in a more unbiased way compared to ISAS-Expanded mCRC.

The assessment of safety from other indications and with different dosing regimens are considered of limited relevance for the current safety assessment.

Incidence of Adverse Events by Preferred Term

FRESCO-2 and FRESCO studies

In FRESCO and FRESCO-2 (see Table 31), the incidences of TEAEs were higher in fruquintinib 5 mg 3/1 group than the placebo group (98.6% vs 88.3% and 98.9% vs 92.6% respectively). The PTs under most frequently reported TEAEs were consistent across both studies. Though some of the TEAEs were more frequently reported in FRESCO compared to FRESCO-2 (e.g., palmar-plantar erythrodysaesthesia syndrome [49.3% vs 19.3% in fruquintinib 5 mg 3/1 group], dysphonia [37.8% vs 16.2% in fruquintinib 5 mg 3/1 group]), there were no marked differences in incidences of these events with toxicity Grade ≥3.

Table 31: Most Frequent Treatment-Emergent Adverse Events (≥ 10% Incidence in FRESCO-2 Fruquintinib Group, Any TEAE Column) by Preferred Term in Study 2013-013-00CH1 (FRESCO) and 2019-013-GLOB1 (FRESCO-2), Safety Analysis Set

Preferred Term	FRESCO				FRESCO-2			
	Fruquintinib 5 mg 3/1 (N = 278)		Placebo (N = 137)		Fruquintinib 5 mg 3/1 (N = 456)		Placebo (N = 230)	
	Any	G ≥ 3	Any	G ≥ 3	Any	G ≥ 3	Any	G ≥ 3
Patients With Any TEAE	274 (98.6)	170 (61.1)	121 (88.3)	27 (19.7)	451 (98.9)	286 (62.7)	213 (92.6)	116 (50.4)
Hypertension	159 (57.2)	60 (21.6)	21 (15.3)	3 (2.2)	168 (36.8)	62 (13.6)	20 (8.7)	2 (0.9)
Asthenia	35 (12.6)	2 (0.7)	3 (2.2)	0	155 (34.0)	35 (7.7)	52 (22.6)	9 (3.9)
Decreased appetite	69 (24.8)	6 (2.2)	19 (13.9)	1 (0.7)	124 (27.2)	11 (2.4)	40 (17.4)	3 (1.3)
Diarrhoea	69 (24.8)	9 (3.2)	7 (5.1)	0	110 (24.1)	16 (3.5)	24 (10.4)	0
Hypothyroidism	46 (16.5)	0	3 (2.2)	0	94 (20.6)	2 (0.4)	1 (0.4)	0
Fatigue	39 (14.0)	5 (1.8)	15 (10.9)	2 (1.5)	91 (20.0)	18 (3.9)	37 (16.1)	2 (0.9)
Palmar-plantar erythrodysaesthesia syndrome	137 (49.3)	30 (10.8)	4 (2.9)	0	88 (19.3)	29 (6.4)	6 (2.6)	0
Abdominal pain	47 (16.9)	9 (3.2)	15 (10.9)	2 (1.5)	83 (18.2)	14 (3.1)	37 (16.1)	7 (3.0)
Nausea	21 (7.6)	1 (0.4)	12 (8.8)	0	79 (17.3)	3 (0.7)	42 (18.3)	2 (0.9)
Proteinuria	120 (43.2)	9 (3.2)	34 (24.8)	0	79 (17.3)	8 (1.8)	12 (5.2)	2 (0.9)
Constipation	42 (15.1)	0	13 (9.5)	2 (1.5)	78 (17.1)	2 (0.4)	22 (9.6)	0
Dysphonia	105 (37.8)	0	2 (1.5)	0	74 (16.2)	0	12 (5.2)	0
Stomatitis	47 (16.9)	1 (0.4)	0	0	67 (14.7)	8 (1.8)	8 (3.5)	1 (0.4)
Vomiting	22 (7.9)	0	12 (8.8)	0	66 (14.5)	7 (1.5)	28 (12.2)	4 (1.7)

Weight decreased	59 (21.2)	4 (1.4)	12 (8.8)	0	56 (12.3)	3 (0.7)	21 (9.1)	1 (0.4)
Arthralgia	25 (9.0)	0	1 (0.7)	0	50 (11.0)	4 (0.9)	10 (4.3)	0
AST increased	76 (27.3)	3 (1.1)	24 (17.5)	2 (1.5)	48 (10.5)	10 (2.2)	11 (4.8)	3 (1.3)
Back pain	42 (15.1)	5 (1.8)	9 (6.6)	0	47 (10.3)	6 (1.3)	17 (7.4)	3 (1.3)
Pyrexia	31 (11.2)	1 (0.4)	9 (6.6)	0	46 (10.1)	2 (0.4)	23 (10.0)	0
ALT increased	62 (22.3)	2 (0.7)	15 (10.9)	2 (1.5)	47 (10.3)	14 (3.1)	9 (3.9)	1 (0.4)

AE = adverse event; ALT=alanine aminotransferase; AST = aspartate aminotransferase; BSC = best supportive care; G = Grade; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; TEAE = treatment-emergent adverse event. Adverse events were coded using MedDRA, version 25.0. Number (%) of patients with TEAE by PT in decreasing order of frequency (by the Fruquintinib - any Grade column in FRESCO-2). If the frequencies are tied, alphabetical order was applied. Percentages were based on the number of patients in each treatment group unless otherwise specified. Patients with > 1 TEAE were counted once at the worst severity category. A patient with multiple TEAE entries in the same PT was only counted once within a particular PT.

Pooled safety data

Incidence of Adverse Events by Preferred Term

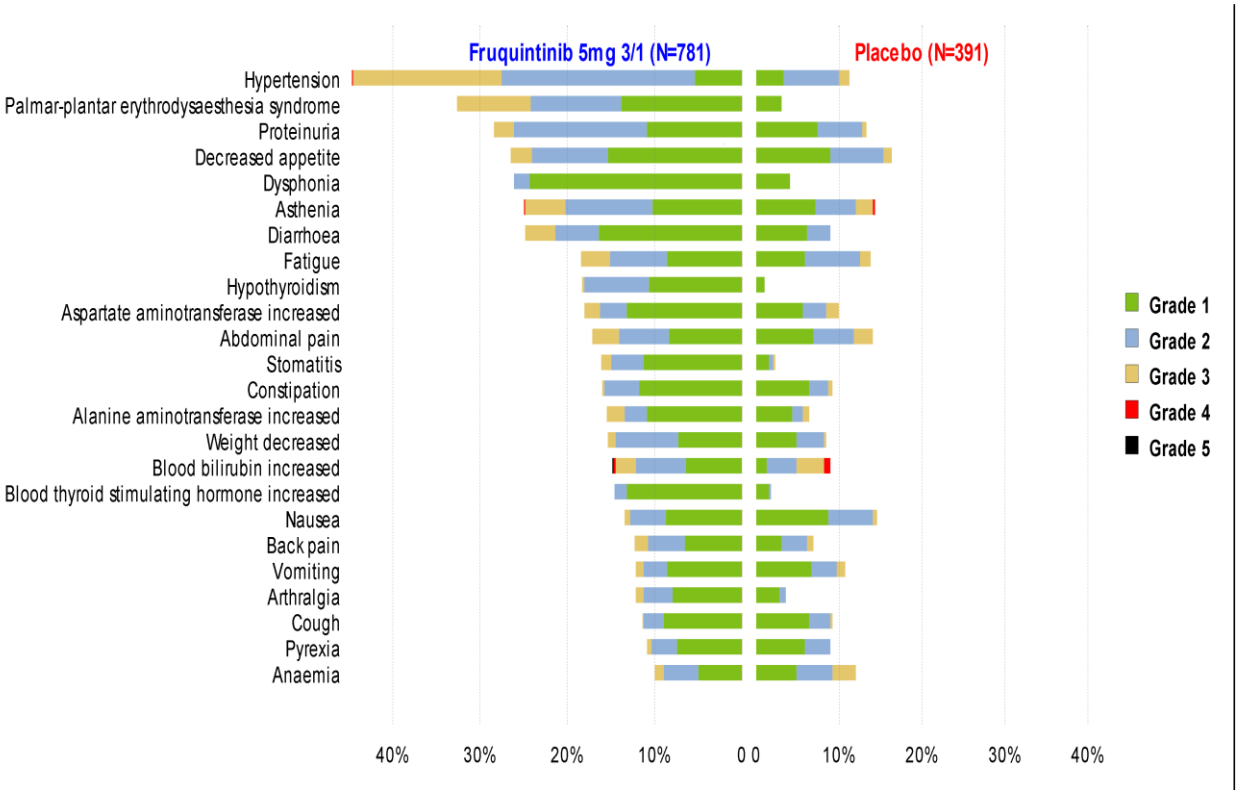
TEAEs that occurred with incidences ≥ 10% at PT level (based on ISAS—Expanded mCRC) by PT, and CTCAE grade (sorted by the ISAS—Expanded mCRC, any CTCAE grade column) are presented in Table 32 and Figure 23.

Table 32: Treatment-Emergent Adverse Events Occurring With Incidences ≥ 10% at PT Level (for ISAS—Expanded mCRC) by PT, and CTCAE Grade (sorted by decreasing frequency for ISAS—Expanded mCRC, any CTCAE Grade)

Preferred Term	ISAS—mCRC				ISAS—Expanded mCRC	
	Fruquintinib 5 mg 3/1 (N = 781)		Placebo (N = 391)		Fruquintinib 5 mg 3/1 (N = 911)	
	CTCAE Grade		CTCAE Grade		CTCAE Grade	
	Any n (%)	≥ 3 n (%)	Any n (%)	≥ 3 n (%)	Any n (%)	≥ 3 n (%)
Patients with any TEAE	770 (98.6)	489 (62.6)	355 (90.8)	151 (38.6)	899 (98.7)	578 (63.4)
Hypertension	349 (44.7)	134 (17.2)	44 (11.3)	5 (1.3)	426 (46.8)	164 (18.0)
Palmar-plantar erythrodysaesthesia syndrome	255 (32.7)	66 (8.5)	12 (3.1)	0	315 (34.6)	76 (8.3)
Proteinuria	222 (28.4)	18 (2.3)	52 (13.3)	2 (0.5)	282 (31.0)	19 (2.1)
Dysphonia	204 (26.1)	0	16 (4.1)	0	255 (28.0)	0
Decreased appetite	207 (26.5)	19 (2.4)	64 (16.4)	4 (1.0)	253 (27.8)	20 (2.2)

Diarrhoea	194 (24.8)	27 (3.5)	35 (9.0)	0	240 (26.3)	34 (3.7)
Asthenia	195 (25.0)	37 (4.7)	56 (14.3)	9 (2.3)	223 (24.5)	39 (4.3)
Fatigue	144 (18.4)	26 (3.3)	54 (13.8)	5 (1.3)	180 (19.8)	29 (3.2)
Aspartate aminotransferase increased	141 (18.1)	14 (1.8)	39 (10.0)	6 (1.5)	172 (18.9)	17 (1.9)
Abdominal pain	134 (17.2)	24 (3.1)	55 (14.1)	9 (2.3)	163 (17.9)	32 (3.5)
Hypothyroidism	143 (18.3)	2 (0.3)	4 (1.0)	0	163 (17.9)	2 (0.2)
Constipation	125 (16.0)	2 (0.3)	36 (9.2)	2 (0.5)	154 (16.9)	2 (0.2)
Stomatitis	126 (16.1)	9 (1.2)	9 (2.3)	1 (0.3)	151 (16.6)	10 (1.1)
Alanine aminotransferase increased	121 (15.5)	16 (2.0)	25 (6.4)	3 (0.8)	149 (16.4)	20 (2.2)
Blood thyroid stimulating hormone increased	114 (14.6)	0	7 (1.8)	0	145 (15.9)	0
Weight decreased	120 (15.4)	7 (0.9)	33 (8.4)	1 (0.3)	139 (15.3)	8 (0.9)
Blood bilirubin increased	116 (14.9)	21 (2.7)	35 (9.0)	16 (4.1)	132 (14.5)	24 (2.6)
Nausea	105 (13.4)	5 (0.6)	57 (14.6)	2 (0.5)	132 (14.5)	6 (0.7)
Arthralgia	95 (12.2)	7 (0.9)	14 (3.6)	0	123 (13.5)	8 (0.9)
Back pain	96 (12.3)	12 (1.5)	27 (6.9)	3 (0.8)	115 (12.6)	13 (1.4)
Vomiting	95 (12.2)	7 (0.9)	42 (10.7)	4 (1.0)	113 (12.4)	8 (0.9)
Cough	89 (11.4)	1 (0.1)	36 (9.2)	1 (0.3)	110 (12.1)	1 (0.1)
Pyrexia	85 (10.9)	4 (0.5)	35 (9.0)	0	100 (11.0)	5 (0.5)
Platelet count decreased	76 (9.7)	9 (1.2)	6 (1.5)	1 (0.3)	92 (10.1)	9 (1.0)

AE = adverse event; CTCAE = common terminology criteria for adverse events; ISAS = integrated safety analysis set; mCRC = metastatic colorectal cancer; PT = preferred term The term "3/1" means a dosing schedule of 3-weeks on/ 1-week off during each 28-day cycle. AEs were coded using MedDRA version 25.0. Unless otherwise specified, percentages are based on the number of patients in each group (ie N). A patient with multiple TEAE entries in the same PT was only counted once within a particular PT. Number (%) of patients with TEAE, sorted by PT in decreasing order of frequency (by ISAS—Expanded mCRC column). If the frequencies tie, an alphabetic order was applied. Source: Table ISS 5.3.2.2.2



CTCAE = common terminology criteria for adverse events; ISAS = integrated safety analysis set; mCRC = metastatic colorectal cancer; PT = preferred term Source: Figure ISS 1.3.5.6

Figure 23: Bar Plot of Adverse Events Occurring in at Least 10% of Patients by PT and CTCAE Grade - ISAS—mCRC

In the pivotal FRESCO-2 study the overall incidence of TEAE during treatment was quite consistently higher in the fruquintinib than in the placebo treatment group. These TEAEs included hypertension; gastrointestinal adverse events; the hand–foot syndrome; dysphonia, and proteinuria. Importantly, deaths were on the contrary more numerous in the placebo group, for which, no specific reason was found even on clarification.

In the supportive safety pools, the overall fruquintinib safety profile appeared similar to that of the pivotal study, as appropriately depicted by CTCAE grade in the bar plot above for the ISAS-mCRC pool. Very few differences were seen to the pivotal study. Importantly, no major differences were seen and overall, no new or unexpecting findings were clearly evident.

Adverse Events by Severity

FRESCO-2 and FRESCO studies

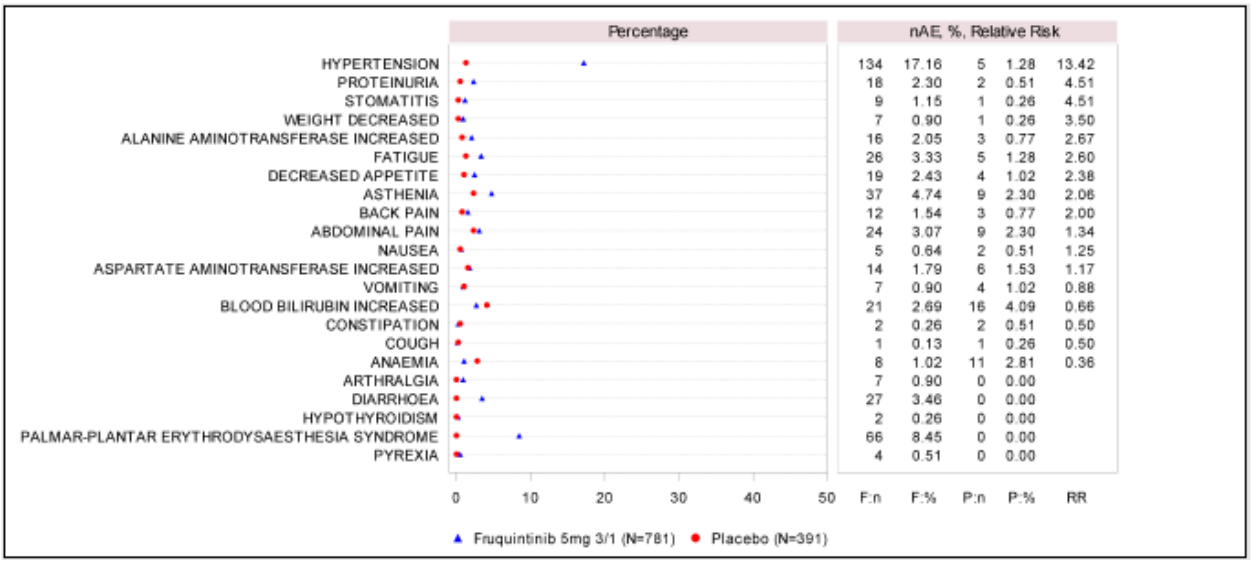
In Fresco-2 Grade ≥ 3 TEAEs were reported in a higher percentage of patients in the fruquintinib group (62.7% [286 patients]) than in the placebo group (50.4% [116 patients]), while Grade 5 TEAEs were reported in a lower percentage of patients in the fruquintinib group (10.7% [49 patients]) than in the placebo group (19.6% [45 patients]). In the fruquintinib group compared with the placebo group, the most frequently reported Grade ≥ 3 TEAEs (≥ 5% of patients) were hypertension (13.6% vs 0.9%), asthenia (7.7% vs 3.9%), palmar-plantar erythrodysaesthesia syndrome (6.4% vs 0%), and disease progression (6.1% vs 12.2%). Grade 4 TEAEs were reported in 18 patients (3.9%) in the fruquintinib group and 6 patients (2.6%) in the placebo group. TEAEs leading to death (Grade 5) were reported in 49 patients (10.7%) in the fruquintinib group and 45 patients (19.6%) in the placebo group. The most

frequent TEAE leading to death in the fruquintinib, and placebo groups was disease progression, which occurred in 5.9% vs 11.7% of patients, respectively.

Pooled safety data

Safety data were presented for the pooled ISAS-mCRC and ISAS-Extended mCRC. Of these pooled datasets the ISAS-mCRC is considered more relevant for safety assessment (see Table 32).

Most of the Grade ≥ 3 TEAEs were Grade 3 in severity; Grade 4 TEAEs were reported in 3.8% of patients in fruquintinib group, which was comparable to that in placebo group (2.8%). There was a lower rate of fatal events (Grade 5) reported in the fruquintinib group compared to placebo (7.7% vs 12.5%). In fruquintinib 5 mg 3/1 group, the Grade ≥ 3 TEAEs with incidences ≥ 2.0% and > 2- fold of that in placebo group include: hypertension (17.2% vs 1.3%), palmar-plantar erythrodysaesthesia syndrome (8.5% vs 0%), asthenia (4.7% vs 2.3%), diarrhoea (3.5% vs 0%), fatigue (3.3% vs 1.3%), decreased appetite (2.4% vs 1.0%), proteinuria (2.3% vs 0.5%), and ALT increased (2.0% vs 0.8%).



CTCAE = common terminology criteria for adverse events; ISAS = integrated safety analysis set; mCRC = metastatic colorectal cancer; PT = preferred term. Source: Figure ISS 1.3.5.5

Figure 24: Double-Dot Plot of Adverse Events of CTCAE Grade ≥ 3 Occurring in At Least 10% of Patients by PT-ISAS-mCRC

Based on the assessment of FRESCO-2 data, while differences compared to the pooled data are evident, the data show broadly sufficient similarity in the safety pattern with the pooled safety data already presented. The main focus on safety data assessment is on pooled ISAS-mCRC safety population, and presentation of this safety data in the SmPC is considered appropriate.

Although FRESCO-2 had a heavily pretreated population with a relatively high rate of preexisting comorbidities at study entry, the rates of the most frequent Grade ≥ 3 TEAEs of hypertension (13.6%), asthenia (7.7%), and palmar-plantar erythrodysaesthesia syndrome (6.4%) were much higher than in the placebo group, these events resulted still in low discontinuation rates.

In FRESCO-2, grade 4 TEAEs were overall clearly less frequent than Grade 3 events but also reported more often (3.9%) in the fruquintinib than (2.6%) in the placebo groups. The Grade 5 cases (deaths), on the other hand, were less frequent in the fruquintinib treatment. No major differences were seen between the pooled analyses and the pivotal data.

It was especially noted that in the FRESCO study deaths were more frequent than in the pivotal FRESCO-2 data.. No unambiguous reasons for this finding were seen.

Adverse Events by Relationship to Study Treatment

FRESCO-2 and FRESCO studies

The most frequently reported treatment-related TEAEs (≥ 15% of all patients) of any grade in the fruquintinib group compared with the placebo group in FRESCO-2 and FRESCO studies are shown in Table 31.

Pooled safety data

Treatment-related-TEAEs with incidences ≥ 5% at PT level (for ISAS—Expanded mCRC) by SOC, PT, and CTCAE grade (sorted by SOC, PT, decreasing frequency for ISAS—Expanded mCRC, any CTCAE grade) are presented in Table 33.

Table 33: Treatment-Related TEAEs Occurring with Incidences ≥ 5% at PT Level (for ISAS—Expanded mCRC) by SOC, PT, and CTCAE Grade (sorted by decreasing frequency for ISAS—Expanded mCRC, any CTCAE Grade)

System Organ Class Preferred Term	ISAS—mCRC				ISAS—Expanded mCRC	
	Fruquintinib 5 mg 3/1 (N = 781)		Placebo (N = 391)		Fruquintinib 5 mg 3/1 (N = 911)	
	CTCAE Grade		CTCAE Grade		CTCAE Grade	
	Any n (%)	≥ 3 n (%)	Any n (%)	≥ 3 n (%)	Any n (%)	≥ 3 n (%)
Patients with any treatment-related TEAE	705 (90.3)	318 (40.7)	243 (62.1)	41 (10.5)	828 (90.9)	381 (41.8)
Gastrointestinal disorders	**394 (50.4)**	**61 (7.8)**	**89 (22.8)**	**4 (1.0)**	**458 (50.3)**	**74 (8.1)**
Diarrhoea	150 (19.2)	25 (3.2)	20 (5.1)	0	182 (20.0)	30 (3.3)
Stomatitis	118 (15.1)	8 (1.0)	6 (1.5)	0	141 (15.5)	9 (1.0)
Nausea	55 (7.0)	3 (0.4)	29 (7.4)	1 (0.3)	73 (8.0)	4 (0.4)
Vomiting	48 (6.1)	3 (0.4)	18 (4.6)	1 (0.3)	57 (6.3)	4 (0.4)
Investigations	**333 (42.6)**	**50 (6.4)**	**83 (21.2)**	**10 (2.6)**	**411 (45.1)**	**67 (7.4)**
Blood thyroid stimulating hormone increased	98 (12.5)	0	6 (1.5)	0	128 (14.1)	0
Aspartate aminotransferase increased	102 (13.1)	4 (0.5)	19 (4.9)	3 (0.8)	120 (13.2)	4 (0.4)
Alanine aminotransferase increased	82 (10.5)	7 (0.9)	14 (3.6)	2 (0.5)	100 (11.0)	8 (0.9)
Blood bilirubin increased	77 (9.9)	8 (1.0)	13 (3.3)	4 (1.0)	90 (9.9)	10 (1.1)
Platelet count decreased	66 (8.5)	8 (1.0)	5 (1.3)	1 (0.3)	77 (8.5)	8 (0.9)
Weight decreased	53 (6.8)	4 (0.5)	12 (3.1)	0	62 (6.8)	5 (0.5)
Occult blood positive	40 (5.1)	0	9 (2.3)	0	49 (5.4)	0
Blood alkaline phosphatase increased	33 (4.2)	4 (0.5)	9 (2.3)	2 (0.5)	48 (5.3)	7 (0.8)

White blood cell count decreased	34 (4.4)	0	3 (0.8)	0	46 (5.0)	0
Skin and subcutaneous tissue disorders	**330 (42.3)**	**67 (8.6)**	**33 (8.4)**	**0**	**397 (43.6)**	**75 (8.2)**
Palmar-plantar erythrodysaesthesia syndrome	251 (32.1)	65 (8.3)	12 (3.1)	0	307 (33.7)	73 (8.0)
Rash	44 (5.6)	0	6 (1.5)	0	59 (6.5)	0
General disorders and administration site conditions	**334 (42.8)**	**51 (6.5)**	**87 (22.3)**	**6 (1.5)**	**390 (42.8)**	**57 (6.3)**
Asthenia	140 (17.9)	24 (3.1)	38 (9.7)	3 (0.8)	166 (18.2)	25 (2.7)
Fatigue	107 (13.7)	20 (2.6)	32 (8.2)	1 (0.3)	129 (14.2)	23 (2.5)
Mucosal inflammation	58 (7.4)	2 (0.3)	6 (1.5)	0	59 (6.5)	2 (0.2)
Vascular disorders	**313 (40.1)**	**123 (15.7)**	**39 (10.0)**	**6 (1.5)**	**377 (41.4)**	**151 (16.6)**
Hypertension	308 (39.4)	120 (15.4)	36 (9.2)	5 (1.3)	372 (40.8)	148 (16.2)
Respiratory, thoracic and mediastinal disorders	**243 (31.1)**	**5 (0.6)**	**36 (9.2)**	**2 (0.5)**	**295 (32.4)**	**8 (0.9)**
Dysphonia	185 (23.7)	0	14 (3.6)	0	229 (25.1)	0
Epistaxis	37 (4.7)	0	4 (1.0)	0	50 (5.5)	0
Renal and urinary disorders	**229 (29.3)**	**19 (2.4)**	**58 (14.8)**	**2 (0.5)**	**281 (30.8)**	**20 (2.2)**
Proteinuria	202 (25.9)	17 (2.2)	48 (12.3)	1 (0.3)	254 (27.9)	18 (2.0)
Metabolism and nutrition disorders	**189 (24.2)**	**19 (2.4)**	**49 (12.5)**	**6 (1.5)**	**238 (26.1)**	**25 (2.7)**
Decreased appetite	127 (16.3)	9 (1.2)	34 (8.7)	2 (0.5)	153 (16.8)	10 (1.1)
Endocrine disorders	**128 (16.4)**	**2 (0.3)**	**5 (1.3)**	**0**	**141 (15.5)**	**2 (0.2)**
Hypothyroidism	117 (15.0)	2 (0.3)	4 (1.0)	0	130 (14.3)	2 (0.2)
Musculoskeletal and connective tissue disorders	**97 (12.4)**	**8 (1.0)**	**13 (3.3)**	**1 (0.3)**	**128 (14.1)**	**9 (1.0)**
Arthralgia	45 (5.8)	3 (0.4)	4 (1.0)	0	61 (6.7)	3 (0.3)

AE = adverse event; CTCAE = common terminology criteria for adverse events; ISAS = integrated safety analysis set; mCRC = metastatic colorectal cancer; PT = preferred term; SOC = system organ class The term "3/1" means a dosing schedule of 3-weeks on/ 1-week off during each 28-day cycle. AEs are coded using MedDRA version 25.0. Unless otherwise specified, percentages are based on the number of patients in each group (ie N). A patient with multiple TEAE entries in the same SOC (PT) was only counted once within a particular SOC (PT). Number (%) of patients with TEAE, sorted by SOC followed by PT in decreasing order of frequency (by ISAS—Expanded mCRC column). If the frequencies tie, an alphabetic order was applied. Source: Table ISS 5.3.2.7.2

A consistently higher trend of the percentage of patients in the fruquintinib group compared with the placebo group was seen also for the treatment-related TEAEs (86.6% vs 56.5%), treatment-related TEAEs Grade ≥ 3 (36.0% vs 11.3%), and treatment-related serious TEAEs (9.4% vs 3.5%). The safety profile by SOC and by individual PTs (also in the two fruquintinib pools) were again consistent with that expected for this study sample under fruquintinib treatment. No new or unexpected findings were evident.

Selection of Adverse Drug Reactions for Proposed Labelling

For the selection of adverse drug reactions (ADRs) used for the SmPC, ADRs were identified in accordance with European Commission's guidance on the estimation of frequency of adverse reactions (A Guideline on Summary of Product Characteristics, Rev. 2, September 2009), CIOMS VI Working Group (WHO, 2005), and Bradford Hill (Fedak, 2015) criteria for causation and based on an aggregate review of all available safety data and same class effects (Schmidinger, 2013) of VEGF inhibitors.

Methodology for ADR selection

- In the ISAS-mCRC, AE incidence in fruquintinib ≥ 5% overall AE incidence and > 2-fold of that in placebo group or
- Medical assessment of all AEs reported in the fruquintinib clinical development program (including causality determination by use of the Bradford-Hill criteria and mechanism of action of fruquintinib and possible class effects).

Each ADR is categorized by frequency (i.e., very common, common, uncommon, or rare) based on the subject incidence reported in the ISAS—Expanded mCRC. The frequency of some ADRs was determined by grouping PTs that represent the same medical concept. The selected ADRs are presented in section 4.8 of the SmPC.

3.6.11.3. Adverse Drug Reactions (ADRs)

The adverse drug reactions are presented on the table below.

Table 34: Adverse drug reactions

System organ class	Frequency category	Adverse reactions All grades	Fruquintinib 5 mg 3/1 (N = 911) (n, %)
Infections and infestations	Common	Pneumonia	23 (2.5%)
		Upper respiratory tract infection[1]	45 (4.9%)
		Bacterial infections[2]	22 (2.4%)
Blood and lymphatic system disorders	Very Common	Thrombocytopaenia[3]	142 (15.6%)
	Common	Leukopenia[4]	66 (7.2%)
		Neutropenia[5]	48 (5.3%)
Endocrine disorders	Very Common	Hypothyroidism[6]	295 (32.4%)
Metabolism and nutrition disorders	Very Common	Anorexia[7]	324 (35.6%)
	Common	Hypokalaemia	63 (6.9%)
Nervous system disorders	Uncommon	Posterior reversible encephalopathy syndrome*	1 (0.1%)
Vascular disorders	Very Common	Hypertension[8]	449 (49.3%)
	Not known	Aortic dissection†	None reported in fruquintinib clinical trials
Respiratory, thoracic and mediastinal disorders	Very Common	Dysphonia[9]	261 (28.6%)
	Common	Epistaxis	61 (6.7%)
		Throat pain[10]	57 (6.3%)
Gastrointestinal disorders	Very Common	Diarrhoea	240 (26.3%)
		Stomatitis[11]	180 (19.8%)
	Common	Gastrointestinal haemorrhage[12]	61 (6.7%)
		Gastrointestinal perforation[13]	13 (1.4%)
		Pancreatic enzymes increased[14]	37 (4.1%)
		Oral pain[15]	52 (5.7%)
	Uncommon	Pancreatitis[16]	5 (0.5%)
Hepatobiliary disorders	Very Common	Aspartate aminotransferase increased	172 (18.9%)
		Total bilirubin increased[17]	163 (17.9%)
		Alanine aminotransferase increased	149 (16.4%)
	Uncommon	Cholecystitis[18]	5 (0.5%)
Skin and subcutaneous tissue disorders	Very Common	Palmar-plantar erythrodysaesthesia syndrome	315 (34.6%)
	Common	Rash[19]	81 (8.9%)
Musculoskeletal and connective tissue disorders	Very Common	Musculoskeletal discomfort[20]	125 (13.7%)
		Arthralgia	123 (13.5%)
Renal and urinary disorders	Very Common	Proteinuria[21]	323 (35.5%)
General disorders and administrative site conditions	Very Common	Asthenia	223 (24.5%)
		Fatigue	180 (19.8%)
	Common	Mucosal inflammation	63 (6.9%)

	Uncommon	Impaired wound healing*, [22]	1 (0.1%)

The safety data is based on all patients with mCRC who received at least 1 dose (5 mg) of fruquintinib monotherapy (5 mg 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.
*Reported in clinical studies and in the post-marketing setting.
†Reported in the post-marketing setting.
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]Bacterial infections includes asymptomatic bacteriuria, bacterial infection, bacteriuria, cellulitis, clostridium difficile colitis, clostridium difficile infection, enterobacter sepsis, escherichia urinary tract infection, folliculitis, furuncle, paronychia, pharyngitis streptococcal, streptococcal bacteraemia, urinary tract infection bacterial, urinary tract infection staphylococcal
[3]Thrombocytopaenia includes platelet count decreased, thrombocytopaenia
[4]Leukopenia includes leukopenia, white blood cell count decreased
[5]Neutropenia includes neutropenia, neutrophil count decreased
[6]Hypothyroidism includes blood thyroid stimulating hormone increased, hypothyroidism
[7]Anorexia includes appetite decreased, weight loss
[8]Hypertension includes blood pressure diastolic increased, blood pressure increased, diastolic hypertension, hypertension, hypertensive crisis
[9]Dysphonia includes aphonia, dysphonia
[10]Throat pain includes laryngeal discomfort, laryngeal pain, oropharyngeal discomfort, oropharyngeal pain
[11]Stomatitis includes aphthous ulcer, gingival ulceration, mouth ulceration, stomatitis, tongue ulceration
[12]Gastrointestinal haemorrhage includes anal haemorrhage, anastomotic haemorrhage, gastric haemorrhage, gastrointestinal haemorrhage, haematochezia, haemorrhoidal haemorrhage, intestinal haemorrhage, lower gastrointestinal haemorrhage, rectal haemorrhage, upper gastrointestinal haemorrhage
[13]Gastrointestinal perforation includes gastric perforation, gastric ulcer perforation, gastrointestinal perforation, intestinal perforation, large intestine perforation, rectal perforation, small intestinal perforation
[14]Pancreatic enzymes increased includes amylase increased, hyperamylasaemia, hyperlipasaemia, lipase increased
[15]Oral pain includes gingival pain, oral pain, toothache
[16]Pancreatitis includes pancreatitis, pancreatitis acute
[17]Total bilirubin increased includes bilirubin conjugated increased, blood bilirubin increased, blood bilirubin unconjugated increased, hyperbilirubinaemia, jaundice, jaundice cholestatic
[18]Cholecystitis includes cholecystitis, cholecystitis acute, cholecystitis infective
[19]Rash includes rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic
[20]Musculoskeletal discomfort includes bone pain, muscle spasms, musculoskeletal chest pain, musculoskeletal pain, neck pain, pain in extremity
[21]Proteinuria includes albuminuria, protein urine present, proteinuria
[22]Impaired wound healing includes impaired healing, wound dehiscence

3.6.11.4. Serious adverse event/deaths/other significant events

Deaths

FRESCO-2 and FRESCO studies

In FRESCO, a higher percentage of patients experienced TEAEs leading to death in the fruquintinib 5 mg 3/1 group (9 patients [3.2%]) than in the placebo group (2 patients [1.5%]). These events (PT) in the fruquintinib 5 mg 3/1 group were (at 1 patient each, 0.4%): gastrointestinal haemorrhage, haemoptysis, death, multiple organ dysfunction syndrome, sudden death, pneumonia, bacterial infection, lower respiratory tract infection fungal, and cerebral infarction.

In FRESCO-2, a higher percentage of patients experienced a TEAE leading to death in the placebo group (45 patients [19.6%]) than in the fruquintinib 5 mg 3/1 group (48 patients [10.5%]). The most frequent of these events leading to death (fruquintinib 5 mg 3/1 vs placebo) were: Disease progression (5.7% vs 11.7%), pneumonia (0.7% vs 0%), condition aggravated (0.4% vs 0.4%) and general physical health deterioration (0.4% vs 0.9%).

The consistently higher trend of the percentage of patients in the fruquintinib group compared with the placebo group was seen also for the treatment-related TEAEs (86.6% vs 56.5%), treatment-related TEAEs Grade ≥ 3 (36.0% vs 11.3%), and treatment-related serious TEAEs (9.4% vs 3.5%). The safety profile by SOC and by individual PTs (also in the two fruquintinib pools) were again consistent with that

expected for this study sample under fruquintinib treatment. No new or unexpected findings were evident.

The incidence of treatment emergent fatal cases in the FRESCO-2 study was higher in the placebo group (19.5%) than in the fruquintinib group (10.5%). The most frequent event was disease progression (5.7% in fruquintinib group vs. 11.7% in placebo group). All deaths occurring in the fruquintinib treatment arm were deemed as not related to the study medication. However, the Applicant has changed the investigator´s assessment of causality for several subjects, who eventually died due to the event or with the event. Upon request the Applicant subsequently clarified and elaborated on the methodology of causality assessment used, according to which only events without any confounding factors appeared to be considered as related, even though as per guidance all events with at least reasonable relationship should be included. However, this issue will not be pursued further.

Pooled safety data

AEs leading to death in ISAS-mCRC and ISAS-expanded mCRC are presented in Table 35. Overall, the most common cause of death was disease progression. The AEs leading to death that were assessed as related to fruquintinib by the investigator were haemoptysis (N=2), and one event each for blood bilirubin increased, death (cause unknown), pneumonia, lower respiratory tract infection fungal, gastrointestinal haemorrhage, and intestinal perforation.

Table 35: TEAEs Leading to Death at PT level (for ISAS—Expanded mCRC) by SOC and PT (sorted by SOC, PT, decreasing frequency for ISAS—Expanded mCRC)

System Organ Class Preferred Term	**ISAS—mCRC**		**ISAS— Expanded mCRC**
	Fruquintinib 5 mg 3/1 (N = 781) n (%)	**Placebo (N = 391)** n (%)	**Fruquintinib 5 mg 3/1 (N = 911)** n (%)
Patients with any TEAE leading to death	60 (7.7)	49 (12.5)	64 (7.0)
General disorders and administration site conditions	35 (4.5)	35 (9.0)	37 (4.1)
Disease progression	26 (3.3)	27 (6.9)	26 (2.9)
Death	2 (0.3)	2 (0.5)	3 (0.3)
Condition aggravated	2 (0.3)	1 (0.3)	2 (0.2)
General physical health deterioration	2 (0.3)	2 (0.5)	2 (0.2)
Multiple organ dysfunction syndrome	2 (0.3)	1 (0.3)	2 (0.2)
Sudden death	1 (0.1)	2 (0.5)	2 (0.2)
Infections and infestations	8 (1.0)	1 (0.3)	9 (1.0)
Pneumonia	4 (0.5)	0	4 (0.4)
Sepsis	1 (0.1)	0	2 (0.2)
Bacterial infection	1 (0.1)	0	1 (0.1)
Lower respiratory tract infection fungal	1 (0.1)	0	1 (0.1)

Septic shock	1 (0.1)	0	1 (0.1)
COVID-19	0	1 (0.3)	0
Respiratory, thoracic, and mediastinal disorders	**5 (0.6)**	**5 (1.3)**	**6 (0.7)**
Haemoptysis	2 (0.3)	0	3 (0.3)
Acute respiratory distress syndrome	1 (0.1)	0	1 (0.1)
Pneumothorax	1 (0.1)	0	1 (0.1)
Pulmonary embolism	1 (0.1)	1 (0.3)	1 (0.1)
Dyspnoea	0	1 (0.3)	0
Interstitial lung disease	0	1 (0.3)	0
Respiratory distress	0	1 (0.3)	0
Respiratory failure	0	1 (0.3)	0
Gastrointestinal disorders	**4 (0.5)**	**1 (0.3)**	**4 (0.4)**
Gastrointestinal haemorrhage	1 (0.1)	0	1 (0.1)
Intestinal perforation	1 (0.1)	0	1 (0.1)
Subileus	1 (0.1)	0	1 (0.1)
Upper gastrointestinal haemorrhage	1 (0.1)	0	1 (0.1)
Intestinal obstruction	0	1 (0.3)	0
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)	**3 (0.4)**	**2 (0.5)**	**3 (0.3)**
Lung cancer metastatic	1 (0.1)	0	1 (0.1)
Metastases to liver	1 (0.1)	0	1 (0.1)
Tumour invasion	1 (0.1)	0	1 (0.1)
Malignant neoplasm progression	0	1 (0.3)	0
Neoplasm progression	0	1 (0.3)	0
Hepatobiliary disorders	**2 (0.3)**	**2 (0.5)**	**2 (0.2)**
Biliary obstruction	1 (0.1)	0	1 (0.1)
Hepatic failure	1 (0.1)	1 (0.3)	1 (0.1)
Hepatic function abnormal	0	1 (0.3)	0
Nervous system disorders	**2 (0.3)**	**1 (0.3)**	**2 (0.2)**
Cerebral infarction	1 (0.1)	0	1 (0.1)
Encephalopathy	1 (0.1)	0	1 (0.1)
Coma hepatic	**0**	**1 (0.3)**	**0**
Investigations	**1 (0.1)**	**0**	**1 (0.1)**
Blood bilirubin increased	1 (0.1)	0	1 (0.1)
Cardiac disorders	**0**	**1 (0.3)**	**0**
Cardiac arrest	0	1 (0.3)	0
Vascular disorders	**0**	**1 (0.3)**	**0**
Shock	0	1 (0.3)	0

AE = adverse event; ISAS = integrated safety analysis set; mCRC = metastatic colorectal cancer; PT = preferred term; SOC = system organ class
The term "3/1" means a dosing schedule of 3-weeks on/ 1-week off during each 28-day cycle. AEs were coded using MedDRA version 25.0. Unless otherwise specified, percentages are based on the number of patients in each group (i.e. N). A patient with multiple TEAE entries in the same SOC (PT) was only counted once within a particular SOC (PT). Number (%) of patients with

TEAE, sorted by SOC followed by PT in decreasing order of frequency (by ISAS— Expanded mCRC column). If the frequencies tie, an alphabetic order was applied. Source: Table ISS 5.3.2.14.1

Products targeting VEGF signaling pathway in cancer therapy are recognised to be associated with toxicities, which in a small number of cases may be fatal. The incidence of treatment emergent fatal cases was overall higher in the reference treatment group (placebo plus BSC) in both pooled analyses ISAS-mCRC and ISAS-Extended mCRC.

Serious Treatment-emergent Adverse Events

FRESCO-2 and FRESCO studies

Serious TEAEs in patients in FRESCO-2 are presented in Table 36.

Overall, more serious TEAE events were reported in FRESCO-2 compared to FRESCO, however incidences of treatment-related serious TEAEs were comparable and there was no incidence increase reported in fruquintinib 5 mg 3/1 group compared to placebo in FRESCO-2 (Table 36).

Table 36: Serious TEAEs in ≥ 1% of Patients in the Fruquintinib Group by Preferred Term and Grade (Safety Population) in FRESCO-2 study

	Number of Patients (%)			
	Fruquintinib + BSC (N = 456)		Placebo + BSC (N = 230)	
Preferred Term	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Patients With at Least 1 Serious TEAE	172 (37.7)[a]	163 (35.7)[a]	88 (38.3)	85 (37.0)
Disease progression	27 (5.9)[a]	27 (5.9)[a]	28 (12.2)	28 (12.2)
General physical health deterioration	10 (2.2)	10 (2.2)	5 (2.2)	5 (2.2)
Pneumonia	8 (1.8)	8 (1.8)	1 (0.4)	1 (0.4)
Abdominal pain	7 (1.5)	7 (1.5)	2 (0.9)	2 (0.9)
Intestinal obstruction	7 (1.5)	6 (1.3)	6 (2.6)	6 (2.6)
Back pain	6 (1.3)	5 (1.1)	1 (0.4)	1 (0.4)
Dyspnoea	6 (1.3)	6 (1.3)	2 (0.9)	2 (0.9)
Hypertension	6 (1.3)	6 (1.3)	0	0
Acute kidney injury	5 (1.1)	4 (0.9)	1 (0.4)	1 (0.4)
Asthenia	5 (1.1)	5 (1.1)	0	0
Pulmonary embolism	5 (1.1)	5 (1.1)	0	0
Pyrexia	5 (1.1)	1 (0.2)	2 (0.9)	0
Sepsis	5 (1.1)	5 (1.1)	0	0
Small intestinal obstruction	5 (1.1)	5 (1.1)	1 (0.4)	1 (0.4)

Abbreviations: AE = adverse event; BSC = best supportive care; CTCAE = Common Terminology Criteria for Adverse Events; DBL = database lock; EDC = electronic data capture; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; TEAE = treatment-emergent adverse event. Notes: AEs were coded using MedDRA, version 25.0. Percentages were based on the number of patients in each treatment group unless otherwise specified. During the period from the date of first study drug administration until 37 days after the last study drug administration or initiation of a new treatment of antitumor therapy, whichever was earlier, an AE was considered a TEAE if the onset date was on or after the start of study treatment or if the onset date was missing, or if the AE had an onset date before the start of the study treatment but worsened in severity. After this period, treatment related serious TEAEs were also considered TEAEs. Patients with more than 1 TEAE were counted once at the worst severity category. A patient with multiple TEAE entries in the same PT was only counted once within a particular PT. Number (%) of patients with TEAE by PT in decreasing order of frequency (by the Fruquintinib + BSC Any Grade column). If the frequencies tied, alphabetical order was applied

Pooled safety data

Serious TEAEs that occurred in more than 5 patients (≥ 0.7% incidence) at PT level for ISAS-Expanded mCRC are presented in the table below.

Table 37: Serious TEAEs Occurring in More than 5 Patients (≥ 0.7% incidence) at PT level (for ISAS—Expanded mCRC) by SOC, PT, and CTCAE Grade (sorted by SOC, PT, decreasing frequency for ISAS—Expanded mCRC, any CTCAE Grade)

System Organ Class Preferred Term	ISAS—mCRC				ISAS—Expanded mCRC	
	Fruquintinib 5 mg 3/1 (N = 781)		Placebo (N = 391)		Fruquintinib 5 mg 3/1 (N = 911)	
	CTCAE Grade		CTCAE Grade		CTCAE Grade	
	Any n (%)	≥ 3 n (%)	Any n (%)	≥ 3 n (%)	Any n (%)	≥ 3 n (%)
Patients with any serious TEAE	228 (29.2)[a]	208 (26.6)[a]	101 (25.8)	96 (24.6)	274 (30.1)[a]	251 (27.6)[a]
Gastrointestinal disorders	**79 (10.1)**	**69 (8.8)**	**28 (7.2)**	**28 (7.2)**	**94 (10.3)**	**83 (9.1)**
Intestinal obstruction	16 (2.0)	14 (1.8)	7 (1.8)	7 (1.8)	16 (1.8)	14 (1.5)
Abdominal pain	8 (1.0)	8 (1.0)	2 (0.5)	2 (0.5)	14 (1.5)	14 (1.5)
Small intestinal obstruction	6 (0.8)	5 (0.6)	1 (0.3)	1 (0.3)	8 (0.9)	7 (0.8)
General disorders and administration site conditions	**55 (7.0)**	**48 (6.1)**	**41 (10.5)**	**39 (10.0)**	**61 (6.7)**	**54 (5.9)**
Disease progression	27 (3.5) [a]	27 (3.5) [a]	28 (7.2)	28 (7.2)	27 (3.0) [a]	27 (3.0) [a]
General physical health deterioration	10 (1.3)	10 (1.3)	5 (1.3)	5 (1.3)	10 (1.1)	10 (1.1)
Asthenia	6 (0.8)	5 (0.6)	0	0	7 (0.8)	6 (0.7)
Pyrexia	7 (0.9)	2 (0.3)	2 (0.5)	0	7 (0.8)	2 (0.2)
Infections and infestations	**32 (4.1)**	**31 (4.0)**	**13 (3.3)**	**13 (3.3)**	**43 (4.7)**	**42 (4.6)**
Pneumonia	11 (1.4)	10 (1.3)	1 (0.3)	1 (0.3)	14 (1.5)	13 (1.4)
Sepsis	5 (0.6)	5 (0.6)	0	0	7 (0.8)	7 (0.8)
Respiratory, thoracic and mediastinal disorders	**19 (2.4)**	**18 (2.3)**	**12 (3.1)**	**11 (2.8)**	**26 (2.9)**	**24 (2.6)**
Dyspnoea	6 (0.8)	6 (0.8)	2 (0.5)	2 (0.5)	9 (1.0)	9 (1.0)
Hepatobiliary disorders	**19 (2.4)**	**18 (2.3)**	**10 (2.6)**	**9 (2.3)**	**24 (2.6)**	**22 (2.4)**
Hepatic function abnormal	4 (0.5)	3 (0.4)	2 (0.5)	2 (0.5)	6 (0.7)	4 (0.4)
Renal and urinary disorders	**16 (2.0)**	**14 (1.8)**	**3 (0.8)**	**3 (0.8)**	**17 (1.9)**	**14 (1.5)**
Acute kidney injury	6 (0.8)	5 (0.6)	1 (0.3)	1 (0.3)	6 (0.7)	5 (0.5)
Vascular disorders	**15 (1.9)**	**15 (1.9)**	**4 (1.0)**	**4 (1.0)**	**17 (1.9)**	**17 (1.9)**
Hypertension	10 (1.3)	10 (1.3)	0	0	12 (1.3)	12 (1.3)
Musculoskeletal and connective tissue disorders	**14 (1.8)**	**11 (1.4)**	**3 (0.8)**	**3 (0.8)**	**15 (1.6)**	**12 (1.3)**
Back pain	7 (0.9)	6 (0.8)	1 (0.3)	1 (0.3)	7 (0.8)	6 (0.7)
Investigations	**9 (1.2)**	**7 (0.9)**	**5 (1.3)**	**4 (1.0)**	**10 (1.1)**	**8 (0.9)**
Blood bilirubin increased	6 (0.8)	4 (0.5)	2 (0.5)	1 (0.3)	7 (0.8)	5 (0.5)

AE = adverse event; CTCAE = common terminology criteria for adverse events; ISAS = integrated safety analysis set; mCRC = metastatic colorectal cancer; PT = preferred term; SAE = serious adverse event; SOC = system organ class The term "3/1" means a dosing schedule of 3-weeks on/ 1-week off during each 28-day cycle. AEs were coded using MedDRA version 25.0. Unless otherwise specified, percentages are based on the number of patients in each group (ie, N). A patient with multiple TEAE entries in the same SOC (PT) was only counted once within a particular SOC (PT). Number (%) of patients with TEAE, sorted by SOC followed by PT in decreasing order of frequency (by ISAS—Expanded mCRC column).

Other Significant Adverse Events

Adverse Events of Special Interest - AESI

AEs of special interest (AESI) are summarized separately based on the AEs observed within the VEGFR TKIs drug class and the AEs reported with the fruquintinib program.

FRESCO-2 and FRESCO studies

By design, the identified AESIs were set as hypertension, dermatological toxicity, thyroid dysfunction, proteinuria, haemorrhages, gastrointestinal perforation, infections, embolic and thrombotic events, hepatic function abnormal, LVEF decreased. These are typical AESIs for VEGF inhibition, and as such their inclusion in the list of AESI is justified.

Pooled safety data

Hypertension

In ISAS—mCRC, the incidences of AESIs of hypertension in the fruquintinib group was 47.5%. There was a 3-fold increase in incidence of hypertension events in fruquintinib group compared to placebo (47.5% vs 11.8%). Also, the incidence of Grade ≥3 hypertension events was much higher in fruquintinib group compared to placebo group (18.4% vs 1.3%). The incidences of serious events, events leading to dose reduction, interruption, and treatment discontinuation in fruquintinib group compared to placebo group were 1.5% vs 0%, 3.7% vs 0.3%, 3.1% vs 0.3%, and 0.5 % vs 0%, respectively. The majority of events recovered or resolved following dose interruption or reduction. Dose modification for grade ≥3 hypertension and warning/precaution for use were included in section 4.2 of the SmPC and guidance on monitoring and controlling of hypertension in section 4.4.

AEs of potential hypertension complications reported in patients who experienced hypertension (including ischemic heart disease, cardiac failure, central nervous system vascular disorders, and chronic kidney disease) were analysed. There were no increases in incidences of these events in fruquintinib group compared to placebo group.

Dermatological toxicity

In ISAS—mCRC the incidences of the AESIs of dermatological toxicity were 46.5%. There was a 3-fold increase in incidence of dermatological toxicity events in fruquintinib group compared to placebo (46.5% vs 11.5%); the incidence of Grade ≥3 dermatological toxicity (mostly HFS) in fruquintinib group was 8.8%, whereas only 1 patient experienced Grade ≥3 dermatological toxicity in placebo group (0.3%). The most common events (≥ 5.0%) within the AESI category were palmar-plantar erythrodysaesthesia syndrome (32.7%) in the fruquintinib group vs 8.5% in the placebo group) and rash (6.4% vs. 2.6%) and pruritus (2.2% vs 1.5%). The incidences of serious events, events leading to dose reduction, interruption, and treatment discontinuation in fruquintinib group compared to placebo group were 0.4% vs 0%, 6.3% vs 0.3%, 6.9% vs 0%, and 0.6% vs 0%, respectively. Dermatological toxicities will be monitored in PSURs.

Hepatic function abnormal

In ISAS—mCRC, there was a small increase in incidence of hepatic function abnormal events in fruquintinib 5 mg 3/1 group compared to placebo (36.4% vs 23.5%); however, the incidences of Grade ≥3 events, serious events, and fatal hepatic events were comparable between fruquintinib group and placebo group, which were 8.8% vs 9.5%, 2.3% vs 3.1%, and 0.3% vs 0.8%, respectively. The most common events (≥ 5.0%) within the AESI category were AST increased (18.1%), ALT increased (15.5%) and blood bilirubin increased (14.9%). Most of the events were Grade 1 or Grade 2. The incidences of events leading to dose reduction, interruption, and treatment discontinuation in

fruquintinib group compared to placebo group were 2.0% vs 0%, 4.6% vs 4.3%, and 1.5% vs 2.6%, respectively.

In ISAS Expanded mCRC, two patients experienced hepatic function abnormal events that led to death; one event was blood bilirubin increased that was assessed by the investigator as related to fruquintinib but also considered as possibly related to the progression of liver metastasis. The remaining event was hepatic failure that was assessed as unrelated to fruquintinib.

Overall, in the ISAS—mCRC, the percentages of patients who had elevated liver function tests (LFTs) (ALT, AST, ALP, and total bilirubin) were quite consistently higher in the fruquintinib 5 mg 3/1 group than in the placebo group. However, only ALT increased was included as an ADR in section 4.8. It was, however, considered questionable that AST, ALT increased, and blood bilirubin increased were not identified as ADRs of fruquintinib considering their incidence, the non-clinical findings, and the known risk of hepatotoxicity for other VEGFR TKIs, all supportive of a causal relationship between fruquintinib and LFTs elevations. Thus, hepatobiliary disorders should also be included in the description of selected ADRs in section 4.8 in the SmPC considering also the serious and fatal cases reported. Upon request the Applicant agreed to add AST and bilirubin increased in the list of ADRs, but further justified that a causal association at this stage could not be established for ALP. However, ALP increased as a potential ADR will be diligently followed based on possible future clinical studies and pharmacovigilance data through routine pharmacovigilance activities (i.e., signal detection).

Proteinuria In ISAS—mCRC, the incidences of the AESIs of proteinuria was slightly higher in fruquintinib group compared to placebo group (32.9% vs 15.1%). The incidence of Grade ≥3 proteinuria events was higher in fruquintinib group compared to placebo group (2.8% vs 0.5%). The incidences of serious events, events leading to dose reduction, interruption, and treatment discontinuation in fruquintinib group compared to placebo group were, 0.1% vs 0%, 3.2% vs 0.3%, 5.9% vs 1.8%, and 1.8% vs 0.3%, respectively. Most events recovered or resolved following dose interruption or reduction. Dose modifications and special warnings and precautions for use due to proteinuria are adequately reflected in sections 4.2 and 4.4 of the SmPC.

Thyroid dysfunction In ISAS—mCRC, the incidences of the AESIs of thyroid dysfunction were 33.3%. There was a 7-fold increase in incidence of thyroid dysfunction events in fruquintinib group compared to placebo (33.3% vs 4.3%); the most frequently reported events were hypothyroidism (18.3% vs 1.0%) and blood thyroid stimulating hormone increased (14.6% vs 1.8%). The incidence of Grade ≥3 thyroid dysfunction in fruquintinib group was low (0.3%), and no patient experienced Grade ≥3 thyroid dysfunction in placebo group. The incidences of serious events and events leading to dose interruption in fruquintinib group compared to placebo group were, 0.1% vs 0%, and 0.5% vs 0%, respectively. The thyroid function events were generally manageable with standard care. None of the events led to dose reduction or treatment discontinuation.

Haemorrhages In ISAS—mCRC, the incidences of the AESIs of haemorrhage were 26.5% for fruquintinib. There was an increase in incidence of haemorrhagic events in fruquintinib group compared to placebo (26.5% vs 14.6%); the incidences of Grade ≥3 events and serious events were 2.0% vs 1.0% and 2.3% vs 1.0%, respectively. The most common events (≥ 5.0%) within the AESI category were occult blood positive (7.0%) and epistaxis (5.6%). Four patients (0.5%) in fruquintinib group experience fatal haemorrhagic events and included 2 cases of haemoptysis, one case of gastrointestinal haemorrhage and one case of upper gastrointestinal haemorrhage; no fatal events in placebo group were observed. The incidences of events leading to dose reduction, interruption, and treatment discontinuation in fruquintinib group compared to placebo group were 0.8% vs 0.5%, 1.7% vs 0.5%, and 1.2% vs 0.5%, respectively.

In ISAS Expanded mCRC, an additional case of fatal haemoptysis was reported in the fruquintinib group. The 2 cases of haemoptysis were confounded with pulmonary metastasis and radioactive seed

implantation (brachytherapy) in lung prior to fruquintinib therapy and the remaining case of gastrointestinal haemorrhage was confounded with advanced colorectal cancer. Dose modifications and a special warnings and precautions for use are included in sections 4.2 and 4.4 of the SmPC. Information on fatal haemorrhage events is included the description of the haemorrhagic events in Section 4.8 of the SmPC.

Infections In ISAS—mCRC, there was increase in incidences of infections in fruquintinib group compared to placebo (23.4% vs 13.3%). The most common infection events (≥ 5.0%) were urinary tract infection (6.0%) and upper respiratory tract infection (3.2%, including nasopharyngitis, pharyngitis, and upper respiratory tract infection). Grade ≥3 infections were higher in fruquintinib group compared to placebo (6.0% vs 3.8%). Incidence of serious events was comparable between fruquintinib group and placebo group (4.1% vs 3.3%); serious events of pneumonia, sepsis, and urinary tract infection were reported in more than 1 patient. Pneumonia and sepsis were reported more frequently in fruquintinib group compared to placebo, which were 1.4% vs 0.3% and 0.6% vs 0%, respectively, however, the incidence of serious urinary tract infection was lower in fruquintinib group compared to placebo (0.4% vs 0.8%). The incidences of events leading to dose reduction, interruption, and treatment discontinuation in fruquintinib group compared to placebo group were 0.5 % vs 0.3%, 4.6% vs 2.0%, and 0.9% vs 0.5%, respectively.

In ISAS-Expanded—mCRC fruquintinib, a total of 9 patients experienced infections that led to death, which were pneumonia (N=4), sepsis (N=2), bacterial infection (N=1), lower respiratory tract infection fungal (N=1) and septic shock (N=1). Of these, lower respiratory tract infection fungal and one event of pneumonia were assessed as related to fruquintinib by the investigator, however these events were confounded with tumour lung metastasis, pre-existing condition of anorexia and severe nutrition disorder. A description of infections is included in the SmPC Section 4.8 under description of selected ADRs.

Embolic and thrombotic events In ISAS—mCRC, there was an increase in incidence of thromboembolic events in fruquintinib group compared to placebo (3.6% vs 1.5%); the incidences of Grade ≥3 events, serious events and fatal events were 2.2% vs 0.8%, 1.4.% vs 0.8%, and 0.3% vs 0.3%, respectively. The incidences of events leading to dose reduction, interruption, and treatment discontinuation in fruquintinib group compared to placebo group were 0.3 % vs 0%, 0% vs 0.3%, and 1.3% vs 0.8%, respectively. A total of 2 (0.2%) patients experienced fatal thromboembolic events (i.e., cerebral infarction and pulmonary embolism), but neither of the events were assessed as related to fruquintinib.

Gastrointestinal perforation In ISAS—mCRC, there was an increase in incidence of GI perforation events in fruquintinib group compared to placebo (2.8% vs 0.5%); the incidences of Grade ≥3 events and serious events were 1.9% vs 0.5% and 2.0% vs 0.5%, respectively. A total of 1 (0.1%) patient experienced fatal event of intestinal perforation and the event was assessed initially as related to fruquintinib, but the event was confounded with low volume peritoneal disease, prior bevacizumab treatment and multiple abdominal surgeries.

Left ventricular ejection fraction decreased In ISAS—mCRC, there was a lower incidence of LVEF decreased events in fruquintinib 5 mg 3/1 group compared to placebo (0.6% vs 1.5%), and the incidences for Grade ≥3 events and serious events were comparable between the 2 groups. None of the events led to fruquintinib discontinuation.

Overall, the AESIs observed also in the fruquintinib-treated patients in the pooled analysis were consistent with the known class toxicities. The overall safety profile on the different categories of AESIs was much alike between the two pools, reflecting undoubtedly again the major overlap of the pools. The frequencies TEAEs of the different AESI categories and the CTCAE grades were consistently higher

in the fruquintinib treatment group compared to the placebo group. The severity of the AESIs were mostly of the lower 1 and 2 grades.

The incidences of Grade ≥3 events, serious TEAEs and incidences of events leading to dose reduction, interruption, and treatment discontinuation were also consistently higher in fruquintinib group compared to placebo. As exceptions there were a slightly lower incidence of LVEF decreased events in fruquintinib group compared to placebo (0.6% vs 1.5%), as well as the hepatic function abnormal incidences of Grade ≥3 events, serious events, and treatment discontinuation, which were 8.8% vs 9.5% and 2.3% vs 3.1% and 1.5% vs 2.6%, respectively. However, no major toxicities were clearly evident, even on clarification of the Grade 5 (deaths) findings.

3.6.11.5. Laboratory findings

FRESCO-2 and FRESCO studies

Only safety results from ISAS-mCRC pool have been presented below for brevity.

Pooled safety data

Haematology

Following sections focus on shifts related to an increase of at least 2 CTCAE grades from baseline and increases from baseline to CTCAE Grades 3 and 4. For brevity, only **ISAS-mCRC** data are presented.

Anaemia The percentage of patients who shifted to CTCAE Grade ≥ 3 anaemia post- baseline was higher in the placebo group (13 patients [3.5%]) than in the fruquintinib 5 mg 3/1 group (6 patients [0.8%]). In the fruquintinib group, there was no increase in the frequency of shift in anaemia from baseline to the worse post-baseline value compared to that in placebo group.

Neutrophil Count Decreased The majority of patients did not experience a shift in neutrophil count from baseline to the worst value. The percentage of patients who shifted to CTCAE Grade 1 or Grade 2 neutrophil count decreased in the fruquintinib group (71 patients, 9.3%) was higher compared to the placebo group (7 patients, 1.9%). The percentage of patients who shifted to CTCAE Grade ≥ 3 neutrophil count decreased post-baseline was slightly higher in the fruquintinib 5 mg 3/1 group (6 patients [0.8%]) than the placebo group (1 patient [0.3%]).

White Blood Cell Count Decreased The majority of patients did not experience a shift in white blood cell count from baseline to the worst value. The percentage of patients who shifted to CTCAE Grade 1 or Grade 2 white blood cell count decreased in the fruquintinib group (112 patients, 14.6%) was higher compared to the placebo group (13 patients, 3.5%). The percentage of patients who shifted to CTCAE Grade ≥ 3 white blood cell decreased post-baseline was comparable between treatment groups (fruquintinib 5 mg 3/1: 4 patients [0.5%]; placebo: 1 patient [0.3%]).

Platelet Count Decreased The majority of patients did not experience a shift in platelet count from baseline to the worst value. The percentage of patients who shifted to CTCAE Grade 1 or Grade 2 platelet count decreased in the fruquintinib group (216 patients, 28.1%) was higher compared to placebo group (18 patients, 4.8%). The percentage of patients who shifted to CTCAE Grade ≥ 3 platelet count decreased post-baseline was slightly higher in the fruquintinib 5 mg 3/1 group (12 patients [1.6%]) than the placebo group (2 patients [0.5%]) and no fruquintinib-treated patients developed CTCAE Grade 4 platelet count decreased post baseline.

Lymphocyte Count Decreased The majority of patients did not experience a shift in lymphocyte count from baseline to the worst value. The percentage of patients who shifted to CTCAE Grade 1 or Grade 2 lymphocyte count decreased in the fruquintinib group (121 patients, 15.8%) was comparable

to the placebo group (65 patients, 17.3%). The percentage of patients who shifted to CTCAE Grade ≥ 3 lymphocyte count decreased post baseline were comparable between treatment groups (fruquintinib 5 mg 3/1: 28 patients [3.7%]; placebo 10 patients [2.7%]).

To conclude, the Applicant reported on shifts related to an increase of at least 2 CTCAE grades from baseline and increases from baseline to CTCAE Grades 3 and 4. In the fruquintinib group, there was no increase in the frequency of shift in Anaemia, Neutrophil Count Decreased (of note, 4 subjects in fruquintinib group shifted from Grade 0 baseline to Grade 4 neutrophil count decreased), White Blood Cell Count Decreased, Lymphocyte count decreased from baseline to the worse post-baseline value compared to that in placebo group, excepting the results of Platelet Count Decreased. No need for PI implementation based on these findings was seen.

Clinical Chemistry

Shifts described in the following sections are increases of at least 2 CTCAE Grades from baseline and increases from baseline to CTCAE Grades 3 and 4. For brevity, only **ISAS-mCRC** data are presented.

Alkaline Phosphatase Increased The percentage of patients who shifted to CTCAE Grade ≥ 3 ALP increased post baseline was similar between treatment groups (fruquintinib 5 mg 3/1: 22 patients [2.9%]; placebo: 11 patients [2.9%]) and no patients developed CTCAE Grade 4 ALP increased. Generally, a slightly higher percentage of patients in the fruquintinib versus placebo treated groups had changes in ALP levels post-baseline. Seventeen patients (2.2%) in the fruquintinib 5 mg 3/1 group and 14 patients (3.7%) in the placebo group had CTCAE Grade 3 ALP increased at baseline. Of these, no patients in the fruquintinib 5 mg 3/1 group and 1 patient (0.3%) in the placebo group had CTCAE Grade 4 ALP increased at baseline.

Alanine Aminotransferase Increased The percentage of patients who shifted to CTCAE Grade ≥ 3 ALT increased post-baseline was higher in the fruquintinib 5 mg 3/1 group (29 patients [3.8%]) than the placebo group (5 patients [1.3%]) and no patients in either group developed CTCAE Grade 4 ALT increased post baseline.

Aspartate Aminotransferase Increased The percentage of patients who shifted to CTCAE Grade ≥ 3 AST increased post-baseline was higher in the fruquintinib 5 mg 3/1 group (30 patients [3.9%]) than the placebo group (8 patients [2.2%]) and no patients developed CTCAE Grade 4 AST increased post-baseline.

Blood Bilirubin Increased No patients in either treatment group had CTCAE Grade ≥ 3 blood bilirubin increased at baseline. The percentage of patients who shifted to CTCAE Grade ≥ 3 blood bilirubin increased post-baseline was higher in the placebo group (31 patients [8.3%]) than the fruquintinib 5 mg 3/1 group (49 patients [6.4%]). Of these, 1 patient in the fruquintinib 5 mg 3/1 group and no patients in the placebo group developed CTCAE Grade 3 blood bilirubin increased post baseline.

Serum Amylase Increased The percentage of patients who shifted to CTCAE Grade ≥ 3 serum amylase increased post baseline was higher in the fruquintinib 5 mg 3/1 group (8 patients [2.5%]) than the placebo group (0 patients). None of these 8 patients had acute pancreatitis.

Creatinine Increased The percentage of patients who shifted to CTCAE Grade ≥ 3 creatinine increased post baseline was higher in the placebo group (4 patients [1.1%]) than the fruquintinib 5 mg 3/1 group (2 patients [0.3%]) and no patients developed CTCAE Grade 4 creatinine increased post baseline.

Summary of Abnormal Hepatic Laboratory Values The percentage of patients who had elevated liver function test (LFT) (ALT, AST, ALP total bilirubin) was higher in the fruquintinib 5 mg 3/1 group

than in the placebo group. The percentages of patients who met the Hy's law criteria for potential drug induced liver injury (DILI) were similar between treatment groups.

Alanine Aminotransferase Out of a total of 781 patients in the fruquintinib 5 mg 3/1 group and 391 patients in the placebo group, a total of 767 patients in the fruquintinib 5 mg 3/1 group and 374 patients in the placebo group had non-missing ALT values. No patient in either treatment group had > 20 x ULN. The percentage of patients who had ALT elevation > 3 x ULN and ≤ 20 x ULN were higher in the fruquintinib group (107 patients, 14%) compared to the placebo group (22 patients, 5.9%). One patient (0.1%) in the fruquintinib 5 mg 3/1 group and no patients in the placebo group had > 5 x ULN for more than 5 weeks.

In the fruquintinib 5 mg 3/1 group, 541 patients who had liver metastasis, and 226 patients who did not have liver metastasis, had non-missing ALT values. The percentages of patients with or without liver metastasis in each criterion were similar (< 5% difference) except for the following (with metastasis vs without metastasis): > 3 x ULN and ≤ 5 x ULN (10% vs 4.4%). In the placebo group, 263 patients who had liver metastasis, and 111 patients who did not have liver metastasis, had non-missing ALT values. The percentages of patients with or without liver metastasis in each criterion were similar (< 5% difference).

Aspartate Aminotransferase Out of a total 781 patients in the fruquintinib 5 mg 3/1 group and 391 patients in the placebo group, 767 patients in the fruquintinib 5 mg 3/1 group and 374 patients in the placebo group had non-missing AST values. No patient in either treatment group had > 20 x ULN. The percentage of patients who had AST elevation > 3 x ULN and ≤ 20 x ULN were comparable between the fruquintinib group (135 patients, 17.6%) and placebo group (63 patients,16.8%). One patient (0.1%) in the fruquintinib 5 mg 3/1 group and 2 patients (0.5%) in the placebo group had > 5 x ULN for more than 5 weeks.

In the fruquintinib 5 mg 3/1 group, 541 patients who had liver metastasis, and 226 patients who did not have liver metastasis, had non-missing AST values. The percentages of patients with or without liver metastasis in each criterion were similar (< 5% difference) except for the following (with metastasis vs without metastasis): > 3 x ULN and ≤ 5 x ULN (15.0% vs 3.1%). In the placebo group, 263 patients who had liver metastasis, and 111 patients who did not have liver metastasis, had non-missing AST values. The percentages of patients with or without liver metastasis in each criterion were similar (< 5% difference) except for the following (with metastasis vs without metastasis): > 3 x ULN and ≤ 5 x ULN (13.7% vs 0%), > 5 x ULN and ≤ 8 x ULN (7.2% vs 0.9%).

Total Bilirubin Out of a total of 781 patients in the fruquintinib 5 mg 3/1 group and 391 patients in the placebo group, 767 patients in the fruquintinib 5 mg 3/1 group and 373 patients in the placebo group had non-missing values for total bilirubin. Of these, 80 patients (10.4%) in the fruquintinib 5 mg 3/1 group and 32 patients (8.6%) in the placebo group had 1.5 x ULN and ≤ 2 x ULN, 86 patients (11.2%) in the fruquintinib 5 mg 3/1 group and 39 patients (10.5%) in the placebo group had > 2 x ULN.

In the fruquintinib 5 mg 3/1 group, 541 patients who had liver metastasis, and 226 patients who did not have liver metastasis, had non-missing values for total bilirubin. The percentage of patients with or without liver metastasis was similar (< 5% difference) for criterion of > 1.5 x ULN and ≤ 2 x ULN, but the patients with liver metastasis had higher incidence of bilirubin > 2 x ULN compared to those without liver metastasis (14.6% vs 3.1%). In the ISAS—mCRC placebo group, 262 patients who had liver metastasis, and 111 patients who did not have liver metastasis, had non-missing values for total bilirubin. The percentages of patients with or without liver metastasis in each criterion were (with metastasis vs without metastasis): 1.5 x ULN and ≤ 2 x ULN (12.2% vs 0%); > 2 x ULN (14.5% vs 0.9%).

Alkaline Phosphatase Out of a total of 781 patients in the fruquintinib 5 mg 3/1 group and 391 patients in the placebo group, 767 patients in the fruquintinib 5 mg 3/1 group and 374 patients in the placebo group had non-missing ALP values. Of these, 254 patients (33.1%) in the fruquintinib 5 mg 3/1 group and 90 patients (24.1%) in the placebo group had > 1.5 x ULN and ≤ 2 x ULN, 269 patients (35.1%) in the fruquintinib 5 mg 3/1 group and 137 patients (36.6%) in the placebo group had > 2 x ULN.

In all, 541 patients who had liver metastasis, and 226 patients who did not have liver metastasis, had non-missing ALP values. The percentages of patients with liver metastasis in each criterion were higher than the patients without liver metastasis (with metastasis vs without metastasis): > 1.5 x ULN and ≤ 2 x ULN (38.8% vs 19.5%) and > 2 x ULN (45.7% vs 9.7%). In the ISAS—mCRC placebo group, 263 patients who had liver metastasis, and 111 patients who did not have liver metastasis, had non-missing ALP values. The percentages of patients with or without liver metastasis in each criterion were (with metastasis vs without metastasis): > 1.5 x ULN and ≤ 2 x ULN (27.4% vs 16.2%); > 2 x ULN (47.5% vs 10.8%) (Table ISS 5.4.1.5).

Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) The percentages of patients in the eDISH quadrants were comparable between the fruquintinib group and placebo group. In both the fruquintinib group and placebo group, the percentages of patients with liver metastasis in each criterion were higher than the patients without liver metastasis. The standard eDISH plot typically provides a useful screening tool to assess a drug's liver safety profile.

Hy's Law Hy's Law criteria include increases of ALT or AST more than 3 x ULN and increases of bilirubin more than 2 x ULN, with ALP < 2 x ULN. In the ISAS—mCRC, out of a total of 781 patients in the fruquintinib 5 mg 3/1 group and 391 patients in the placebo group, 767 patients in the fruquintinib 5 mg 3/1 group and 373 patients in the placebo group had non-missing Hy's Law values. Two patients (0.3%) in the fruquintinib 5 mg 3/1 group and 3 patients (0.8%) in the placebo group met Hy's Law criteria. The percentages of patients with or without liver metastasis who experienced liver function abnormality meeting Hy's law criteria were (with metastasis vs without metastasis): 0.2% vs 0.4%.

Liver function tests showed a comparable percentage of patients in both the fruquintinib group and placebo group who developed LFT elevations of at least 3 × upper limit of normal (ULN) for AST or ALT and 1.5 to 3 × ULN for total bilirubin. Of these, 2 (0.3%) patients in the fruquintinib group vs 3 (0.8%) patients in the placebo group developed LFT elevations that met Hy's law criteria.

Overall, in the ISAS—mCRC, the percentage of patients who had elevated liver function test (LFT) (ALT, AST, ALP, and total bilirubin) was quite consistently higher in the fruquintinib 5 mg 3/1 group than in the placebo group. ALT, AST and total bilirubin elevations with fruquintinib are included in the list of ADRs.

Urinalysis

Data collected across studies used various reporting and data collection practices. Therefore, data were not pooled.

Overall, for chemistry parameters in the ISAS—mCRC, most patients experienced no or Grade ≤2 CTCAE grade shifts from baseline to the worst value. Shifts to Grade ≥ 3 were observed for ALT increase, AST increase, and amylase increased that were more frequently reported in fruquintinib group compared to placebo group, 3.8% vs 1.3%, 3.9% vs 2.2%, 2.5% vs 0%, respectively.

Vital Signs

In the **ISAS—mCRC**, the percentage of patients who experienced increases in systolic blood pressure (SBP) and diastolic blood pressure (DBP) from baseline was higher in the fruquintinib 5 mg 3/1 group

than the placebo group (47.9% vs 14.7% for SBP increases > 20 mmHg and 27.5% vs 5.9% for DBP increases > 20 mmHg).

However, the percentage of patients who experienced decreases in SBP and DBP from baseline was comparable between treatment groups (20.1% vs 19.5% for SBP decreases > 20 mmHg and 3.8% vs 4.0% for DBP decreases > 20 mmHg).

The percentage of patients who experienced increases in heart rate from baseline was comparable for the fruquintinib 5 mg 3/1 group and the placebo group (26.7% vs 23.3% for increases > 20 beats/min). However, the percentage of patients who experienced decreases in heart rate from baseline was higher in the fruquintinib 5 mg 3/1 group than the placebo group (16.2% vs 8.1% for decreases > 20 beats/min).

The percentage of patients who experienced increases in weight from baseline was comparable for the fruquintinib 5 mg 3/1 group and the placebo group (9.3% vs 10.5% for increases ≥ 5%). However, the percentage of patients who experienced decreases in weight from baseline was much higher in the fruquintinib 5 mg 3/1 group than in the placebo group (69.3% vs 27.7%).

Overall, other than increases in blood pressure, no major differences were seen in the results on the vital signs, excepting the following: it was noted that the percentage of patients who experienced decreases in weight from baseline was much higher in the fruquintinib 5 mg 3/1 group than in the placebo group (69.3% vs 27.7%).

Weight decrease, and other related cancer toxicities, including fatigue, stomatitis, mucositis, decreased appetite, cachexia are toxicities know to be associated with end-stage cancer. They are often dose limiting, substantially influence treatment compliance, especially when dosing orally, affect QoL and are known to be associated with increased mortality. In current clinical praxis this issue has been well recognised as relevant and substantial. Early diagnosis, early intervention and appropriate management is important to improve patient outcome by, for example, avoiding dose reductions, interruptions, and discontinuation.

In light of the fruquintinib safety results, where an increase (as compared to placebo) in both dose interruption and dose reduction was seen consistently in several safety categories in the fruquintinib treatment group, there is a need for adequate measures for the prevention of these toxicities.

3.6.11.6. In vitro biomarker test for patient selection for safety

N/A.

3.6.11.7. Safety in special populations

FRESCO-2 and FRESCO studies

Pooled safety data

Intrinsic factors

Age: The safety profile between age subgroups were generally comparable and consistent. No comparison, however, could be made for the 85 years of age or older category which only contained 1 patient in the ISAS—mCRC, placebo group. The population PK model (see PK section) showed that age tested as a covariate had no statistically significant effect on the PK parameters of fruquintinib.

Age category 1 (< 65 and ≥ 65 years of age) In the ISAS—mCRC fruquintinib 5 mg 3/1 group, the percentages of patients who experienced TEAEs and serious TEAEs of any grade, TEAEs that led to

dose reduction, treatment discontinuation, and death, CTCAE Grade ≥ 3 TEAEs, serious TEAEs and AESIs were comparable between age groups. The only exception was that a higher percentage of patients < 65 experienced AESIs of any grade compared with patients ≥ 65 years of age (91.1% vs 78.5%).

Age category 2 (< 65, ≥ 65 to < 74, ≥ 74 to < 85, ≥ 85) is presented on Table 38. The percentage of patients who experienced AESIs of any grade was higher in patients < 65 years of age than in patients ≥ 65 to < 74 or ≥ 74 to < 85 years of age. The percentage of patients who experienced serious TEAEs of any grade and TEAEs leading to dose reduction was higher in patients ≥ 74 to < 85 compared with patients < 65 years or ≥ 65 to < 74 years of age. The percentages of patients who had CTCAE Grade ≥ 3 TEAEs and AESIs were comparable between age groups. The percentages of patients who had CTCAE Grade ≥ 3 serious TEAEs was higher in the in patients ≥ 74 to < 85 years of age.

Gender: In the population PK analysis (see PK section), gender had no statistically significant effect on the PK parameters of fruquintinib. The percentages of patients who experienced TEAEs and serious TEAEs of any grade, CTCAE Grade ≥ 3 TEAEs, treatment emergent AESI, TEAEs of any grade leading to treatment discontinuation and death were generally comparable between genders. The percentage of patients who experienced TEAEs leading to dose reduction was, however, higher in females compared with males. The percentages of patients who had CTCAE Grade ≥ 3 TEAEs and serious TEAEs were comparable between genders. The percentage of patients who had CTCAE Grade ≥ 3 treatment emergent AESIs was higher in females compared to males.

Region: The safety profile between different regions were generally comparable and consistent No comparison could be made for the Australia category, which only contained 10 patients. In the population PK analysis (see PK section), no statistically significant effects on the PK of fruquintinib were identified for region/country (Japanese vs. Chinese vs. rest of the world).

Region Category 1 (China, outside of China) Percentages of patients who experienced TEAEs, Grade ≥ 3 TEAE, TEAEs of any grade leading to dose reduction and treatment discontinuation and treatment emergent AESIs were comparable between the two regions. The percentages of patients who experienced serious TEAEs of any grade and TEAEs leading to death were higher in the region outside China. The percentage of patients who experienced treatment emergent AESIs of any grade was higher in China compared with outside China. The percentages of patients who had Grade ≥ 3 TEAEs and treatment emergent AESIs were comparable between Category 1 regions. The percentages of patients who had Grade ≥ 3 serious TEAEs was higher in the region outside China.

Region Category 3 (North America, Europe, Australia, Asia) The percentage of patients who experienced TEAEs and TEAEs leading to dose reduction and treatment discontinuation were comparable between all regions. The percentages of patients who had serious TEAEs and TEAEs leading to death were higher in North America and Europe compared with Asia in both datasets. The percentage of patients who had AESIs was higher in Asia than North America and Europe. In the ISAS—mCRC, the percentages of patients who had CTCAE Grade ≥ 3 TEAEs were comparable between the regions. In the ISAS—Expanded mCRC, the percentages of patients who had CTCAE Grade ≥ 3 TEAEs were higher in North America compared with Europe and Asia.

ECOG Performance Status: The safety profile between ECOG categories was generally comparable and consistent. The safety profile of fruquintinib in the overall analysis populations is consistent with that of the majority of the ECOG categories. Safety profile of patients between ECOG groups was consistent. The percentages of patients who experienced any type of TEAE were comparable between ECOG subgroups. In the population PK analysis (see PK section), no statistically significant effects on the PK of fruquintinib were identified for ECOG performance status.

Liver metastases present at baseline: The safety profile of fruquintinib in the overall analysis populations is consistent with that of the majority of patients with or without liver metastases at baseline. No trends were evident.

Race and ethnicity: The safety profile of fruquintinib in the overall analysis populations is consistent with that of the majority of patients under the race categories. No trends were evident.

Overall, the percentages of patients who experienced TEAEs and TEAEs leading to dose reduction, treatment discontinuation, and death were comparable between subgroups in both datasets. The percentage of patients who experienced serious TEAEs was higher in White patients compared with patients of other races. The percentage of patients who experienced AESIs was higher in other races compared with White patients. The safety profiles of fruquintinib 5 mg 3/1 for patients of White/Caucasian and Asian subgroups was for the majority, comparable for the ISAS—Expanded mCRC and ISAS—mCRC. Conclusions could not be drawn for Black/African American patients or patients who identified as Other due to small sample sizes. In the population PK analysis, race (White, Black, Asian, Hawaiian/Pacific Islander, multiple races, and other races) or ethnicity (Hispanic/Latino vs. non-Hispanic/Latino) had no statistically significant effect on the PK parameters of fruquintinib.

Baseline BMI: The percentage of patients who experienced TEAEs of any grade, AESIs, and TEAEs leading to dose reduction were comparable between BMI subgroups in both datasets. The percentages of patients who experienced any type of TEAE were comparable between patients with BMI 18.5 to < 24 and patients with BMI ≥ 24. The percentage of patients who experienced CTCAE Grade ≥ 3 TEAEs, serious TEAEs, and TEAEs leading to treatment discontinuation and death were higher in the BMI < 18.5 subgroup compared with other subgroups, possibly due to the much smaller sample size of this subgroup. In the population PK analysis (see PK section), body weight was found to have no clinically meaningful effects on fruquintinib exposure.

Duration of Metastatic Disease: Safety profile between different durations of metastatic disease was comparable and consistent. However, the percentages of patients who experienced serious TEAEs, and TEAEs leading to dose reduction and treatment discontinuation were higher in the metastasis longer than 18 months subgroup.

Other Intrinsic Factors: The population PK analysis (see PK section) showed no statistically significant effects on the PK of fruquintinib for mild renal impairment (CrCL 60-89 mL/min), moderate renal impairment (CrCL 30-59 mL/min), and mild hepatic impairment (based on NCI criteria). Interim PK results from ongoing dedicated PK studies indicated no clinically important differences in fruquintinib exposures in non-cancer subjects with moderate hepatic impairment (Child-Pugh Class B) or moderate to severe renal impairment (CrCL 15-59 mL/min) compared to historical data in healthy subjects. The effect of severe hepatic impairment on fruquintinib PK is unknown.

Extrinsic Factors: Food effect studies in healthy volunteers showed that food (high-fat meals) did not have clinically meaningful effect on the absorption of fruquintinib. Fruquintinib was well tolerated under both fed and fasted conditions in both studies.

Table 38: TEAEs by Age Group (ISAS-mCRC Population)

	Fruquintinib 5 mg 3/1				Placebo			
	Age <65 N = 507 n (%)	Age 65-74 N = 227 n (%)	Age 75-84 N = 47 n (%)	Age 85+ N = 0 n (%)	Age <65 N = 243 n (%)	Age 65-74 N = 128 n (%)	Age 75-84 N = 19 n (%)	Age 85+ N = 1 n (%)
Total TEAE	499 (98)	224 (99)	47 (100)	0	216 (89)	121 (95)	18 (95)	0
Serious TEAEs	141 (28)	64 (28)	22 (47)	0	51 (21)	39 (30)	11 (58)	0
Fatal	37 (7)	18 (8)	4 (9)	0	23 (9)	21 (16)	5 (26)	0
Hospitalization/prolong existing hospitalization	130 (26)	53 (23)	19 (40)	0	41 (17)	31 (24)	9 (47)	0
Life-threatening	12 (2)	4 (2)	3 (6)	0	1 (<1)	7 (5)	0	0
Disability/incapacity	1 (<1)	3 (1)	1 (2)	0	1 (<1)	2 (2)	1 (5)	0
Other (medically significant)	10 (2)	5 (2)	1 (2)	0	4 (2)	0	1 (5)	0
AE leading to drop-out	84 (17)	46 (20)	12 (26)	0	31 (13)	22 (17)	6 (32)	0
Psychiatric disorders	53 (10)	25 (11)	5 (11)	0	15 (6)	6 (5)	3 (16)	0
Nervous system disorders	102 (20)	58 (26)	12 (26)	0	30 (12)	18 (14)	3 (16)	0
Accidents and injuries	12 (2)	7 (3)	1 (2)	0	4 (2)	5 (4)	0	0
Cardiac disorders	41 (8)	17 (7)	4 (9)	0	14 (6)	8 (6)	0	0
Vascular disorders	248 (49)	95 (42)	19 (40)	0	36 (15)	22 (17)	2 (11)	0
Cerebrovascular disorders	6 (1)	2 (<1)	0	0	0	1 (<1)	0	0
Infections and infestations	128 (25)	49 (22)	6 (13)	0	37 (15)	12 (9)	3 (16)	0
Anticholinergic syndrome	0	0	0	0	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures [a]	35 (7)	20 (9)	1 (2)	0	13 (5)	5 (4)	0	0
Other AE appearing more frequently in older participants [b]								
Asthenia	98 (19)	83 (37)	14 (30)	0	19 (8)	30 (23)	7 (37)	0
Decreased appetite	116 (23)	76 (33)	15 (32)	0	29 (12)	30 (23)	5 (26)	0
Mucosal inflammation	21 (4)	33 (15)	8 (17)	0	1 (<1)	3 (2)	2 (11)	0

AE: adverse event; ISAS: Integrated Safety Analysis Set; mCRC: metastatic colorectal cancer; TEAE: treatment-emergent adverse event. Pooled PTs of orthostatic hypotension, fall, syncope, dizziness, ataxia, loss of consciousness, tooth fracture, femur fracture, lumbar vertebral fracture, spinal compression fracture. [b] AE appearing more frequently in older participants is defined as AE Preferred Terms appearing more frequently in older participants by 10% based on the indicated population.

Pregnancy and Lactation

There are no data on the use of fruquintinib in pregnant women. Fruquintinib has the potential to cause foetal harm when administered to pregnant women because of its mechanism of action. In an embryofoetal developmental study in rats at an exposure below the clinical exposure, embryotoxic and teratogenic effects were observed and consisted of foetal external, visceral, and skeletal malformations.

Immunological events

The applicant has not presented any immunological data, and this is considered acceptable for tyrosine kinase inhibitors, with low immunological potential.

3.6.11.8. Safety related to drug-drug interactions and other interactions

Effect of Other Drugs on Fruquintinib

Coadministration of fruquintinib with rabeprazole, a proton pump inhibitor, or itraconazole, a CYP3A inhibitor, did not affect the exposure of fruquintinib; therefore, no dose adjustment is necessary when fruquintinib is coadministered with an acid reducing agent or any CYP3A inhibitor. Coadministration of fruquintinib with rifampin, a strong CYP3A inducer, decreased fruquintinib AUC (area under the concentration-time curve) by 65%. Physiologically based pharmacokinetic (PBPK) analysis predicted that fruquintinib AUC was decreased by 28% when coadministered with efavirenz, a moderate CYP3A inducer, but no significant effect on fruquintinib AUC when coadministered with dexamethasone, a weak CYP3A inducer. Consequently, fruquintinib should not be administered with strong CYP3A inducers.

Effect of Fruquintinib on Other Drugs

In vitro, fruquintinib was shown to inhibit P-gp and BCRP transporters. A clinical DDI study showed that coadministration of a single dose of 5 mg fruquintinib with dabigatran etexilate, a P-gp substrate, or rosuvastatin, a BCRP substrate, resulted in no clinically meaningful changes in the systemic exposure of dabigatran or rosuvastatin. Based on PBPK modelling, repeated doses of 5 mg fruquintinib were predicted to have no clinically relevant impact on the exposure of digoxin, a P-gp substrate, or rosuvastatin. Based on the totality of data, no dose adjustment for concomitant medications that are substrates of P-gp or BCRP is necessary when coadministered with fruquintinib.

3.6.11.9. Discontinuation due to adverse events

FRESCO-2 and FRESCO studies

Treatment-emergent Adverse Events Leading to Drug Discontinuation

In FRESCO, a higher percentage of patients experienced TEAEs leading to drug **discontinuation** in the fruquintinib 5 mg 3/1 group (42 patients [15.1%]) than the placebo group (8 patients [5.8%]); but in FRESCO-2, a comparable percentage of patients experienced TEAEs leading to treatment discontinuation between treatment groups (fruquintinib 5 mg 3/1: 93 patients [20.4%]; placebo: 49 patients [21.3%]).

In FRESCO, the most frequent of these events, any grade, (fruquintinib 5 mg 3/1 vs placebo) were: proteinuria (2.2% vs 0.7%), hepatic function abnormal (1.4% vs 0%), protein urine present (1.1% vs 0%), and intestinal obstruction (1.1% vs 0.7%).

In FRESCO-2, the most frequently reported events (fruquintinib 5 mg 3/1 vs placebo) were: asthenia (1.5% vs 0.9%), disease progression (1.3% vs 3.5%), and general physical health deterioration (1.1% vs 2.2%).

Treatment-emergent Adverse Events Leading to Dose Reduction or Interruption

In both the FRESCO and FRESCO-2 studies, a higher percentage of patients experienced TEAEs leading to dose interruption or dose reduction in the fruquintinib 5 mg 3/1 group than the placebo group.

In FRESCO, a higher percentage of patients experienced TEAEs leading to dose **interruption** in the fruquintinib 5 mg 3/1 group (98 patients [35.3%]) than the placebo group (14 patients [10.2%]). Likewise, a higher percentage of patients experienced TEAEs leading to dose reduction in the fruquintinib 5 mg 3/1 group (67 patients [24.1%]) than in the placebo group (6 patients [4.4%]) (2013-013-00CH1 [FRESCO] CSR, Table 18). In FRESCO, the most frequent events, leading to dose interruption or dose reduction (fruquintinib 5 mg 3/1 vs placebo) were: Palmar- plantar erythrodysaesthesia syndrome (13.3% vs 0%), proteinuria (9.7% vs 0.7%), and thrombocytopenia (5.4% vs 0.7%).

In FRESCO-2, a higher percentage of patients experienced TEAEs leading to dose **interruption** in the fruquintinib 5 mg 3/1 group (213 patients [46.7%]) than in the placebo group (61 patients [26.5%]). In FRESCO-2, the most frequent events (fruquintinib 5 mg 3/1 vs placebo) were: Palmar-plantar erythrodysaesthesia syndrome (6.1% vs 0%), proteinuria (4.6% vs 0.9%), and asthenia (2.9% vs 0.4%). A higher percentage of patients experienced TEAEs leading to dose reduction in the fruquintinib 5 mg 3/1 group (110 patients [24.1%]) than in the placebo group (9 patients [3.9%]). The most frequent events (fruquintinib 5 mg 3/1 vs placebo) were: Palmar-plantar erythrodysaesthesia syndrome (5.0% vs 0%), asthenia (3.3% vs 1.3%), and hypertension (2.9% vs 0.4%).

Pooled safety data

Adverse Events Leading to Treatment Discontinuation

In the ISAS—mCRC, a slightly higher percentage of patients in the fruquintinib 5mg 3/1 group than placebo group had experienced TEAEs of any CTCAE grade that led to treatment discontinuation. Out of a total 781 patients in the fruquintinib 5 mg 3/1 group and 391 patients in the placebo group, 142 patients (18.2%) versus 59 patients (15.1%), respectively, had TEAEs that led to treatment discontinuation.

A comparable percentage of patients had Grade ≥ 3 TEAEs that led to treatment discontinuation in both groups: 111 patients (14.2%) in the fruquintinib 5 mg 3/1 group versus 52 patients (13.3%) in the placebo group. The CTCAE Grade ≥ 3 events reported in more than 4 patients in the fruquintinib 5 mg 3/1 group (≥ 0.6% incidence; fruquintinib 5 mg 3/1 vs placebo) were: disease progression (0.8% vs 2.0%), intestinal obstruction (0.6% vs 0.5%), hepatic function abnormal (0.6% vs 0.3%), and proteinuria (0.6% vs 0%).

A comparable percentage of patients in the fruquintinib 5 mg 3/1 group and placebo group experienced serious TEAEs of any CTCAE grade that led to treatment discontinuation. Out of a total 781 patients in the fruquintinib 5 mg 3/1 group and 391 patients in the placebo group, 88 patients (11.3%) versus 46 patients (11.8%), respectively, had serious TEAEs resulting in treatment discontinuation.

The percentage of patients who experienced Grade ≥ 3 serious TEAEs that led to treatment discontinuation was comparable in both groups: A total of 82 patients (10.5%) in the fruquintinib 5 mg 3/1 group and 44 patients (11.3%) in the placebo group. The CTCAE Grade ≥ 3 events occurring in more than 4 patients in the fruquintinib 5 mg 3/1 group (≥ 0.6% incidence; fruquintinib 5 mg 3/1 vs placebo) were: disease progression (0.6% vs 2.0%) and intestinal obstruction (0.6% vs 0.5%).

Treatment-emergent Adverse Events Leading to Dose Reduction

A higher percentage of patients in the fruquintinib 5 mg 3/1 group than the placebo group had TEAEs of any CTCAE grade that led to dose reduction. Out of a total of 781 patients in the fruquintinib 5 mg 3/1 group and 391 patients in the placebo group, 190 patients (24.3%) versus 15 patients (3.8%), respectively, had TEAEs that led to dose reduction.

A higher percentage of patients in the fruquintinib 5 mg 3/1 group (118 patients [15.1%]) than in the placebo group (7 patients [1.8%]) had Grade ≥ 3 TEAEs that led to dose reduction.

The percentage of patients who experienced serious TEAEs of any CTCAE grade that led to dose reduction was higher in the fruquintinib 5 mg 3/1 group than in the placebo group. Out of a total 781 patients in the fruquintinib 5 mg 3/1 group and 391 patients in the placebo group, 13 patients (1.7%) versus 3 patients (0.8%), respectively, had serious TEAEs of any CTCAE grade that led to dose reduction.

The percentage of patients who experienced CTCAE Grade ≥ 3 serious TEAEs that led to dose reduction was generally comparable between treatment groups: 10 patients (1.3%) in the fruquintinib 5 mg 3/1 group versus 3 patients (0.8%) in the placebo group.

A slightly higher percentage of patients in the fruquintinib group (18.2%) and placebo (15.1%) experienced TEAEs leading to **treatment discontinuation**. The most frequent events (≥0.5%) leading to dose discontinuation in the fruquintinib group (vs placebo) were proteinuria (1.4% vs 0.3%), asthenia (1.0% vs 0.5%), disease progression (0.8% vs 2.0%), hepatic function abnormal (0.8% vs 0.3%), general physical health deterioration, (0.6% vs 1.3%), and intestinal obstruction (0.6% vs 0.5%), and Palmar-plantar erythrodysaesthesia syndrome (0.5% vs 0%).

In the extended mCRC, the frequency of treatment discontinuation due to adverse reactions is 7.6%. The most common adverse reaction leading to treatment discontinuation is proteinuria (1.6%).

Overall, palmar-plantar erythrodysaesthesia syndrome, hypertension, and proteinuria were the most frequent TEAEs leading to dose **reduction** and dose **interruption**. Palmar-plantar erythrodysaesthesia syndrome resulted in ≥ 5% dose reduction or interruption rates (6.4% and 6.5% of dose reduction and interruption, respectively). However, the dose discontinuation rate for palmar-plantar erythrodysaesthesia syndrome was clearly lower 0.5%, suggesting that most of these events were adequately managed with dose modifications. Similarly, the treatment discontinuation rate for the most common TEAE of hypertension was 0.4%, suggesting that it also could be managed adequately

Treatment-emergent Adverse Events Leading to Dose Interruption

In the ISAS—mCRC, a higher percentage of patients in the fruquintinib 5mg 3/1 group than placebo group experienced TEAEs of any CTCAE grade that led to dose interruption. Out of a total 781 patients in the fruquintinib 5 mg 3/1 group and 391 patients in the placebo group, 327 patients (41.9%) versus 80 patients (20.5%), respectively, had TEAEs that led to dose interruption.

The percentage of patients who experienced CTCAE Grade ≥ 3 TEAEs that led to dose interruption was higher in the fruquintinib 5 mg 3/1 group (181 patients [23.2%]) than in the placebo group (40 patients [10.2%]). The CTCAE Grade ≥ 3 events reported in more than 4 patients in the fruquintinib 5 mg 3/1 group (≥ 0.6% incidence; fruquintinib 5 mg 3/1 vs placebo) were: palmar-plantar erythrodysaesthesia syndrome (3.6% vs 0%), hypertension (2.6% vs 0%), asthenia (1.3% vs 0.5%), fatigue (1.2% vs 0%), diarrhoea (1.0% vs 0%), proteinuria (0.9% vs 0.3%), abdominal pain (0.8% vs 1.0%), intestinal obstruction (0.8% vs 0.5%), alanine aminotransferase increased, pneumonia (both 0.8% vs 0.3%), and platelet count decreased (0.6% vs 0%).

In the ISAS—mCRC, a higher percentage of patients in the fruquintinib 5 mg 3/1 group than placebo group experienced serious TEAEs of any CTCAE grade that led to dose interruption. Out of a total 781 patients in the fruquintinib 5 mg 3/1 group and 391 patients in the placebo group,75 patients (9.6%) versus 26 patients (6.6%), respectively, had serious TEAEs that led to dose interruption.

In the fruquintinib group, 24.3% of patients had TEAEs leading to **dose reduction**, which was higher than the placebo group (3.8%). The most frequent events (≥1%) leading to dose **reduction** in the fruquintinib group (vs placebo) were palmar plantar erythrodysaesthesia syndrome (6.3% vs 0%), hypertension (3.6% vs 0.3%), proteinuria (2.6% vs 0.3%), asthenia (2.0% vs 0.8%), diarrhoea (1.5%

vs 0%), blood bilirubin increased (1.0% vs 0%), and fatigue (1.0 vs 0.5%), platelet count decreased (0.8% vs 0%), and decreased appetite (0.6% vs. 0.3%).

In the extended mCRC, the frequency of dose reduction due to adverse reactions is 20.5%. The most common adverse reactions leading to dose reduction are PPES (6.4%), hypertension (3.7%), and proteinuria (3.4%).

The percentage of patients who experienced Grade ≥ 3 serious TEAEs that led to dose interruption was slightly higher in the fruquintinib 5 mg 3/1 group (66 patients [8.5%]) than in the placebo group (22 patients [5.6%]). The CTCAE Grade ≥ 3 events that occurred in more than 1 patient in the fruquintinib 5 mg 3/1 group (≥ 0.3% incidence; fruquintinib 5 mg 3/1 vs placebo) were: intestinal obstruction (0.6% vs 0.5%), pneumonia (0.6% vs 0.3%), hypertension (0.5% vs 0%), abdominal pain (0.4% vs 0.3%), small intestinal obstruction, (0.4% vs 0%), vomiting (0.3% vs 0.5%), back pain (0.3% vs 0.3%), asthenia, femur fracture, general physical health deterioration, hepatic failure, hyponatraemia, rectal haemorrhage, sepsis, sub ileus, urinary tract infection (0.3% vs 0% each).

3.6.11.10. Post marketing experience

Fruquintinib has been marketed in China as Elunate since China approval on 04 September 2018. The latest periodic safety update report is Version 6.0, covering the reporting period from 04 September 2021 to 03 September 2022. Estimated cumulative exposure, based on cumulative sales and the median treatment exposure (4.0 cycles) is 52462 patients (from IBD) and 22721 patients (during the reporting period only). During the reporting period, a total of 1824 adverse reaction case reports, containing 4809 adverse drug reactions (ADRs), were received for fruquintinib, including 1511 reports from PMSS 2018-013-00CH2 and 313 from other sources. One case of Posterior Reversible Encephalopathy Syndrome (PRES) and 1 case of aortic dissection were received from post-marketing surveillance. No other important safety findings have been identified during the reporting period and cumulatively. During the reporting period, there was no change in the reference safety information since first marketing authorization in China.

Post marketing Surveillance Study (Study 2018-013-00CH2 (NCT04005066): PMSS)

This study in Chinese cancer patients is a post marketing commitment to the China National Medicinal Products Agency (NMPA). Enrolment was completed on 11 February 2022 and 96 sites were initiated. As of 03 September 2022, 3003 patients were enrolled in 2 cohorts and exposed to fruquintinib: 1. patients with mCRC treated in accordance with the fruquintinib (Elunate) package insert; and 2. patients with other indications suitable for treatment according to investigator's judgment.

Overall, these currently available post marketing safety data for fruquintinib appear consistent with the clinical trial data with no new or unexpected safety findings. However, considering the limitations (Chinese target population with differing and varying indications and treatment modalities) of these data, they can, at best, be considered supportive.

In the initial submission, PRES was listed in the SmPC section 4.8 table 3 on ADRs with the frequency of 0.1% based on one case of grade 4 PRES reported in the fruquintinib group vs 0 in placebo in the pooled data (ISAS-mCRC). An additional case was reported in post marketing data. Aortic dissection was added in the list ADRs. No other potential ADRs were evident on clarification in the Applicant´s on-line pharmacovigilance database since the end of the reporting period of 03 September 2022.

3.6.12. Discussion on clinical safety

Overall description of the safety database

For the EU MAA, the safety data for fruquintinib monotherapy in metastatic colorectal cancer (mCRC) patient population is mainly derived from a single pivotal phase 3, randomised, placebo-controlled FRESCO-2 study (fruquintinib N=465, placebo N=230).

Supportive phase 3 evidence arise from the FRESCO study (fruquintinib N=278, placebo N=137) including only Chinese patients and representing patients in an earlier treatment line setting. Subjects from FRESCO-2 study are considered more representative of the targeted patient population, which is expected to be more heavily pre-treated than the FRESCO population. The FRESCO-2 population is also more representative of the European population compared to study population of FRESCO, which only included Chinese subjects. The FRESCO-2 study is thus the key study on which the benefit/risk assessment will be based on.

In addition, results from pooled data analyses from clinical monotherapy studies were presented from two overlapping data pools. Firstly, ISAS—mCRC pool consists of 3 randomised, placebo-controlled studies, including Phase 3 study FRESCO-2, Phase 3 study FRESCO (excluding patients from the open-label Japanese safety lead-in), and a Phase 2 study [2012-013-00CH1]) in 1172 patients with mCRC (fruquintinib 5 mg 3/1 group N=781, placebo group N=391). Secondly, the ISAS-Extended mCRC pool consists of pooled results from 6 studies in patients with mCRC who received at least 1 dose of fruquintinib monotherapy 5 mg 3/1 (fruquintinib N=911) that includes ISAS—mCRC and 3 open-label studies (2009-013-00CH1, 2012-013- 00CH3, and 2015-013-00US1), and the Japanese safety lead-in portion of study 2019-013-GLOB1/FRESCO. The pooling strategy to evaluate the safety of fruquintinib appears meaningful and justified. Overall, the safety pools seem representative of the target population for whom fruquintinib is indicated. Among the pooled analysis sets ISAS—mCRC is considered the most relevant population for safety assessment. In this analysis population, a total of 781 patients were exposed to fruquintinib monotherapy and 391 patients were exposed to placebo in a double-blinded manner. However, for identification of potential ADRs the use of the most comprehensive pool in mCRC patients (i.e., ISAS—Expanded mCRC) with the dosing regimen proposed for the indication, is considered adequate.

Overall, the extent of exposure is considered sufficient to be able to identify the most common adverse events. The focus of the assessment is on mCRC patients who have received fruquintinib according to the intended labelling.

The investigational therapy was fruquintinib, given as monotherapy 5 mg 3/1 plus 'best supportive care' (BSC) and the reference therapy was placebo plus BSC (hereafter denoted as fruquintinib and placebo, respectively). As there are currently no effective treatments for patients who have progressed on standard, approved therapies, and treatment options include reuse of prior therapies, clinical trials or BSC, the placebo plus BSC was considered an appropriate choice for the comparator arm.

Overall, the presented exposure data appear adequate to provide sufficient evidence to support safety evaluation of fruquintinib treatment in the target indication. The observed differences seen between the treatment groups in the number of treatment cycles (higher in the fruquintinib group) or dose intensity (better in the placebo group) can be explained by the study design, characteristics of the treatments and the patient population.

Phase 3 study FRESCO-2 safety data

Treatment-Emergent Adverse Events

In the pivotal phase 3 study almost all patients in both treatment groups experienced TEAEs. This is not unexpected considering the advanced cancer disease and characteristics of the patient population with already several previous treatment lines.

The most common TEAEs by Preferred Terms (PTs) in FRESCO-2 study (fruquintinib compared with placebo were hypertension (36.8% vs 7.7%), asthenia (34.0% vs 7.7%), decreased appetite (27.2% vs 17.4%), diarrhoea (24.1% vs 10.4%), hypothyroidism (20.5% vs 0.4%), fatigue (20.0% vs 16.1%), and palmar-plantar erythrodysaesthesia syndrome (19.3% vs 2,6%). The most common ≥ G3 TEAEs by PTs in FRESCO-2 study (fruquintinib compared with placebo) were hypertension (13.6% vs. 0.9%), asthenia (7.7% vs 3.9%), palmar-plantar erythrodysaesthesia syndrome (6.4% vs. 0%), fatigue (3.9 % vs 0.9%), diarrhoea (3.5% vs. 0%) and abdominal pain (3.1% vs 3.0%).

Incidences of the overall TEAEs, and grade ≥ 3 TEAEs by PTs were quite consistently higher in the fruquintinib treatment group compared to placebo, which by design is also not unexpected. The reported TEAEs and ≥ G3 TEAEs are typical for this type of medicinal products, including hypertension, a common and dose-dependent adverse effect of all VEGF inhibitors; gastrointestinal adverse effects, very common in patients on VEGFR–TKI treatment; the hand–foot syndrome, the most common skin toxicities for VEGFR inhibitors; dysphonia, a common adverse effect of new-generation VEGF inhibitors, and proteinuria, also a common finding among them. The frequently reported adverse events are generally consistent with the mechanism of action of fruquintinib and the disease under study in a heavily pre-treated mCRC population.

Serious Adverse events and deaths

Overall, the incidence of treatment emergent fatal cases in the FRESCO-2 study was higher in the placebo group (19.5%) than in the fruquintinib group (10.5%). The most frequent event was disease progression (5.7% in fruquintinib group vs 11.7% in placebo group). However, all deaths occurring in the fruquintinib plus BSC treatment arm were deemed not related to the study medication. From the narratives it was apparent that the Applicant has changed the investigator´s assessment of causality for several subjects, who eventually died due to the adverse event or with the adverse event. Furthermore, the Applicant had also changed the causality assessment for several non-fatal adverse events. Upon request, the Applicant provided a more detailed description of the causality assessment overall and particularly concerning several highlighted patient cases. It is evident that only events without any confounding factors appeared to be considered as related, even though as per guidance all events with at least reasonable relationship should be included. However, this issue was not pursued further, as it was not expected to impact the overall benefit/risk assessment.

Treatment reductions, interruptions, and permanent discontinuations

A comparable percentage of patients experienced TEAEs leading to permanent treatment discontinuation between the treatment groups (fruquintinib 20.4% vs. placebo 21.3%). On the other hand, the individual frequencies of SAEs and AEs leading to permanent dose discontinuation were, overall, relatively low. The most frequently reported events leading to permanent discontinuation (fruquintinib vs. placebo) were asthenia (1.5% vs 0.9%), disease progression (1.3% vs 3.5%), and general physical health deterioration (1.1% vs 2.2%). However, TEAEs leading to temporary discontinuation or dose reduction were more frequent in the fruquintinib treatment group. There were also differences seen according to gender. No specific reasons were clearly evident for these findings.

Safety results by sub-groups

In general, the safety profile of fruquintinib monotherapy was consistent and comparable across different sub-groups studied. No pronounced differences in TEAEs were observed in the subgroups

(e.g., age, region, ECOG Performance Status, race and ethnicity, baseline BMI, duration of metastatic disease). Only pooled data was presented for the subgroups, but this was considered sufficient.

Slight discrepancies were also noted in the safety results according to gender: the percentage of patients who experienced TEAEs leading to dose reduction was higher in females compared with males and the percentage of patients who had CTCAE Grade ≥ 3 treatment emergent AESIs was higher in females compared to males. However, on further analyses no clear reasons behind these findings were evident. None of the characteristic, for example, weight, body surface area, hormonal aspects, or treatment compliance or other attributes studied appeared to explain the putative gender differences. Gender difference appeared to be independent of PK parameters. On the basis of the provided data, it could thus not be ascertained if the observed difference in OS by gender was or was not associated to a possible clinically meaningful gender difference in the safety/tolerability of the fruquintinib.

Supportive and pooled safety data

Safety data arising from the other phase 3 study (FRESCO), is considered at best supportive for this application, because of differences and limitations in study design and the study population. These differences are discussed in detail in the efficacy section. Differences were also seen in the safety results of FRESCO study in comparison to the pivotal FRESCO-2 study, particularly a higher number of deaths. No unambiguous reasons for the differences were found. The applicant's decision not to pool the safety data from these two phase 3 studies is, thus, justified and agreed.

Safety data were presented for the pooled ISAS-mCRC and ISAS-Extended mCRC. Of these pooled datasets the ISAS-MRC is considered more relevant for safety assessment.

The most commonly reported TEAEs (≥20%) in fruquintinib compared to placebo in ISAS-mCRC were hypertension (44.7% vs 11.3%), palmar-plantar erythrodysaesthesia syndrome/hand-foot syndrome (32.7% vs 3.1%), proteinuria (28.4% vs 13.3%), dysphonia (26.1% vs 4.1%), decreased appetite (26.5% vs 16.4%), diarrhoea (24.8% vs 9.0%) and asthenia (25.0% vs 14.3%), which are typical for a TKI anti-VEGFR. Overall, the pooling of data did not give rise to new or unexpected safety findings. The safety profiles in the two pools ISAS-mCRC and ISAS-Extended mCRC were much alike, which is well explained by the major overlapping of the pools. In both pools the incidence of TEAEs were in general high for both fruquintinib- and placebo-treated patients, as were also treatment-related TEAEs. This is not unexpected taking into account the advanced cancer disease and patient population with already several previous treatment lines. The pattern of AEs similar to the pivotal study was evident for the most part also in the pooled analysis, and no major increase in toxicity was clearly evident. Also serious AEs occurred at a comparable rate across the 2 treatment arms in ISAS-mCRC (29.2% in fruquintinib and 25.8% in placebo).

Adverse events of special interest (AESIs)

A wide range of potential AESIs were assessed and the AESIs chosen were hypertension, dermatological toxicity, thyroid dysfunction, proteinuria, haemorrhages, gastrointestinal perforation, infections, embolic and thrombotic events, hepatic function abnormal, LVEF decreased, based on pooled safety data.

The Incidence of hypertension was 47.5% in the fruquintinib group vs 11.8% in placebo. Also, the incidence of Grade ≥3 hypertension events was higher in fruquintinib group compared to placebo group (18.4% vs 1.3%), which is described in section 4.8 of the SmPC. Serious hypertension was reported in 1.5% of subjects in fruquintinib group. Dose modification for grade ≥3 hypertension were included in the SmPC. In addition, a warning is included in section 4.4 of the SmPC to inform that pre-existing hypertension should be monitored and adequately controlled in accordance with standard medical practice prior to initiating treatment with fruquintinib . Information is also included that

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

Dermatological toxicities were more often reported in fruquintinib group than in placebo. Adequate dose modifications for dermatological toxicity are included in section 4.2 of the SmPC. A warning about palmar-plantar erythrodysaesthesia syndrome (PPE) is included in section 4.4. Dermatological toxicities will be monitored in PSURs.

Low grade and non-serious proteinuria were reported more often in fruquintinib-treated patients than in placebo-treated patients (17.3% vs 5.2%). Dose modification guidelines and warnings/precautions for use are included in sections 4.2 and 4.4. of the SmPC, and it is also indicated that monitoring for blood pressure should start before treatment initiation and should continue during treatment with fruquintinib in accordance with standard medical practices. 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.

A warning about gastrointestinal perforation is reflected in section 4.4 of the SmPC informing that symptoms of GI perforation should be periodically monitored during treatment with fruquintinib and that fruquintinib should be permanently discontinued in patients developing GI perforation.

Embolic and thrombotic events were more often reported in fruquintinib group compared to placebo group in ISAS-mCRC (3.6% vs 1.5%), mostly pulmonary embolism (1.2% vs 0.3%). The majority of events were severe (Grade ≥3: 2.2% vs 0.8%) and serious embolic and thrombotic events were reported in 1.4.% vs 0.8% subjects in fruquintinib and placebo groups, respectively. Two (0.3%) fatal cases occurred in fruquintinib group (i.e., cerebral infarction and pulmonary embolism). Arterial and venous thromboembolic events are included under warnings/precautions for use in section 4.4 of the SmPC informing that 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.

In ISAS-mCRC the incidence of haemorrhagic events in fruquintinib group was higher than in the placebo group (26.5% vs 14.6%). The incidences of Grade ≥3 events and serious events were 2.0% vs 1.0% and 2.3% vs 1.0%, respectively. Fatal haemorrhagic events were reported in 4 (0.5%) subjects in fruquintinib group vs 0 in placebo group, and included 2 cases of haemoptysis, one case of gastrointestinal haemorrhage and one case of upper gastrointestinal haemorrhage. In the ISAS-expanded mCRC, an additional case of fatal haemoptysis was reported in the fruquintinib group. Of these fatal events, 3 (i.e., haemoptysis [N=2] and gastrointestinal haemorrhage [N=1]) were assessed as related to fruquintinib by the investigator. Dose modifications and a special warning and precaution for use are included in sections 4.2 and 4.4 of the SmPC. The warning in 4.4 informs that haematologic and coagulation profiles should be monitored in accordance with standard medical practices 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. The fatal haemorrhagic events are also discussed in section 4.8 of the SmPC.

Impaired wound healing was reported in 1 patient (0.1%) treated with fruquintinib in clinical studies. A warning is reflected in section 4.4 of the proposed SmPC to inform that patients are recommended to withhold fruquintinib for at least 2 weeks prior to surgery and that fruquintinib should not be resumed for at least 2 weeks after surgery, as clinically indicated when there is evidence of adequate wound healing.

Overall, it can be agreed that AESIs observed in the fruquintinib-treated patients were in general consistent with the known class toxicities. The AESIs were as expected consistently higher in the fruquintinib treatment group compared to placebo considering also the AESIs set by design. This is reflected in the PI (see above, and also separate PI).

Laboratory results
Neutropenia, leukopenia, and thrombocytopenia were included in the list of ADRs of fruquintinib.

The percentages of patients who had elevated liver function tests (LFTs) (ALT, AST, ALP, and total bilirubin) were quite consistently higher in the fruquintinib 5 mg 3/1 group than in the placebo group. However, initially only ALT increased was included as an ADR. On request, AST increased and blood bilirubin increased were also identified as ADRs of fruquintinib considering their incidence, the non-clinical findings, and the known risk of hepatotoxicity for other VEGFR TKIs. Justification for not including ALP as an ADR were provided. Hepatobiliary disorders are also included in the description of selected ADRs in section 4.8 of the SmPC considering the serious and fatal cases reported.

Furthermore, the data presented show that LFTs elevations were more pronounced in the fruquintinib group among those with liver metastases at baseline compared to placebo-group. As LFT elevations are expected with the progression of liver metastases, this would be expected to be more common in the placebo group. However, no differences were clearly evident in LFTs in fruquintinib and placebo groups among those with concomitant liver progression and those without liver progression.

The clinical relevance of the observed platelet count shifts were clarified and the present dose modification guidance due to decreased platelet count are considered adequate.

LVEF decreased occurred less frequently in fruquintinib compared to placebo (0.6% vs 1.5%) in ISAS-mCRC.

Adverse drug reactions in the SmPC

The applicant has used the pooled data from ISAS-Extended mCRC (n=911) for ADR identification. This is considered appropriate, as it includes patients with metastatic CRC (irrespective of treatment line) and treated with the intended clinical dose. However, the identification of ADRs for SmPC needed further revision. In the light of the EC SmPC guideline (2009) also rare ADR events should be reported. Particularly the frequency of ≥ 5% overall AE incidence and > 2-fold of that in placebo group was not considered sufficient and originally the list of ADRs included only very common and common ADRs. Subsequently, upon request, the Applicant clarified the criteria they have used in selection of ADRs, and based on assessment of requested data and clarifications additional events were added on the list of ADRs**.**

Post marketing data Overall, currently available post marketing safety data for fruquintinib appear consistent with the clinical trial data with no new or unexpected safety findings. However, considering the limitations (Chinese target population with differing and varying indications and treatment modalities) of these data, they can, at best, be considered supportive. In the initial submission, PRES was listed in the SmPC section 4.8 table on ADRs with the frequency of 0.1% (uncommon) based on one case of grade 4 PRES reported in the fruquintinib group vs 0 in placebo in the pooled data (ISAS-mCRC). However, as an additional case was reported in post marketing data, and this event is an ADR reported for VEGF inhibitors, a warning with the description of frequency of this event was reflected in SmPC Section 4.4. The warning here also informs that a diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI) and that in patients developing PRES, discontinuation of fruquintinib, along with control of hypertension and supportive medical management of other symptoms, are recommended.

Furthermore, one case of aortic dissection was received from post-marketing surveillance and aortic dissection was added in the list ADRs in section 4.8 with frequency not known (cannot be estimated from available post-marketing data), given that it is a serious and life-treating event, reported also for many other VEGF inhibitors. No other potential ADRs were evident on clarification in the Applicant´s on-line pharmacovigilance database since the end of the reporting period of 03 September 2022.

Additional safety considerations

No data are available on pregnancy in humans. Considering that fruquintinib has, because of its mechanism of action, a potential to cause foetal harm when administered to pregnant women, and further taking into account the severity of the pertinent non-clinical findings, the SmPC text in section 4.6 has been revised to better represent the available data to provide advice concerning the length of contraception after fruquintinib treatment, and the length of abstaining from breastfeeding.

From the safety database all the adverse reactions reported in clinical trials and post-marketing data have been included in the SmPC.

Additional expert consultations

N/A

Assessment of paediatric data on clinical safety

N/A

3.6.13. Conclusions on the clinical safety

Overall, the safety profile of fruquintinib monotherapy plus best supportive care (BSC), in the pivotal phase 3 study (FRESCO-2) in heavily pretreated mCRC patients appeared to be manageable compared to placebo plus BSC. Open issues have been sufficiently clarified. No new or unexpected findings were apparent and the safety profile of fruquintinib is, in general, in accordance with what is expected for this type of medicinal product involving the VEGF inhibition pathway and with what has been previously reported for this type of heavily pretreated mCRC patients.

In the pivotal phase 3 FRESCO-2 study the most frequently observed TEAEs for fruquintinib were hypertension, asthenia, decreased appetite, diarrhoea, hypothyroidism, fatigue, and palmar-plantar erythrodysaesthesia syndrome, which are all known adverse events with medications involving the VEGF inhibition pathway.

Incidences TEAEs leading to permanent discontinuation, and SAEs were not significantly different between the two groups. Importantly, treatment emergent deaths were less frequent in patients on the fruquintinib therapy. Pooling of data did not give rise to new or unexpected safety findings.

The safety profile is considered acceptable in the intended population with advanced cancer in a late line setting.

3.7. Risk Management Plan

3.7.4. Safety concerns

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table 39: SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

3.7.4.1. Discussion and Conclusions on the safety specification

The undesirable effects of identified for fruquintinib are in line with the known risks for products involving vascular endothelial growth factor pathway inhibition. None of these risks are considered to require additional pharmacovigilance actions or additional risk minimisation measures. The safety specification is considered acceptable.

3.7.4.2. Protected Personal Data (PPD) and Commercially Confidential Information (CCI) considerations for the RMP Safety Specification

The Safety Specification of the RMP does not contain PPD/CCI.

The applicant is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Protected Personal Data (PPD) and identification of Commercially Confidential Information (CCI) in the updated RMP submitted with the responses.

3.7.5. Pharmacovigilance plan

No additional pharmacovigilance activities are planned.

The PRAC, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

3.7.6. Risk minimisation measures

The PRAC having considered the data submitted was of the opinion that:

the proposed routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

3.7.7. Conclusion

The CHMP considers that the risk management plan version 0.3 (dated 12 March 2024) is acceptable.

3.8. Pharmacovigilance

3.8.4. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

3.8.5. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 04.09.2018. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

3.9. Product information

3.9.4. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3.9.5. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Fruzaqla (fruquintinib) is included in the additional monitoring list as it contains a new active substance which on 1 January 2011, was not contained in any medicinal product authorised in the EU.

4. Benefit-Risk Balance

4.1. Therapeutic Context

4.1.4. Disease or condition

The following indication is approved:

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.

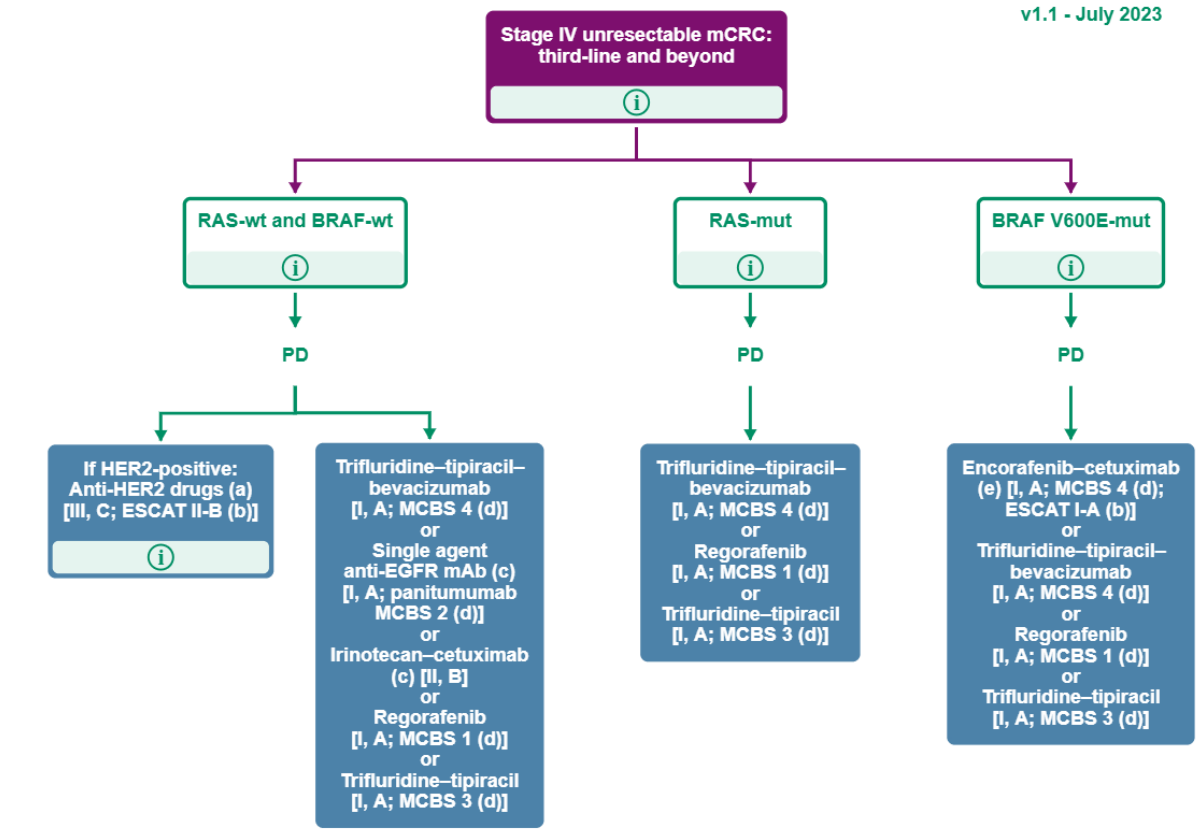
CRC is the third most common cancer worldwide, with 1.1 million new cases per year, and is the 2nd leading cause of cancer death (Sung et al. CA Cancer J Clin 2021). In the EU it is the second most frequently occurring cancer and accounted for the second highest number of cancer deaths in 2018. For an advanced CRC without possibility for treatment with a curative intent (generally requiring systemic therapy and surgery and/or ablative techniques), the goal of the treatment is to improve tumour-related symptoms, delay progression, and prolong survival, while maintaining a good quality of life (Cervantes et al. Ann of Oncol 2022).

4.1.5. Available therapies and unmet medical need

In advanced CRC systemic therapy with a non-curative intent follows the continuum of care concept, exposing the patient to active medicinal products sequentially. 1st line therapy is usually followed by maintenance therapy. After 2nd line therapy, 3rd line and beyond therapy can be considered.

Established 1st and 2nd line systemic treatments include cytotoxic chemotherapy with fluoropyrimidine-, oxaliplatin-, and irinotecan-based-regimens (Benson, 2021, Van Cutsem, 2014). These can be administered with or without anti-angiogenic biologic agents (anti-VEGF or anti-VEGFR-2), such as bevacizumab, aflibercept, or ramucirumab; or, for patients with *RAS* wild-type tumours, anti-EGFR therapy, such as cetuximab or panitumumab. A small proportion (3%-5%) of patients with sporadic advanced CRC have dMMR/MSI-H (Koopman, 2009) and are eligible for approved immunotherapy. An additional approved option for selected patients (8% to 12%) with *BRAF* V600E-mutated tumours is encorafenib in combination with cetuximab. Larotrectinib or entrectinib can be considered for NTRK fusion positive mCRC (1%). Additional treatment options include trifluridine-tipiracil, regorafenib, trifluridine-tipiracil-bevacizumab, and antiHER2-agents for HER2-positive tumours (3-4%).

According to ESMO guideline (2023), use of ICIs is for 1st – 2nd line, BRAFi for 2nd – 3rd line and beyond, trifluridine-tipiracil and regorafenib for 3rd line and beyond, antiHER2 for 2nd line and beyond, and TRKi for 3rd line and beyond. Antiangiogenic therapy is an established therapy in mCRC, with EU approvals for bevacizumab, aflibercept, and ramucirumab. The recommendations for 3rd line and beyond therapy as recommended by ESMO are shown below in Figure 25. Of these HER2-directed therapies are not at present approved in the EU. The latest treatment option in 3rd line is trifluridine-tipiracil-bevacizumab, with a positive opinion by the EC in 2023 and addition to ESMO living guidelines as of July 2023. When the patient has exhausted available standard therapies, a high unmet medical need prevails.



Purple: general categories or stratification; blue: systemic anticancer therapy; white: other aspects of management.

EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; mAb, monoclonal antibody; MCBS, ESMO-Magnitude of Clinical Benefit Scale; mCRC, metastatic colorectal cancer; mut, mutant; PD, progressive disease; wt, wild-type.

(a) For a summary of recommended anti-HER2 regimens for mCRC see Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2022.10.003.

(b) ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and

Precision Medicine Working Group. (Mateo, 2018) See Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.10.003, for more information on ESCAT scores.

(c) In *RAS*-wt patients not previously treated with anti-EGFR monoclonal antibodies.

(d) ESMO-MCBS v1.1 (Cherny, 2017) was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).

(e) Treatment for *BRAF*-mut patients if not used in the second line.

Figure 25: 3rd line and beyond therapy as recommended by ESMO (Cervantes et al. Ann Oncol 2022, updated in ESMO Metastatic Colorectal Cancer Living Guidelines, v1.1 July 2023)

4.1.6. Main clinical studies

FRESCO-2 is a global, multi-centre, double-blind, phase 3 trial in mCRC comparing fruquintinib and BSC to placebo and BSC, carried out in USA, Europe, Japan, and Australia. Subjects with mCRC must have been previously treated with standard approved therapies: fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and, if RAS wild-type, an anti-EGFR therapy. Subjects with dMMR/MSI-H tumours must have been treated with ICIs. Subjects must have

progressed on or been intolerant to either trifluridine-tipiracil or regorafenib, and use of both was permitted. Prior use of BRAF inhibitor for BRAFmt tumours was added in amendment #2. Thus, the treatment setting in FRESCO-2 is 4th line and beyond.

934 patients were enrolled, of which 691 were randomized in 2:1 ratio to fruquintinib 5 mg (n=461) or to placebo (n=230), PO, QD, on a 3 weeks on/1 week off schedule. Randomization was stratified by 1) prior therapy with trifluridine-tipiracil vs regorafenib vs both trifluridine-tipiracil and regorafenib, 2) RAS status (wt vs mt), and 3) duration of metastatic disease (≤ 18 months vs > 18 months). At the final analysis, 70.9% of patients had died and 87.6% had died or had PD, indicating maturity of the data.

The prior diagnostics and management of patients mainly follow current European guidelines, as 99.9% had received prior fluoropyrimidine, 99.6% oxaliplatin, 99.6% irinotecan, 96.4% VEGFi, and as 36.9% were RASwt, 38.8% had received EGFRi. 52.2% had received trifluridine-tipiracil, 8.4% regorafenib, and 39.4% both. 502 patients (72.6%) had 4 or more prior treatment lines for metastatic disease and the median number of prior anticancer treatment lines for metastatic disease was 4. Thus, the patients had exhausted viable treatment options and placebo was an acceptable comparator.

The primary endpoint was OS. The key secondary endpoint was PFS evaluated by the investigator. Secondary efficacy endpoints were ORR, DCR, and DOR.

4.2. Favourable effects

FRESCO-2 met its primary endpoint of OS, with a statistically significant improvement among patients in the fruquintinib arm compared with the placebo arm (HR, 0.662; 95% CI, 0.549-0.800; stratified log-rank test P <0.001), with the reduction in risk of death by 34%. The absolute increase in median OS was 2.6 months, with a median OS in the fruquintinib group of 7.4 months (95% CI, 6.7-8.2) vs. 4.8 months (95% CI, 4.0-5.8) in the placebo group.

FRESCO-2 met its key secondary endpoint of investigator-assessed PFS, with a statistically significant improvement (HR, 0.321; 95% CI, 0.267-0.386; P < 0.001), indicating a 68% reduction in risk of death or progression. Median PFS in the fruquintinib group was 3.7 months (95% CI, 3.5-3.8) compared with 1.8 months (95% CI, 1.8-1.9) in the placebo group.

The confirmed ORR (CR + PR) was 1.5% (7 patients with PR) in the fruquintinib group and 0% in the placebo group (2-sided P = .059).

The DCR (CR + PR + SD for at least 7 weeks) was statistically significantly higher in the fruquintinib group (256 patients [55.5%]) compared with the placebo group (37 patients [16.1%]) (2-sided P < .001).

In the very rare cases were patients achieved a PR, DoR was 10.7 months (95% CI: 3.9-not estimable), with 5/7 for whom no death or PD occurred at the DCO. This suggests that when responses are achieved, DoR is clinically relevant.

4.3. Uncertainties and limitations about favourable effects

Not applicable.

4.4. Unfavourable effects

In the single pivotal phase 3 FRESCO-2 study, the overall frequencies of TEAEs in the different TEAE categories for fruquintinib vs placebo were respectively: any TEAE 98.9% vs 92.6%; Grade ≥ 3 TEAEs 62.7% vs. 50.4%, treatment-related TEAEs 86.6% vs. 56.5%; treatment-related Grade 3 TEAEs 36.0% vs 11.3%; serious TEAEs 37.5% vs. 38.3%; AESIs 80.7% vs. 53.0%; TEAEs leading to treatment discontinuation 20.4% vs. 21.3%; TEAEs leading to dose reduction 24.1% vs. 3.9%; TEAEs leading to dose interruption 46.7% vs. 26.5%; TEAEs leading to death 10.5% vs. 19.6%.

The most common TEAEs by Preferred Terms in FRESCO-2 study for fruquintinib vs. placebo were hypertension (36.8% vs 7.7%), asthenia (34.0% vs 7.7%), decreased appetite (27.2% vs 17.4%), diarrhoea (24.1% vs 10.4%), hypothyroidism (20.5% vs 0.4%), fatigue (20.0% vs 16.1%), and palmar-plantar erythrodysaesthesia syndrome (19.3% vs 2,6%).

The most common ≥ G3 TEAEs by PTs in FRESCO-2 study for fruquintinib vs. placebo were hypertension (13.6% vs. 0.9%), asthenia (7.7% vs 3.9%), palmar-plantar erythrodysaesthesia syndrome (6.4% vs. 0%), fatigue (3.9 % vs 0.9%), diarrhoea (3.5% vs. 0%) and abdominal pain (3.1% vs 3.0%).

Serious TEAEs between treatment groups fruquintinib vs. placebo were reported by 37.5% vs 38.3% of patients. The most frequent serious events were disease progression (5.9% vs 12.2%), general physical health deterioration (2.2% vs 2.2%), pneumonia (1.8% vs. 0.4%), abdominal pain (1.5% vs 0.9%), and intestinal obstruction (1.5% vs 2.6%). The incidence of treatment emergent fatal cases in the FRESCO-2 study was higher in the placebo group (19.5%) than in the fruquintinib group (10.5%). The most frequent event was disease progression (5.7% in fruquintinib group vs. 11.7% in placebo group).

TEAEs leading to permanent treatment discontinuation between the treatment groups were comparable: fruquintinib 20.4% vs placebo 21.3%.

Posterior reversible encephalopathy syndrome (PRES), a rare and serious event associated with using VEGF pathway inhibitors, was reported with fruquintinib: one (0.1%) case of grade 4 PRES was reported in ISAS-mCRC, and one case occurred in post-marketing with fruquintinib.

There were no new or unexpected safety findings in the fruquintinib in FRESCO-2 study or pooled safety database when compared to the known safety profiles previous fruquintinib monotherapy studies and similar medicinal products also involving the VEGF inhibition pathway.

In the pooled data, the overall incidence of AESIs in ISAS-mCRC was higher in fruquintinib-treated subjects than in the placebo group, i.e. hypertension (47.5% vs 11.8%), dermatological toxicities (46.5% vs 11.5%, including palmar-plantar erythrodysaesthesia syndrome reported in 32.7% vs 8.5%), hepatic function abnormal events (36.4% vs 23.5%, including 2 fatal cases), proteinuria (32.9% vs 15.1%), thyroid dysfunction (33.3% vs 4.3%), haemorrhagic events (26.5% vs 14.6% including 4 [0.5%] fatal cases), embolic and thrombotic events (3.6% vs 1.5%, including two [0.3%] fatal cases), gastrointestinal perforation (2.8% vs 0.5%, with mainly serious cases).

4.5. Uncertainties and limitations about unfavourable effects

Based on data presented no apparent reasons were evident for the observed higher dose reduction figures and higher frequencies of Grade ≥ 3 AESIs among females. More specifically, no specific characteristics or other attributes were evident that could explain these gender differences, for example, weight, body surface area, hormonal aspects, or treatment compliance, among others.

4.6. Effects Table

Table 40: Effects Table for fruquintinib in mCRC according to FRESCO-2

Effect	Short Description	Unit	Fruquintinib (n=461)	Placebo (n=230)	Uncertainties/ Strength of evidence	References
Favourable Effects (FRESCO -2 study)						
Median OS	From date of randomization to death from any cause	Months (95% CI)	7.4 (6.7-8.2)	4.8 (4.0-5.8)	Fit and highly selected study population	FRESCO-2 CSR
			Stratified HR (95% CI) 0.662 (0.549, 0.800) Adjusted 2-sided *P* <.001		Mature data (70.9% died)	
Median PFS	From date of randomization to progression or death from any cause	Months (95% CI)	3.7 (3.5, 3.8)	1.8 (1.8, 1.9)	Investigator-assessed. Double-blind potentially not holding due to AEs	FRESCO-2 CSR
			Stratified HR (95% CI) 0.321 (0.267, 0.386) Adjusted 2-sided *P* <.001		Mature data (87.6% died or had PD)	
Unfavourable Effects (FRESCO-2 study)						
Grade ≥ 3		n (%)	286 (62.7)	116 (50.4)		FRESCO-2 CSR
TEAEs treatment-related		n (%)	395 (86.6)	130 (56.5)	treatment related = implying causality	FRESCO-2 CSR
Treatment-related, Grade ≥ 3		n (%)	164 (36.0)	26 (11.3)		FRESCO-2 CSR
Serious treatment related TEAE		n (%)	171 (37.5)	88 (38.3)		FRESCO-2 CSR
TEAE leading to treatment discontinuation		n (%)	93 (20.4)	49 (21.3)		FRESCO-2 CSR
TEAE leading to dose interruption		n (%)	213 (46.7)	61 (26.5)		FRESCO-2 CSR
TEAE leading to dose reduction		n (%)	110 (24.1)	9 (3.9)		FRESCO-2 CSR
Hypertension	All grade; Gr ⩾ 3	n (%)	168(36.8); 62 (13.6)	20 (8.7); 2 (0.9)		FRESCO-2 CSR
Palmar-plantar erythrodysaesthesia syndrome	All grade; Gr ⩾ 3	n (%)	88 (19.3); 29 (6.4)	6 (2.6); 0		FRESCO-2 CSR
Proteinuria	All grade; Gr ⩾ 3	n (%)	79 (17.3); 8 (1.8)	12 (5.2);2 (0.9)		FRESCO-2 CSR

Abbreviations: AE = adverse event, ALT = alanine aminotransferase, AST= aspartame aminotransferase, BOR = best overall response, CI = confidence interval, CR = complete response, CSR = clinical study report, DCR = disease control rate, Gr = Grade according to NCI Common Terminology Criteria for Adverse Events (CTCAE), HR = hazard ratio, N = number of patients, ORR = overall response rate, OS = overall survival, PD = progressive disease, PFS = progression-free survival, PR = partial response, SD = stable disease, TEAE = treatment emergent adverse event,.

4.6.4. Importance of favourable and unfavourable effects

Advanced CRC treated with non-curative intent is a lethal cancer with an unmet medical need. The continuum of care means sequential systemic therapy, in which best survival times are reached with 1st line therapy. When moving to 2nd and 3rd line therapies, the obtained OS benefits shorten. For selected patients, 4th line therapy and beyond can be considered.

As a phase 3 trial comparing fruquintinib to placebo and with OS as a robust primary endpoint FRESCO-2 was methodologically sound. The final analysis was made with a high maturity of the data. FRESCO-2 did not contain a cross-over option, protecting the OS data from confounding effects of one-way cross-over.

The heavily pretreated population in FRESCO-2 illustrates a last line treatment setting. In all 95.7% of patients had received at least 3 lines to metastatic disease, thus receiving fruquintinib or placebo as a 4th line and beyond therapy. As prior treatment with standard approved therapies was mandatory, choices for next line therapy were very limited or non-existent. This is also evident from the fact, that placebo-control was accepted by a variety of ethical boards and health authorities.

The most important favourable effect and primary outcome in FRESCO-2 is a statistically significant increase of 2.6 months in median OS in fruquintinib arm compared to placebo arm. Although it is modest, it is also interpreted as a 50% increase in OS, as median OS (95% CI) in placebo arm was 4.8 months (4.0, 5.8) and 7.4 months (6.7, 8.2) in fruquintinib arm. Such benefit is clinically relevant in these patients without viable therapeutic alternatives. 96.4% of patients had been treated with prior anti-VEGF, yet the treatment effect with fruquintinib, a VEGFR1-3 inhibitor, was seen. 39.4% of patients had received both trifluridine-tipiracil and regorafenib, indicating a heavily pretreated population, but demonstrating a similar treatment effect in OS and PFS as the overall population. The key secondary outcome, which strengthens the primary outcome, is a statistically significant doubling of median PFS (3.7 months (95% CI: 3.5, 3.8) with fruquintinib, 1.8 months (95% CI: 1.8, 1.9) with placebo). This is very short in this last line setting, but is consistent with the observed OS increase.

The safety data for fruquintinib is derived mainly from the single pivotal phase 3 FRESCO-2 study (fruquintinib N=465, placebo N=230) in a mCRC population relevant for the European setting. Supportive phase 3 safety data come from the FRESCO study (fruquintinib N=278, placebo N=137) including only Chinese patients. The pool of placebo-controlled studies comprises 1172 patients (fruquintinib N=781, placebo group N=391) and an overlapping expanded pool incorporates in addition the open label studies in mCRC (fruquintinib N=911) of the current safety database. The database is considered sufficiently large for identification of the most frequent adverse reactions.

There were no new or unexpected safety findings in the fruquintinib safety database compared to the known safety profiles of similar medicinal products also involving the VEGF inhibition pathway and to safety findings previously reported for similar patient populations. The presented safety database was considered adequate for benefit/risk assessment. There still remains some uncertainties, e.g., it could not be ascertained if the observed OS gender difference was or was not associated to a possible clinically meaningful gender difference in the safety/tolerability of fruquintinib. However, this issue is not pursued further, as it is not expected to impact on the overall safety assessment.

The most frequently reported SAEs in fruquintinib group in ISAS-mCRC were intestinal obstruction, pneumonia, and hypertension, and the TEAEs leading to death occurring most frequently with fruquintinib were disease progression and pneumonia. There was a comparable rate of SAEs between fruquintinib and placebo groups, and the 12.3% increase of Grade ≥3 toxicity in fruquintinib group in FRESCO-2 could be supportive of an acceptable safety profile in the intended population.

The findings in FRESCO-2 are a part of a continuum with studies indicating the efficacy and safety of antiangiogenic therapy in mCRC. For an extension of indication in 3rd line in the EU in 2023, the combination with trifluridine-tipiracil and bevacizumab improved OS with 3.3 months in mCRC patients, of whom 72% had prior treatment with an anti VEGF antibody. Thus, the present efficacy and safety findings are indirectly supported by other trial data, including also earlier data for bevacizumab, aflibercept, and ramucirumab in mCRC.

4.6.5. Balance of benefits and risks

Efficacy

Although modest, the observed overall survival benefit of 2.6 months in fit patients with refractory mCRC without evidence-based viable treatment options is considered clinically relevant. This was further strengthened by the benefit observed in median PFS and in BOR.

Safety

Fruquintinib treatment compared to placebo is, as expected, associated with some toxicity, but no new major safety concerns were clearly evident. While the toxicity of fruquintinib is not negligible, the safety profile is considered acceptable in the intended population with advanced cancer in a late line setting.

Quality

The quality of this product is considered adequate. It is expected that the product, when used in accordance with the conditions defined in the SmPC, should have the predicted clinical performance.

In conclusion, the efficacy of fruquintinib outweighs its toxicity, which is typical of other TKIs involving VEGF(R) pathway with a safety profile that is considered acceptable in the intended population with advanced cancer in a late line setting. The overall benefit/risk balance of Fruzaqla is positive.

4.6.6. Additional considerations on the benefit-risk balance

Third party intervention during the evaluation of Fruzaqla

The CHMP received, during the assessment of this application, a statement from Digestive Cancers Europe (DiCE) Patient Advisory Committee on fruquintinib for the treatment of mCRC patients. The statement discussed treatment options in 3rd line and asked for approval in 3rd line and beyond.

The CHMP considered this intervention in the context of its assessment and concluded that the observations put forward were already known by the CHMP, and as such had no impact on the CHMP assessment or its conclusions.

4.7. Conclusions

The overall benefit/risk balance of Fruzaqla is positive, subject to the conditions stated in section 'Recommendations'.

5. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Fruzaqla is favourable in the following indication(s):

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.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that fruquintinib is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.