Global Trial of Fruquintinib in Refractory Metastatic Colorectal Cancer

Dasari, et al.

FRESCO-2 Study Protocol

FRESCO-2 Statistical Analysis Plan (SAP)

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 COLON CANCER (FRESCO-2)

Short Title	A global, randomized, placebo-controlled phase 3 study of fruquintinib in patients with refractory metastatic colorectal cancer
Acronym	FRESCO-2
Investigational Product(s)	Fruquintinib
Protocol Number	2019-013-GLOB1
Version Number	1.0
Version Date	27 February 2020
Amendment	Original protocol
IND Number	131038
Principal Investigator	TBD
Sponsor	Hutchison MediPharma Limited NO.4, Lane 720, Cailun Road, Zhangjiang Hi-tech Park, Shanghai, China Post Code: 201203

Confidentiality Statement

STATEMENT OF COMPLIANCE

The study will be conducted in compliance with this clinical study protocol, Good Clinical Practices (GCP) as outlined by ICH E6(R2), and all applicable local and national regulatory requirements. Enrollment at any clinical study site may not begin prior to that site receiving approval from the ethics committee of record for the protocol and all materials provided to potential participants.

Any amendments to the protocol or changes to the consent document will be approved before implementation of that amendment. Reconsent of previously enrolled participants may be necessary depending on the nature of the amendment.

The Principal Investigator will ensure that changes to the study plan as defined by this protocol will not be made without prior agreement from the Sponsor and documented approval from the ethics committee of record, unless such a change is necessary to eliminate an immediate hazard to the study participants.

All personnel involved in the conduct of this study have completed Human Patients Protection and GCP Training as outlined by their governing institution.

SPONSOR'S APPROVAL

Title	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 (FRESCO-2)
Protocol Number	2019-013-GLOB1
Version Number	1.0
Version Date	25 Feb 2020
Amendment	Original Protocol

The design of this study as outlined by this protocol has been reviewed and approved by the sponsor's responsible personnel as indicated in the signature table below.

Name: [last name, first name] [redacted]	**Title:** Chief Medical Officer Hutchison MediPharma International, Inc
Signature: [redacted]	**Date:**[DD Month YYYY] [redacted]

Name: [last name, first name] [redacted]	**Title:** Chief Scientific Officer Head of Clinical and Regulatory Hutchison MediPharma, Limited
Signature: [redacted]	**Date:**[DD Month YYYY] [redacted]

INVESTIGATOR'S AGREEMENT

I have read the protocol, appendices, and accessory materials related to Study 2019-013-GLOB1 and agree to the following:

- To conduct this study as described by the protocol and any accessory materials
- To protect the rights, safety, and welfare of the participants under my care
- To provide oversight of all personnel to whom study activities have been delegated
- To control all investigational products provided by the sponsor and maintain records of the disposition of those products
- To conduct the study in accordance with all applicable local and national regulations, the requirements of the ethics committee of record for my clinical site, and Good Clinical Practices as outlined by ICH E6(R2).
- To obtain approval for the protocol and all written materials provided to participants prior to initiating the study at my site
- To obtain informed consent – and updated consent in the event of new information or amendments – from all participants enrolled at my study site prior to initiating any study-specific procedures or administering investigational products to those participants
- To maintain records of each patient's participation and all data required by the protocol

Name [Last name, first name]	**Title** [Title at institution]	**Institution** [Address]
Signature		**Date** [DD Month YYYY]

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase/glutamic-pyruvic transaminase
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase/glutamic-oxalacetic transaminase
$AUC_{0\text{-}24\ hr}$	Area under the concentration-time curve from 0 to 24 hours after drug administration
BCRP	Breast cancer resistance protein
BSC	Best supportive care
CDK	Cyclin-dependent kinase
CEA	Carcino-embryonic antigen
CHL	Chinese Hamster Lung
c-MET	Mesenchymal epithelial cells transforming factor
CR	Complete response
CRC	Colorectal cancer
CRO	Contract research organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
DCR	Disease control rate
dMMR	Deficient mismatch repair
DoR	Duration of response
IDMC	Independent Data Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of treatment
EC	Ethics Committee
EOT	End of Treatment
FDA	Food and Drug Administration

Abbreviation	Definition
FDG-PET	Fluorodeoxyglucose positron emission tomography
IB	Investigator's brochure
IC50	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonization
IDMC	Independent data monitoring committee
INR	International normalized ratio
ITT	Intent-to-treat
IWRS	Interactive web response system
LDH	Lactic dehydrogenase
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MID	Minimally important difference
mL	Milliliter
MRI	Magnetic resonance imaging
MSI-H	High levels of microsatellite instability
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	The National Cancer Institute Common Terminology Criteria for Adverse Event
NE	Not evaluable
NOAEL	No observed adverse effect level
NSCLC	Non-small-cell lung cancer
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive disease
PDGFR	Platelet-derived growth factor receptor
PFS	Progression-free survival
PK	Pharmacokinetic
PO	*Per os* (oral administration)
PPE	Palmar-plantar erythrodysesthesia
PR	Partial response

Abbreviation	Definition
PS	Performance status
PT	Preferred term
PTT	Prothrombin time
QD	*Quaque die* (once daily)
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SD	Stable disease
SOC	System organ class
TSH	Thyroid stimulating hormone
TTD	Time to deterioration
TTP	Time to progression
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
WHO	World Health Organization

1. SYNOPSIS

Title	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 Colon Cancer (FRESCO-2)
Short Title	A global, randomized, placebo-controlled phase 3 study of fruquintinib in patients with refractory metastatic colorectal cancer
Acronym	FRESCO-2
Phase	3
Study Design	This is a global, randomized, double-blind, placebo-controlled, multicenter phase 3 clinical trial to compare the efficacy and safety of fruquintinib plus best supportive care (BSC) versus placebo plus BSC in subjects with refractory metastatic colorectal cancer (mCRC). Approximately 522 subjects will be randomized in a 2:1 ratio to either the fruquintinib plus BSC treatment group or the placebo plus BSC treatment group. Randomization will be stratified by the following factors: • Prior therapy with trifluridine/tipiracil (TAS-102) versus regorafenib versus both trifluridine/tipiracil (TAS-102) and regorafenib • RAS status (wild type versus mutant) • Duration of metastatic disease (<18 months versus ≥18 months) Subjects will receive study treatment with each 4-week cycle consisting of 3 weeks of daily oral (PO) study medication and 1 week of study drug interruption (3 weeks on/1 week off). Tumor evaluation will be performed by imaging (computed tomography [CT] or magnetic resonance imaging [MRI] scan) every 8 weeks until there is progression of disease (PD), death, new anti-cancer treatment, or study completion, whichever comes first. Safety parameters will include adverse events (AE), and results from laboratory tests, vital signs, ECG, and echocardiogram. Post-discontinuation anti-tumor treatment and survival follow up after PD will also be recorded.
Rationale	Colorectal cancer (CRC) is the second most common malignancy in both men and women and the third most common cause of cancer-related death in the US, with an estimated 145,600 new cases and 51,020 deaths in 2019. Similarly, CRC is a major global health issue, with an estimated 1.8 million new cases and 880,000 deaths in 2018 worldwide (Bray 2018). There is no standard of care for patients who have progressed on approved standard-of-treatments, including chemotherapy, relevant biologics and TAS-102 and/or regorafenib. Patients who are well enough to receive additional therapy following all standard therapies either are considered for treatment on a clinical trial when available or are re-challenged with agents such as 5-FU or bevacizumab. Consequently, there is an unmet medical need for new medications that are safe and effective in patients with refractory mCRC who have progressed on, or had intolerable toxicity from, available standard systemic therapies, and for whom no effective therapy or standard of care exists. Fruquintinib is a novel, potent, and highly selective small molecule tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFR)-1, -2, and -3. In the FRESCO trial conducted in China, fruquintinib improved the median overall survival in patients with mCRC in a third-line or later setting when compared to placebo (median overall survival 9.3 months versus

	6.6 months; hazard ratio for death 0.65 (95% CI: 0.51-0.83; p < 0.001)(Li 2018). The results from this pivotal trial led to fruquintinib's approval in China. The safety profile of fruquintinib from an ongoing phase 1/1b study in the US is consistent with that of clinical studies performed in China, as well as published data for other small molecule VEGF inhibitors. The pharmacokinetic (PK) profile of fruquintinib in the US phase 1/1b study is also comparable to the PK profile in patients treated with fruquintinib in China at the same dose and dosing regimen (5 mg PO, QD, 3 weeks on, 1 week off, for each 4-week cycle). These data showing favorable efficacy and acceptable safety indicates fruquintinib is a promising candidate for development as a new treatment for patients with refractory mCRC and may address an unmet medical need globally. This global, multicenter, randomized, double-blind, placebo-controlled clinical trial will compare the efficacy and safety of fruquintinib in combination with BSC, to placebo in combination with BSC, in patients with refractory metastatic colorectal cancer who have progressed on, or were intolerant to, TAS-102 and/or regorafenib. Patients must have also received prior standard therapies, including two lines of chemotherapy (fluoropyrimidine-, oxaliplatin-, and irinotecan-based), a biological VEGF inhibitor, and, if RAS wild type, an EGFR inhibitor. Patients with MSI-H/MMR deficient tumors must have also received an immune checkpoint inhibitor if approved and available and if deemed appropriate.
Target Population	The study population will consist of subjects ≥18 years of age with histologically and/or cytologically documented metastatic colorectal adenocarcinoma who progressed on, or were intolerant to, all standard chemotherapies and relevant biologics and TAS-102 and/or regorafenib.
Inclusion/Exclusion Criteria	**Inclusion Criteria** Subjects may be enrolled in this study only if they satisfy all the following criteria: 1. Provide written informed consent; 2. Age ≥18 years; 3. Histologically and/or cytologically documented metastatic colorectal adenocarcinoma; 4. 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 one 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. 5. Subjects with microsatellite-high (MSI-H) or mismatch repair deficient (dMMR) tumors must have been treated with immune checkpoint inhibitors if approved and available in the subject's country and if deemed appropriate; 6. Subjects who received oxaliplatin in the adjuvant setting must have progressed within 6 months of completing adjuvant therapy; 7. Body weight ≥40kg; 8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1;

9. Have measurable disease according to RECIST Version 1.1 (RECIST v1.1), assessed locally. Tumors that were treated with radiotherapy are not measurable per RECIST v1.1, unless there has been documented progression of those lesions.
10. Expected survival >12 weeks.
11. For female subjects of childbearing potential and male subjects with partners of childbearing potential, agreement to use a highly effective form(s) of contraception, that results in a low failure rate (<1% per year) when used consistently and correctly, starting during the screening period, continuing throughout the entire study period, and for 90 days after taking the last dose of study drug. Such methods include: oral hormonal contraception (combined estrogen/ progestogen, or progestogen-only) associated with inhibition of ovulation together with a barrier method (eg, diaphragm, always containing a spermicide), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal ligation, vasectomized partner, or sexual abstinence. Oral contraception should always be combined with an additional contraceptive method (ie, barrier method) because of a potential interaction with the study drug. The same criteria are applicable to male subjects involved in this clinical trial if they have a partner of childbirth potential, and male subjects must always use a condom.

Exclusion Criteria:

Subjects are not eligible for enrollment into this study if they have any of the following criteria:

1. Absolute neutrophil count (ANC) $<1.5\times10^9$/L, platelet count $<100\times10^9$/L, or hemoglobin <9.0 g/dL. Blood transfusion within 1 week prior to enrollment for the purpose of increasing the likelihood of eligibility is not allowed;
2. 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;
3. ALT or AST >2.5 × ULN in subjects without hepatic metastases;

   ALT or AST >5 × ULN in subjects with hepatic metastases;
4. Serum electrolytes, potassium, calcium, or magnesium levels outside of the normal laboratory reference range, and clinically significant in the investigator's judgment;
5. 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.
6. 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 conversion between qualitative and quantitative results, please see Appendix 8;
7. Uncontrolled hypertension, defined as: systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg despite optimal medical management;
8. International Normalized Ratio (INR) >1.5 x ULN or activated partial thromboplastin time (aPTT) >1.5 × ULN, unless the subject is currently receiving or intended to receive anticoagulants for prophylactic purposes;
9. History of, or active gastric/duodenal ulcer or ulcerative colitis, active hemorrhage of an unresected gastrointestinal tumor, history of perforation or fistulas; or any other condition that could, in the

	investigator's judgment, result in gastrointestinal hemorrhage or perforation; within the 6 months prior to screening; 10. History or presence of hemorrhage from any other site (eg, hemoptysis or hematemesis) within 2 months prior to screening; 11. History of a thromboembolic event, including deep vein thrombosis (DVT), pulmonary embolism (PE), or arterial embolism within 6 months prior to screening. 12. Stroke and/or transient ischemic attack within 12 months prior to screening; 13. Clinically significant cardiovascular disease, including but not limited to acute myocardial infarction or coronary artery bypass surgery within 6 months prior to enrollment, 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; 14. Mean corrected QT interval using the Fridericia method (QTcF) >480 msec or any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as hypokalemia, congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in a first-degree relative. 15. Concomitant medications with a known risk of causing QT prolongation and/or torsades de pointes (See list in Appendix 3 source list is continuously updated online at www.crediblemeds.org). 16. Systemic anti-neoplastic therapies (except for those described in Exclusion Criterion 18) or any investigational therapy within 4 weeks prior to the first dose of study drug, including chemotherapy, radical radiotherapy, hormonotherapy, biotherapy and immunotherapy; 17. Systemic small molecule targeted therapies (eg, tyrosine kinase inhibitors) within 5 half-lives or 4 weeks (whichever is shorter) prior to the first dose of study drug; 18. Palliative radiotherapy for bone metastasis/lesion within 2 weeks prior to the initiation of study drug; 19. Brachytherapy (ie, implantation of radioactive seeds) within 60 days prior to the first dose of study drug. 20. Use of strong inducers or inhibitors of CYP3A4 within 2 weeks before the first dose of study drug; (see Appendix 3 for a list of applicable drugs); 21. Surgery or invasive procedure (ie, a procedure that includes a biopsy; central venous catheter placement is allowed) within 60 days prior to the first dose of study drug or unhealed surgical incision; 22. Any unresolved toxicities from a previous antitumor treatment greater than National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE) v5.0 grade 1 (except for alopecia or neurotoxicity grade≤2). 23. Known human immunodeficiency virus (HIV) infection; 24. Known history of active viral hepatitis. For subjects with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated. Subjects with HCV infection who are currently on treatment are eligible if they have an undetectable HCV viral load. 25. Clinically uncontrolled active infection requiring IV antibiotics; 26. Tumor invasion of a large vascular structure (eg, pulmonary artery, superior or inferior vena cava);

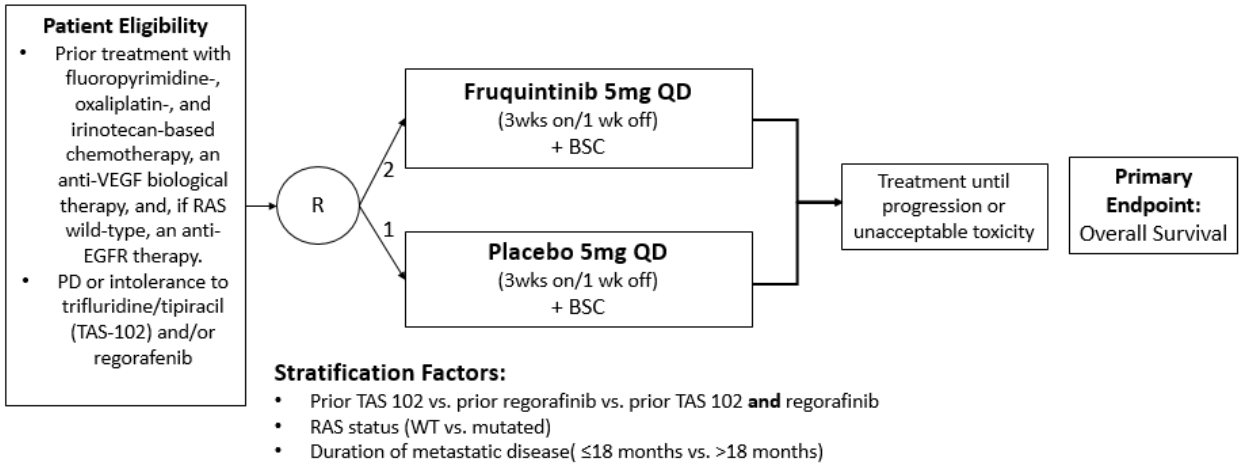
	27. Women who are pregnant or lactating; 28. Brain metastases and/or spinal cord compression untreated with surgery and/or radiotherapy, and without clinical imaging evidence of stable disease for 14 days or longer; subjects requiring steroids within 4 weeks prior to start of study treatment are excluded; 29. No other malignancy, except for non-melanoma skin cancer, *in situ* cervical ca or bladder ca (Tis and T1) that have been adequately treated during the 5 years prior to screening; 30. Inability to take medication orally, dysphagia or an active gastric ulcer resulting from previous surgery (eg, gastric bypass) or a severe gastrointestinal disease, or any other condition that investigators believe may affect absorption of the investigational product; 31. Other disease, metabolic disorder, physical examination anomaly, abnormal laboratory result, or any other condition (eg, current alcohol or drug abuse) that investigators suspect may prohibit use of the investigational product, affect interpretation of study results, or put the subject at undue risk of harm based on the investigator's assessment; 32. Known hypersensitivity to fruquintinib or any of its inactive ingredients.
Number of Subjects	Approximately 522 subjects will be randomized 2:1 (fruquintinib plus BSC: placebo plus BSC).
Length of Participation	Subjects may continue to receive treatment until they meet a criterion for discontinuation.
Intervention	**Investigational Drug:** Fruquintinib (HMPL-013) capsule 5 mg will be administered PO, QD, 3 weeks on, 1 week off (4-week cycles). Doses may be given either in the fasting state or after meals. If dose adjustment is required, 1 mg fruquintinib capsules will be used. **Reference Drug:** Placebo capsules matching fruquintinib 5 mg will be administered PO, QD, 3 weeks on, 1 week off (4-week cycles). Doses may be given either in the fasting state or after meals. If dose adjustment is required, 1 mg matching placebo capsules will be used.
Primary Objective	To evaluate the overall survival of fruquintinib plus BSC compared to placebo plus BSC in subjects with refractory mCRC.
Secondary Objective(s)	• To evaluate progression-free survival (PFS) of fruquintinib plus BSC compared to placebo plus BSC • To evaluate the objective response rate (ORR), disease control rate (DCR), and duration of response (DoR) • To assess the safety and tolerability of fruquintinib plus BSC compared to placebo plus BSC • To characterize the PK exposure of fruquintinib and metabolite M11 in subjects with refractory mCRC • To evaluate the effect of fruquintinib on cardiac repolarization, as detected by changes in electrocardiogram (ECG) QTc intervals, and the potential relationship with fruquintinib and M11 plasma concentrations • To evaluate the relationship between fruquintinib exposure and endpoints for efficacy and safety • To evaluate quality of life (QoL) as assessed by using QLQ-C30: cancer-specific; and EQ-5D-5L questionnaires • To assess resource utilization

Exploratory Objective(s)	To assess potential predictive biomarkers of response to fruquintinib
Number of Sites	This study will be conducted at approximately 100 sites globally.
Study Duration	Recruitment period is estimated to take approximately 13 months. Estimated duration for the entire study from time the study is open to enrollment until completion of data analyses is approximately 20 months.
Independent Data Safety Monitoring Committee	The IDMC will be comprised of at least 4 independent oncologists from representative geographies and at least 1 independent statistician.

1.1. Study Schematic

The study schematic is presented in Figure 1.

Figure 1 Study Design Schema



1.2. Schedule of Events

The schedules of events (SOE) are presented in Table 1, Table 2, and Table 3.

Table 1 Schedule of Events

Protocol Activities	Screening Period		Study Treatment Period							Follow Up		
Cycle			Cycle 1		Cycle 2		Cycle 3		Cycle 4 & beyond	End of Treatment	Safety Follow Up	Survival Follow Up
Visit	Screening		C1D1	C1D21	C2D1	C2D21	C3D1	C3D21	C4D1, C5D1, etc.	7 days after last dose	30 days after EOT visit	Every 12 weeks from EOT visit
Visit Window (days)	-28 to -1	-7 to -1	N/A	±1	±3	±3	±3	±3	±3	±3	±7	±14
Informed Consent [1]	X											
Medical History, Disease History and RAS status [2]	X											
Demographics [3]	X											
Prior and Concomitant Medication/ Concomitant Procedure [4]	X	X	X	X	X	X	X	X	X	X	X	
Comprehensive Physical Examination [5]		X										
Limited Physical Examination [6]				X	X	X	X	X	X	X	X	
ECOG [7]		X		X	X	X	X	X	X	X	X	
Vital Signs [8]		X		X	X	X	X	X	X	X	X	
Hematology [9]		X		X	X	X	X	X	X	X		
Blood Chemistry [10]		X		X	X	X	X	X	X	X		
Coagulation [11]		X		X	X	X	X	X	X			
Thyroid Function [12]		X			X		X		X			
Urinalysis [13]		X			X		X		X			
Serum Pregnancy Test [14]		X									X	
Urine pregnancy test [15]					X		X		X			

Protocol Activities	**Screening Period**		**Study Treatment Period**							**Follow Up**		
Cycle			**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4 & beyond**	**End of Treatment**	**Safety Follow Up**	**Survival Follow Up**
Visit	**Screening**		**C1D1**	**C1D21**	**C2D1**	**C2D21**	**C3D1**	**C3D21**	**C4D1, C5D1, etc.**	**7 days after last dose**	**30 days after EOT visit**	**Every 12 weeks from EOT visit**
Visit Window (days)	**-28 to -1**	**-7 to -1**	**N/A**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±14**
12-lead ECG [16]	X		X	X		X		X				
Echocardiogram [17]/ MUGA	X				X				X[17]			
Tumor Evaluation/Imaging [18]	Screening and every 8 weeks (±1 week) from C1D1 until progression											
Tumor Markers [19]	X				X		X		X	X		
Circulating Tumor DNA [20]	Screening and every 8 weeks (±1 week) from C1D1 until progression											
PK plasma sampling [21]			For PK plasma sampling schedule, see Table 2 and Table 3									
Patient Randomization [22]		X										
Drug/Dispense/Return [23]			X		X		X		X			
Study Treatment [24]			5 mg QD, Days 1 to 21 of each cycle									
Adverse Event [25]	Adverse Events are to be collected continuously throughout the study.											
Survival Follow Up [26]												X
QLQ-C30 Questionnaire		X			X		X		X	X		
EQ-5D-5L Questionnaire		X			X		X		X	X		

C1D1= cycle 1 day 1; C1D21 = cycle 1 day 21; C2D1 = cycle 2 day 1; C2D21 = cycle 2 day 21; C3D1 = cycle 3, day 1; C3D21 = cycle 3 day 21; ECG = Electrocardiogram; ECOG = Eastern Oncology Cooperative Group; EOT = End of treatment; MUGA = multiple-gated acquisition; PK = Pharmacokinetic

1.2.1. Footnotes for Schedule of Events Table 1

1. A written informed consent form should be obtained prior to any protocol-specific procedure or test. Procedural details for informed consent are available in Section 6.1.1.1.

2. Procedural details for medical history are available in Section 6.1.1.2. Tumor diagnosis, tumor treatment history, and evaluation of RAS status is described in Section 6.1.1.3.
3. Procedural details for patient demographics, including baseline characteristics are available in Section 6.1.1.4.
4. Procedural details for concomitant medications/treatments are available in Section 6.1.1.5.
5. Procedural details for comprehensive physical examination are available in Section 6.1.1.6.
6. Procedural details for limited physical examination are available in Section 6.1.1.7.
7. Procedural details for ECOG performance status are available in Section 6.1.1.8.
8. Procedural details for vital signs are available in Section 6.1.1.9.
9. Procedural details for hematology are available in Section 6.1.1.10.
10. Procedural details for blood chemistry are available in Section 6.1.1.11.
11. Coagulation tests include prothrombin time (PTT), international normalized ratio (INR), and activated partial thromboplastin time (APTT). Additional procedural details are available in Section 6.1.1.12.
12. Thyroid function tests include serum free triiodothyronine (fT3), serum free thyroxine (fT4) and thyroid stimulating hormone (TSH). Additional procedural details are available in Section 6.1.1.13.
13. Twenty-four-hour urine for quantitative protein should be collected from all patients with ≥ 2+ proteinuria during screening. If urine protein ≥ 2+ during the period of study treatment, a 24-hour urine protein should be collected within 1 week. Additional procedural details for urinalysis are available in Section 6.1.1.14.
14. All female patients of childbearing potential must complete a blood pregnancy test at screening and at the Safety Follow up Visit. Serum pregnancy test should be repeated for patients with suspected pregnancy. This is not applicable for postmenopausal female patients, but the date of menopause should be recorded instead. Additional procedural details are available in Section 6.1.1.15.
15. All female patients of childbearing potential must complete a urine pregnancy test at each day 1-visit starting at cycle 2.
16. See Table 2 and Table 3 for specific ECG parameters and time points. Electrocardiogram is to be performed before PK and echocardiogram assessments at each relevant visit. Other procedural details for Holter Monitor and 12-lead ECG are available in Section 6.1.1.16.

17. An echocardiogram should be done at Screening, C2D1, and on the first day, every 3 cycles thereafter. Additional procedural details for echocardiogram are available in Section 6.1.1.17. MUGA scans are acceptable if an echocardiogram cannot be performed.
18. Baseline tumor assessment should be completed within 28 days prior to enrollment. Post-baseline tumor evaluations shall be performed on C3D1, C5D1, and day 1 of every other cycle thereafter until progression of disease (PD). Each tumor assessment should document measurable lesions at the scheduled visit ± 7 days. Additional procedural details are available in Section 6.1.1.18.
19. Serum carcino-embryonic antigen (CEA) level is collected at screening and at day 1 of every cycle (±1 week) starting at cycle 2 until disease progression. Additional procedural details are available in Section 6.1.1.19.
20. Collection of circulating tumor DNA (ctDNA). Additional procedural details are available in Section 6.1.1.20.
21. See Table 2 and Table 3 for specific PK time points. Sampling for PK assessments is described in Section 6.1.2.1, and evaluation procedures are described in Section 6.1.2.2
22. Patient randomization occurs on day -2 to day 1. Additional procedural details on patient randomization are available in Section 6.1.1.21.
23. For the method of drug dispensation and return, see Section 7.2.2.
24. Study drug is taken daily on a 3 weeks on, 1 week off schedule for each 28-day cycle. On days with PK collection, treatment should be administered at the site by a delegated study staff member.
25. After informed consent, but prior to initiation of study drug, all SAEs regardless of attribution will be collected. After initiation of study drug, all SAEs and AEs regardless of attribution will be collected until 30 days after the last dose of study drug or a new treatment of anti-tumor therapy, whichever is earlier. After this period, investigators should report only SAEs that are considered to be related to the study drug.
26. Survival follow-up (by telephone) should be performed every 12 weeks (±2 weeks) after the end of treatment (EOT) visit. All subsequent anti-tumor therapy and information about study drug-related SAEs shall be collected. For the patients that discontinue the study without PD, all available tumor assessment results during survival follow up shall be recorded in the eCRF until confirmation of PD. The date and cause of death should be recorded, if applicable. Patients who withdraw consent are encouraged to be followed for survival. If the patient has clearly expressed his/her refusal to be followed after withdrawal of consent, he/she will terminate the study and no follow up for survival will be performed.

Table 2 Schedule of Events for Pharmacokinetic and Electrocardiogram Evaluations for the First Approximately 120 Patients

Study day	Time Relative to Dosing	Study Drug Intake [1]	Pharmacokinetic Samples [2]	Triplicate ECG for QTc Evaluation (Holter Monitor)	Safety ECG (Standard Equipment)
C1D1	Pre-dose [3]		X	X	-
	0 h	X	-	-	-
	1 h		X	X	-
	2 h		X	X	-
	3 h		X	X	-
	4 h		X	X	-
C1D21	Pre-dose [3]		X	X	-
	0 h	X	-	-	-
	1 h		X	X	-
	2 h		X	X	-
	3 h		X	X	-
	4 h		X	X	-
C2D1	Pre-dose [3]		X	-	-
	0 h	X	-	-	-
C2D21	Pre-dose [3]		X	-	-
	0 h	X	-	-	-
	2 h		X	-	X
C3D1	Pre-dose [3]		X	-	-
	0 h	X	-	-	-
C3D21	Pre-dose [3]		X	-	-
	0 h	X	-	-	-
	2 h		X	-	X
C5D1 and every other cycle thereafter	Pre-dose [3]		X	-	-
	0 h	X	-	-	-

C1D1= cycle 1, day 1; C1D21 = cycle 1, day 21; C2D1 = cycle 2, day 1; C2D21 = cycle 2, day 21; C3D1 = cycle 3, day 1; C3D21 = cycle 3, day 21; C5D1 = cycle 1, day 1; ECG = Electrocardiogram

Table 3 Schedule of Events for Pharmacokinetic and Electrocardiogram Evaluations for Patients Enrolled After the First Approximately 120 Patients

Study day	Time Relative to Dosing	Study Drug Intake [1]	Pharmacokinetic Samples [2]	Safety ECG (Standard Equipment)
C1D1	Pre-dose [3]		X	X
	0 h	X	-	-
	2 h		X	X
C1D21	Pre-dose [3]		X	-
	0 h	X	-	-
	2 h		X	X
C2D1	Pre-dose [3]		X	-
	0 h	X	-	-
C2D21	Pre-dose [3]		X	-
	0 h	X	-	-
	2 h		X	X
C3D1	Pre-dose [3]		X	-
	0 h	X	-	-
C3D21	Pre-dose [3]		X	-
	0 h	X	-	-
	2 h		X	X
C5D1 and every other cycle thereafter	Pre-dose [3]		X	-
	0 h	X	-	-

C1D1= cycle 1, day 1; C1D21 = cycle 1, day 21; C2D1 = cycle 2, day 1; C2D21 = cycle 2, day 21; C3D1 = cycle 3, day 1; C3D21 = cycle 3, day 21; C5D1 = cycle 1, day 1; ECG = Electrocardiogram

1.2.2. Footnotes for the Schedule of Events Tables 2 and 3

1. On PK sampling day, study drug must be taken at the investigative site under the supervision of the investigator or designee and should not be taken at home on the morning of the visits. The date and time of the dose administered on the day of PK collection and one day before PK collection must be recorded in the eCRF.
2. The actual date and time of the PK samples must be recorded on the eCRF.
3. Pre-dose PK and ECG should be performed within 30 minutes BEFORE study drug administration.

2. INTRODUCTION

During tumorigenesis, malignancies release growth factors to induce angiogenesis, which provides nutrients and oxygen for rapid tumor growth. The immature arrangement of endothelial cells on the rapidly growing blood vessels can result in exudation of tumor cells into the circulatory system, through which the tumor cells may spread to other tissues, leading to tumor metastasis. Vascular endothelial growth factor receptor (VEGF) is one of the key factors known to induce tumor angiogenesis, and agents that target VEGF and the VEGFR are important therapies for malignant solid tumors, including colorectal cancer (Duda 2016, Jayson 2016).

Fruquintinib (HMPL-013) is a small molecule anti-tumor drug with a novel chemical structure that belongs to the quinazoline class and is a potent and highly selective tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFR). *In vitro* studies demonstrated that fruquintinib is highly selective for VEGFR-1, -2, and -3, which are related to tumor angiogenesis, and possess weak or no measurable activity against other kinases (Sun 2014). Fruquintinib was discovered by Hutchison MediPharma Limited (hereafter referred to as the sponsor) through *in vitro* and *in vivo* biological screening of a large number of synthetic compounds.

Results from preclinical and clinical studies conducted in China and in the US have provided evidence that fruquintinib has anti-cancer activity in solid tumors. The clinical development program in China has been ongoing since 2009. In the phase 3 clinical trial, FRESCO, that led to the drug's approval in China, fruquintinib improved median overall survival in patients with metastatic colorectal cancer (mCRC) in a third-line or later setting when compared to placebo from 6.6 to 9.3 months (hazard ratio for death 0.65; 95% confidence interval [CI] 0.51-0.83; $P < 0.001$).(Li 2018) The cumulative safety data from the clinical trial program has shown that fruquintinib has an acceptable level of toxicity that is consistent with other antiangiogenic drugs, particularly small molecule VEGFR inhibitors. These data provide a strong justification for the investigation of fruquintinib in patients with refractory mCRC globally.

2.1. Background

Colorectal cancer (CRC) is a major global health issue, with an estimated 1.8 million new cases and 880,000 deaths in 2018 worldwide (Bray 2018). The established initial and second-line systemic therapy for mCRC consists of fluoropyrimidine-, oxaliplatin, and irinotecan-based cytotoxic chemotherapy (eg, FOLFOX: [5-Fluorouracil, leucovorin, and oxaliplatin] and FOLFIRI [5-fluorouracil, leucovorin, and irinotecan]). In addition, a biologic anti-VEGF therapy is typically given with chemotherapy (eg, bevacizumab), and if the tumor is RAS wild type, an anti-EGFR therapy (eg, cetuximab) is administered. In the small proportion of patients that are deficient mismatch repair (dMMR)/ high levels of microsatellite instability (MSI-H) in the metastatic setting (Koopman 2009), immunotherapy with nivolumab or pembrolizumab may be used (NCCN 2019).

When there is disease progression after the first two lines of chemotherapy, the established options are either:

- Trifluridine/tipiracil (LONSURF®, TAS-102), an oral combination of trifluridine, a nucleoside metabolic inhibitor, and tipiracil, a thymidine phosphorylase inhibitor; (LONSURF® USPI) or
- Regorafenib (STIVARGA®), a multikinase inhibitor with numerous *in vitro* targets that include VEGFR (STIVARGA® USPI).

There is an unmet medical need for new medications that are safe and effective in patients with refractory mCRC who have progressed on, or had intolerable toxicity from, available standard systemic therapies, and for whom no effective therapy or standard of care exists. A recent estimation of the median overall survival (OS) for patients with mCRC, based on data from phase 3 clinical trials, observation studies, and registries, is 30 months (Grothey 2013, Mayer 2015). During this time, patients may receive several lines of therapy, with one or more "breaks." Both TAS-102 and regorafenib are approved in the third-line or greater (3+ line) of therapy after progression on chemotherapy, and there are no approved treatments following progression on these agents. In this setting, the current options for patients with good performance status are to enter a clinical trial or to be re-challenged with prior chemotherapy (eg, 5-FU). Patients with poor performance status generally enter hospice care.

The purpose of this global, phase 3 clinical trial is to evaluate the efficacy and safety of fruquintinib in patients with refractory mCRC who have progressed on standard approved therapies, including TAS-102 and/or regorafenib.

2.1.1. Administration Regimen

Fruquintinib (HMPL-013) capsule 5 mg will be administered orally (PO) once daily (QD), 3 weeks on, 1 week off (4-week cycles). Doses may be given either in the fasting state or after meals. If dose adjustment is required, 1 mg capsules will be used.

2.1.2. Justification for Dosing Strategy

The optimal fruquintinib dose and dosing regimen were determined in two Chinese phase 1 studies, 2009-013-00CH1 and 2012-013-00CH3, as well as one US phase 1/1b study, 2015-013-00US1. During dose escalation, study 2009-013-00CH1 investigated continuous daily doses of 1 mg, 2 mg, 4 mg, 5 mg, and 6 mg; in addition, 5 mg QD and 6 mg QD were studied on a regimen of 3 weeks on, 1 week off (4-week) cycles. The maximum-tolerated dose (MTD)/ recommended phase 2 dose (RP2D) was 4 mg QD (continuous) or 5 mg QD (3 weeks on, 1 week off).

In study 2012-013-00CH3, the safety and tolerability of these two dosing regimens (4 mg QD continuously versus 5 mg QD, 3 weeks on, 1 week off) were compared in patients with mCRC. The safety profile was better in the 5 mg QD (3 weeks on, 1 week off) group than the 4 mg QD (continuous) group. In addition, there was accumulation of drug over time in the 4 mg QD (continuous) group. Thus, the 5 mg PO, QD, 3 weeks on, 1 week off, dose and regimen was selected as the RP2D and the dosing regimen to be used in subsequent clinical development in China.

The RP2D and dosing regimen were tested in the phase 2 (2012-013-00CH1) and phase 3 (2013-013-00CH1 [FRESCO]) studies, which confirmed that the dose and dosing regimen were safe and effective in patients with refractory mCRC. The 5 mg PO, QD, 3 weeks on, 1 week off is the standard dose and dosing regimen in all other completed, ongoing, and planned studies in patients with advanced cancer.

In the US phase 1/1b study (2015-013-00US1), there were 2 dose cohorts in the dose escalation phase, 3 mg PO, QD (n=7) and 5 mg PO, QD (n=7). Fruquintinib was well tolerated in both dose cohorts. Therefore, 5 mg PO, QD, 3 weeks on, 1 week off was confirmed as the RP2D for global studies, as well.

2.1.3. Supportive Nonclinical Data

2.1.3.1. Pharmacology

Fruquintinib is highly selective for VEGFRs -1, -2, and -3, with a 50% inhibitory concentration (IC_{50}) of 33 nM, 35 nM and 0.5 nM, respectively. Fruquintinib was found to have low activity on other kinases, with IC_{50} greater than 10 μM for cyclin-dependent kinases (CDKs 1, 2, and 5), platelet-derived growth factor receptor β (PDGFRβ), epidermal growth factor receptor (EGFR), and mesenchymal-epithelial transition factor (c-Met) in a panel of 264 kinases, which confirms the selectivity of fruquintinib.

In cellular assays, fruquintinib inhibited VEGFR family kinases and suppressed VEGFR phosphorylation with IC_{50} at low (nanomolar) levels. Consistently, in functional assays, fruquintinib blocked VEGF-dependent human umbilical vein endothelial cell (HUVEC) proliferation and tube formation and also exhibited this anti-angiogenic effect in the chorioallantoic membrane (CAM) model.

In animal models, a pharmacokinetic (PK)/pharmacodynamic study revealed that fruquintinib suppressed VEGF-induced VEGFR2 phosphorylation (p-VEGFR2) in lung tissues of nude mouse in a drug exposure-dependent manner. Fruquintinib also achieved near complete target inhibition (>80%), following a single oral dose of 2.5 mg/kg, which was maintained for >8 hours with a corresponding plasma drug concentration of 176 ng/mL at the 8-hour time point.

In multiple human tumor xenograft models in Nu/Nu mice, fruquintinib demonstrated a dose dependent anti-tumor activity accompanied by strong anti-angiogenesis effect in tumor tissues. In all tumor models tested, fruquintinib showed statistically significant tumor growth inhibition at doses as low as 2 mg/kg/day. Complete target coverage for more than 8 hours, with plasma concentration over 176 ng/mL maintained for 8 hours, was shown to significantly suppress tumor growth.

The combination of fruquintinib with cytotoxic chemotherapies (oxaliplatin or docetaxel), with molecular targeted therapies (EGFR or MET inhibitors) or with an immune checkpoint inhibitor (anti-PD-L1) demonstrated a synergistic or additive anti-tumor effect in multiple preclinical tumor models.

2.1.3.2. Metabolism and Pharmacokinetic Drug Interaction

[redacted]

In vitro, fruquintinib had no significant reversible or [redacted] on CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5 (IC_{50} >10 μM). There was also no induction of CYP1A2, [redacted] and CYP3A4 by fruquintinib at concentrations up to 10 μM.

According to the investigations on drug transporters, fruquintinib was not a substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP) [redacted]

[redacted]

2.1.3.3. Toxicology

[redacted]

2.1.4. Supportive Clinical Data

2.1.4.1. Clinical Pharmacokinetics

Single-dose and multiple-dose PK of fruquintinib have been characterized in Chinese and US patient populations, and single-dose PK has been evaluated in healthy Chinese males.

In Chinese patients with cancer, plasma fruquintinib exposure increased proportionally over the single dose range tested from 1 mg to 6 mg. Fruquintinib was rapidly absorbed with mean T_{max} ranging from 1.5 to 4.7 hours. Mean $t_{1/2}$ ranging from 35.2 hours to 48.5 hours was observed for fruquintinib. Following continuous dosing of fruquintinib 1, 2, 4, 5, or 6 mg QD, plasma fruquintinib concentration reached steady state by 14 days after dosing with exposure accumulating 3- to 4-fold at steady state compared to day 1. Following dosing of fruquintinib at

5 mg QD and 6 mg QD at the 3 week on/1 week off schedule, plasma fruquintinib concentrations declined during the off week, as expected. Preliminary PK results from the US patient population (ongoing Study 2015-013-00US1) that received fruquintinib at 3 mg and 5 mg QD 3 weeks on/1 week off suggested that there were no meaningful differences in fruquintinib exposure between Chinese and US patients. Following fruquintinib 5 mg QD 3 weeks on/1 week off, mean fruquintinib C_{max} and AUC_{tau} values on day 21 were 326 ng/mL and 5969 ng*h/mL in Chinese patients (Study 2012-013-00CH3), respectively, compared with 385 ng/L and 7530 ng*h/mL in US patients, respectively.

The effect of a high fat high calorie meal on the PK of fruquintinib 4 mg (4 x 1 mg capsules) was studied in healthy Chinese males (Study 2012-013-00CH2). Food delayed T_{max} of fruquintinib by 2.6 hours. A slight decrease in fruquintinib C_{max} by 17% was seen, though there was no observed effect on the $AUC_{0-\infty}$. These results were sufficient to recommend dosing of fruquintinib without regard to food.

The results from the mass balance study conducted in healthy Chinese subjects (Study 2015-013-00CH2) indicated that 60.31% of total radioactivity was recovered in urine and 29.80% in feces. A total of 22 metabolites were identified in the plasma, urine, and feces samples. The M11 (N-desmethylation product) and M9 (carboxylic acid product) were the main metabolites, where M11 accounted for 17.31% and M9 accounted for 4.46% of the plasma exposure of total radioactivity. Only a small amount of unchanged fruquintinib was detected in urine, which accounted for 0.50% of the dose administered. The amount of fruquintinib in feces accounted for 5.34% of the dose administered.

M11 is a pharmacologically active metabolite found to inhibit VEGFR2 kinase activity and VEGF-induced VEGFR2 phosphorylation, with a potency approximately 2 to 10 times lower than that of fruquintinib. After multiple doses of fruquintinib 5 mg QD to patients for 21 days (Study 2015-013-00US1, preliminary data), M11 reached T_{max} after 1 hour. The mean (standard deviation) C_{max} and AUC_{0-24} values were 144 (56.2) ng/mL and 3080 (1250) h*ng/mL, respectively. M11 accumulated by 31.5-fold after multiple dosing. The mean (standard deviation) metabolite-to-parent ratio of M11 was 0.409 (0.135) at steady state. Overall, M11 is not expected to have clinically meaningful contribution to the total pharmacological activity of fruquintinib at therapeutic exposure.

2.1.4.2. Clinical Safety

As of the data cut-off date (03 Sep 2019), 7 clinical trials in patients with cancer were completed. In order to conduct a comprehensive and robust safety assessment across the fruquintinib clinical studies, a pooled dataset has been generated and analyzed, which consists of data from 739 patients in 4 completed double-blind studies (2012-013-00CH1, 2013-013-00CH1, 2014-013-00CH1, and 2015-013-00CH1) (Table 20) who received fruquintinib monotherapy. In addition, the safety data from 2 completed early phase open-label studies (phase 1 2009-013-00CH1, phase 1b 2012-013-00CH3) and 1 completed phase 1b/2 study (2014-013-00CH3) has also been analyzed.

As of the data cut-off date, 5 clinical studies in patients with cancer were ongoing. The safety profile of fruquintinib from a US phase 1/1b open-label, multi-center study (2015-013-00US1), from a China phase 2 open-label study of fruquintinib in combination with gefitinib (2016-013-00CH1), and from a China phase 1b/2 open-label study of fruquintinib in combination with sintilimab (2018-013-00CH3) are also presented in this section. No formal analysis is available

for the safety profile of fruquintinib in the other 2 ongoing studies; the China randomized phase 3 study of paclitaxel with or without fruquintinib in metastatic gastric cancer (2017-013-00CH1) remains blinded, and no patients have been enrolled into the China open label single arm study evaluating fruquintinib in elderly patients with NSCLC (2017-013-00CH2).

Adverse Events in Completed Studies:

A total of 739 patients received at least 1 dose of fruquintinib in the 4 completed double-blind, placebo-controlled, monotherapy studies, among whom 729 (98.6 %) patients reported treatment-emergent adverse events (TEAEs). The incidence of the most commonly reported TEAEs (≥10% of patients) are provided in the current investigator's brochure (IB).

In the pooled data of all-causality TEAEs reported, the most commonly reported TEAEs of grade ≥3 (≥5% of patients) included Hypertension (19.9%) and Palmar-plantar erythrodysaesthesia syndrome (10.7%).

Serious Adverse Events in Completed Studies:

A total of 1 or more serious adverse events (SAEs) have been reported by 169 (22.9%) patients out of the 739 patients who received fruquintinib. The most common SAEs (≥1.0%) by MedDRA preferred term (PT) included Infectious pneumonia in 24 (3.2%) patients, intestinal obstruction in 17 (2.3%) patients, pleural effusion in 9 (1.2%) patients, death in 10 (1.4%) patients, hepatic function abnormal in 8 (1.1%) patients, and gastrointestinal haemorrhage in 8 (1.1%) patients. The SAEs in more than 1 patient in the pooled data are summarized in the current IB.

2.1.4.2.1. Clinical Efficacy

Monotherapy Efficacy:

As of the data cut-off date (03 September 2019), the available fruquintinib efficacy data from the completed open-label and double-blind studies showed strong antitumor activity, including improved overall survival (OS) and progression-free survival (PFS), durable partial response (PR) and durable stable disease (SD), and improved overall response rate (ORR) in heavily pre-treated patients with advanced cancer.

Two (2) proof-of-concept studies have been conducted in patients with CRC who were previously treated with two or more lines of standard chemotherapeutic regimens (Study 2012-013-00CH1) and in patients with NSCLC who have failed two lines of standard chemotherapies (Study 2014-013-00CH1). The studies both met their primary efficacy endpoint of PFS and demonstrated a significant improvement in PFS in the fruquintinib arm compared to the placebo arm.

In addition, the phase 3 pivotal trial (FRESCO) was completed in patients with CRC who were previously treated with 2 or more lines of standard chemotherapeutic regimens (Study 2013-013-00CH1). In this study, fruquintinib significantly prolonged the OS compared to placebo with a hazard ratio of 0.65 (95% CI: 0.51-0.83; 2-sided $p < 0.001$). Statistically significant benefits were also seen with fruquintinib in all secondary endpoints, including as PFS, ORR, and disease control rate (DCR).

One phase 3 study of fruquintinib was completed in patients with NSCLC who had failed second-line standard chemotherapy (2015-013-00CH1): there was no significant difference between the fruquintinib group and the placebo group in the primary efficacy endpoint (OS). However, fruquintinib significantly prolonged the PFS comparing to placebo with a HR of 0.34 (95% CI:

0.279, 0.425) with $p < 0.001$ (stratified log-rank test). Statistically significant benefits were also shown with fruquintinib in ORR and DCR.

The efficacy data in the ongoing study of fruquintinib in patients with advanced solid tumors (2015-013-00US1) are not available as of the data cut-off date (03 Sep 2019).

Combination Therapy Efficacy

A phase 1b/2 study had been conducted to investigate the treatment of fruquintinib, in combination with paclitaxel, as second-line therapy in patients with gastric cancer (GC) (2014-013-00CH3). The results showed that the ORR and DCR were 27.3% (9/33) and 63.6% (21/33), respectively. The median PFS and median OS at the RP2D (fruquintinib 4 mg + paclitaxel) were 4.0 months and 8.5 months, respectively.

The efficacy data in 1 ongoing study of fruquintinib in combination with gefitinib in patients with NSCLC (2016-013-00CH1) and in 1 ongoing study of fruquintinib in combination sintilimab patients with advanced solid tumor are not available as of the data cut-off date (03 Sep 2019).

2.1.5. Benefit/Risk Assessment

There are robust cumulative efficacy and safety data for fruquintinib from the entire clinical program in China, as well as the ongoing US phase 1/1b study. As of the data cut-off date (03 September 2019) a total of 1600 patients and 87 healthy volunteers had received at least one dose of fruquintinib or placebo through development programs. Among them, 955 patients and 87 healthy volunteers had received at least one dose of fruquintinib, 284 patients had received at least one dose of blinded treatment (fruquintinib versus placebo), and 361 patients had received at least one dose of placebo.

2.1.5.1. Risk Assessment

A total of 739 patients received at least 1 dose of fruquintinib in the 4 completed double-blind studies, among whom 739 (98.6 %) patients reported TEAEs.

In the pooled data of all-causality TEAEs reported in the 3 completed double-blind, monotherapy studies, the most commonly reported TEAEs of grade ≥3 (≥5% of patients) included hypertension (19.9 %) and palmar-plantar erythrodysaesthesia syndrome (10.7 %).

The incidence of the most commonly reported TEAEs (≥10% of patients) is provided in the current IB.

The safety analysis that resulted in the identified risks was performed on the pooled data set from 4 completed double-blind studies (N= 739 fruquintinib; N= 361 placebo), in which the incidence of adverse events (AEs) in fruquintinib-treated patients was compared with those in the placebo-treated control patients. The identified risks presented by Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) are presented in Table 54 of the current IB.

2.1.5.2. Benefit Assessment

The efficacy data in the phase 1 study conducted in China (Study 2009-013-00CH1) showed encouraging clinical activity for fruquintinib. A response was observed in the majority of heavily pre-treated patients with advanced cancers (see the current IB). The results of two phase 2 proof-of-concept (POC) studies provided evidence of clinical efficacy in patients with metastatic CRC

(Study 2012-013-00CH1, third or later lines therapy) and NSCLC (Study 2014-013-00CH1, third-line therapy) as compared with placebo. The PFS results established POC in both studies by meeting their respective primary efficacy endpoints. Clinical efficacy was also provided by the phase 3, double-blind, placebo-controlled trial, 2013-013-00CH1 (FRESCO).

2.1.5.3. Overall Benefit/Risk Conclusion

The safety profile of fruquintinib is consistent with those of other anti-angiogenic therapies, particularly the small molecule tyrosine kinase inhibitors (ie, sorafenib, regorafenib, axitinib, and sunitinib), as demonstrated by the identified risks for fruquintinib (Section 2.1.5.1). In addition, safety data from the completed and ongoing studies showed that fruquintinib was well tolerated, with most of the AEs reported as grade 1 to 2 (see current IB). There have been no new or unexpected safety findings from the ongoing clinical trials to date.

2.2. Study Rationale

Colorectal cancer (CRC) is a major global health issue, with an estimated 1.8 million new cases and 880,000 deaths in 2018 worldwide (Bray 2018). There is an unmet medical need for new medications that are safe and effective in patients with refractory mCRC who have progressed after treatment with, or had intolerable toxicity from, available standard systemic therapies.

There is no standard of care after patients progress on-chemotherapy, relevant biologics and TAS-102 or regorafenib. In clinical studies performed in China, fruquintinib has demonstrated robust anti-tumor activity and was well tolerated. Fruquintinib is approved in China for the treatment of patients with refractory mCRC. The safety profile of fruquintinib from an ongoing phase 1/1b study in the US is consistent with those from clinical studies performed in China. This global phase 3 trial is being conducted to confirm the results of the FRESCO trial conducted in China in patients with refractory mCRC.

This is a randomized, double-blind, placebo-controlled, clinical trial to compare the efficacy and safety of fruquintinib in combination with the best supportive care (BSC) versus placebo in combination with BSC in patients with refractory mCRC who have progressed on, or were intolerant to TAS-102 and/or regorafenib.

3. OBJECTIVES AND ENDPOINTS

3.1. Primary Objective

To evaluate the overall survival (OS) of fruquintinib plus BSC compared to placebo plus BSC in subjects with refractory mCRC

3.2. Secondary Objectives

- To PFS of fruquintinib plus BSC compared to placebo plus BSC
- To evaluate the objective response rate (ORR), disease control rate (DCR), and duration of response (DoR)
- To assess the safety and tolerability of fruquintinib plus BSC compared to placebo plus BSC
- To characterize the PK exposure of fruquintinib and metabolite M11 in subjects with refractory mCRC
- To evaluate the effect of fruquintinib on cardiac repolarization, as detected by changes in electrocardiogram (ECG) QTc intervals, and the potential relationship with fruquintinib and M11 plasma concentrations
- To explore the relationship between fruquintinib exposure and endpoints for efficacy and safety
- To evaluate quality of life (QoL) as assessed by using QLQ-C30: cancer-specific; and EQ-5D-5L questionnaires
- To assess resource utilization (for example, hospitalizations, concomitant medications)

3.3. Exploratory Objectives

- To assess potential predictive biomarkers of response to fruquintinib

The objectives and corresponding endpoints are summarized in Table 4.

Table 4 Objectives and Corresponding Endpoints

Tier	Objectives	Endpoints
Primary	To evaluate the overall survival (OS) of fruquintinib plus BSC compared to placebo plus BSC in subjects with refractory mCRC	OS
Secondary	To evaluate progression-free survival (PFS) of fruquintinib plus BSC compared to placebo plus BSC	PFS
	To evaluate the objective response rate (ORR), disease control rate (DCR), and duration of response (DoR)	• ORR • DCR • DoR

Table 4 Objectives and Corresponding Endpoints

Tier	Objectives	Endpoints
	To assess the safety and tolerability of fruquintinib plus BSC compared to placebo plus BSC	Safety including TEAEs, SAEs, deaths, ECG's, and clinical laboratory abnormalities
	To characterize the pharmacokinetic (PK) profile of fruquintinib in subjects 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 electrocardiogram (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 quality of life (QoL) as assessed by 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 (for example, hospitalizations, medications)	Resource utilization including all concomitant medications, days in hospital
Exploratory	To assess potential predictive biomarkers of response to fruquintinib	• Change from baseline in ctDNA • Change from baseline in tumor markers (CEA) • Pharmacogenomics

4. STUDY PLAN

Detailed information on the fruquintinib clinical trial program in China and in the US can be found in Appendix 4 of this protocol and also in the fruquintinib IB.

4.1. Study Design

This is a global, randomized, double-blind, placebo-controlled, multicenter phase 3 clinical trial to compare the efficacy and safety of fruquintinib in combination with BSC versus placebo in combination with BSC in advanced colorectal cancer patients who have progressed on or were intolerant to chemotherapy, biologics and TAS-102 or regorafenib.

Metastatic colorectal cancer cannot be cured by surgery. Therefore, treatment principals are primarily aimed at controlling disease progression and prolonging survival. Standard first- and second-line therapy includes cytotoxic drugs such as 5-fluorouracil, oxaliplatin, and irinotecan; anti-VEGF therapy; and, if RAS wild type, anti-EGFR therapy. After the first two lines of chemotherapy, standard third-line treatment is either TAS-102 or regorafenib. 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. Consequently, there is an unmet medical need for additional safe and effective treatment.

4.1.1. Enrollment in Study

After checking the eligibility criteria, subjects will be randomized into either fruquintinib in combination with BSC group (treatment group) or placebo in combination with BSC group (control group) in a 2:1 ratio (Figure 1).

- Treatment 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.

A treatment cycle is 4 weeks. Patients' safety assessment and drug accountability will be performed at each treatment cycle. Continuous drug safety monitoring and assessment will be performed through the whole study period (including a 30-day observation period after the end of treatment).

As described in Section 2, in the phase 3 FRESCO trial that led to the drug's approval in China, fruquintinib improved the median overall survival in patients with metastatic colorectal cancer (mCRC) in a third line or later setting when compared to placebo (median OS 9.3 versus 6.6 months); hazard ratio for death was 0.65 (95% CI, 0.51-0.83; $P < 0.001$) (Li 2018). The results of the FRESCO study indicate that fruquintinib is a candidate therapy for patients with refractory mCRC globally, and provides the strongest rationale for the current clinical trial.

Since the current standard of care for patients with mCRC in the US, EU, and Japan is different than it was in China during the conduct of the FRESCO trial, the current study is necessary to evaluate fruquintinib in a patient population that is representative of global treatment practices. In FRESCO, prior therapy included the standard first two lines of cytotoxic chemotherapy (fluoropyrimidine-, oxaliplatin- and irinotecan-based), but only about 30% of patients had received

prior therapy with a VEGF inhibitor (bevacizumab), and patients with prior exposure to VEGFR inhibitors such as regorafenib were excluded.

4.1.2. Rationale for the Electrocardiogram Collection and Pharmacokinetic Sampling Schedule

In accordance with ICH E14 guideline, QT evaluation is expected to be routine in oncology drug development, and a thorough QT (TQT) study should be conducted, if possible. In the case of fruquintinib, in view of nonclinical (hERG and CV safety study) and clinical data suggesting no apparent relationship between fruquintinib and QT prolongation, an alternative design to the TQT study has been chosen.

In this study, changes in QTc interval following drug administration will be evaluated relative to the baseline measurement. Electrocardiogram time points have been selected to match the expected PK profile of fruquintinib and metabolite M11. The ECG time points have also been selected to explore a potential relationship between exposure and effect on QTc.

In order to assess the QTc interval prior to exposure to fruquintinib, baseline triplicate ECG assessments will be performed prior to first study drug administration on cycle 1 day 1 (within 30 minutes before dosing). A baseline PK sample will also be collected at pre-dose, immediately after the ECGs have been collected and prior to the first dose of fruquintinib or placebo. Subsequently, the purpose of all other ECGs is to assess for potential prolongation of the QTc interval and other ECG changes as a result of fruquintinib administration, with ECG collection coinciding with PK measurements to establish correlations between ECG changes and drug exposure. Triplicate ECGs, followed by blood samples for PK assessment, will be collected at multiple time points post-dose around T_{max} of fruquintinib and M11 after the first dose and at steady-state as described in Table 2.

5. POPULATION

5.1. Recruitment

To randomize 522 patients, approximately 100 sites will be opened globally for patient recruitment.

5.2. Definitions

Subjects officially enter the Screening Period after providing informed consent, either directly or via a legally authorized representative.

Subjects who withdraw from the study after signing the ICF and before the randomization will be considered screen failures. Subjects who failed the original screening may be screened again using their original subject number as assigned by interactive web response system (IWRS). A subject may only be re-screened once.

A randomized subject is one who has been deemed eligible and has been assigned to a treatment group by IRT/IWRS.

5.3. Inclusion Criteria

Subjects may be enrolled in this study only if they satisfy all the following criteria:

1. Provide written informed consent;
2. Age ≥18 years;
3. Histologically and/or cytologically documented metastatic colorectal adenocarcinoma;
4. Subjects must have progressed on or been intolerant 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 agents 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.
5. Subjects with microsatellite-high (MSI-H) or mismatch repair deficient (dMMR) tumors must have been treated with immune checkpoint inhibitors if approved and available in the subject's country and if deemed appropriate;
6. Subjects who received oxaliplatin in the adjuvant setting must have progressed within 6 months of completion of adjuvant therapy;
7. Body weight ≥40kg;
8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1;
9. Have measurable disease according to RECIST Version1.1 (RECIST v1.1), assessed locally. Tumors that were treated with radiotherapy are not measurable per RECIST v1.1, unless there has been documented progression of those lesions.
10. Expected survival >12 weeks.

11. For female subjects of childbearing potential and male subjects with partners of childbearing potential, agreement to use a highly effective form(s) of contraception, that results in a low failure rate (<1% per year) when used consistently and correctly, starting during the screening period, continuing throughout the entire study period, and for 90 days after taking the last dose of study drug. Such methods include: oral hormonal contraception (combined estrogen/ progestogen, or progestogen-only) associated with inhibition of ovulation together with a barrier method (eg, diaphragm, always containing a spermicide), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal ligation, vasectomized partner, or sexual abstinence. Oral contraception should always be combined with an additional contraceptive method (ie, barrier method) because of a potential interaction with the study drug. The same criteria are applicable to male subjects involved in this clinical trial if they have a partner of childbirth potential, and male subjects must always use a condom.

5.4. Exclusion Criteria

Subjects are not eligible for enrollment into this study if they have any of the following criteria:

1. Absolute neutrophil count (ANC) $<1.5\times10^9$/L, platelet count $<100 \times 10^9$/L, or hemoglobin <9.0 g/dL. Blood transfusion within 1 week prior to enrollment for the purpose of increasing the likelihood of eligibility is not allowed;
2. 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;
3. ALT or AST >2.5 × ULN in subjects without hepatic metastases; ALT or AST >5 × ULN in subjects with hepatic metastases;
4. Serum electrolytes, potassium, calcium, or magnesium levels outside of the normal laboratory reference range, and clinically significant in the investigator's judgment;
5. 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.
6. 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;
7. Uncontrolled hypertension, defined as: systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mm Hg despite optimal medical management;
8. International Normalized Ratio (INR) >1.5 x ULN or activated partial thromboplastin time (aPTT) >1.5 × ULN, unless the subject is currently receiving or intended to receive anticoagulants for prophylactic purposes;
9. History of, or active gastric/duodenal ulcer or ulcerative colitis, active hemorrhage of an unresected gastrointestinal tumor, history of perforation or fistulas; or any other condition that could, in the investigator's judgment, result in gastrointestinal hemorrhage or perforation; within the 6 months prior to screening;

10. History or presence of hemorrhage from any other site (eg, hemoptysis or hematemesis) within 2 months prior to screening;
11. History of a thromboembolic event, including deep vein thrombosis (DVT), pulmonary embolism (PE), or arterial embolism within 6 months prior to screening.
12. Stroke and/or transient ischemic attack within 12 months prior to screening;
13. Clinically significant cardiovascular disease, including but not limited to acute myocardial infarction or coronary artery bypass surgery within 6 months prior to enrollment, 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;
14. Mean corrected QT interval using the Fridericia method (QTcF) >480 msec or any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as hypokalemia, congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in a first-degree relative.
15. Concomitant medications with a known risk of causing QT prolongation and/or Torsades de Pointes (See list in Appendix 3; source list is continuously updated online at www.crediblemeds.org).
16. Systemic anti-neoplastic therapies (except for those described in Exclusion Criterion 18) or any investigational therapy within 4 weeks prior to the first dose of study drug, including chemotherapy, radical radiotherapy, hormonotherapy, biotherapy and immunotherapy;
17. Systemic small molecule targeted therapies (eg, tyrosine kinase inhibitors) within 5 half-lives or 4 weeks (whichever is shorter) prior to the first dose of study drug;
18. Palliative radiotherapy for bone metastasis/lesion within 2 weeks prior to the initiation of study drug;
19. Brachytherapy (ie, implantation of radioactive seeds) within 60 days prior to the first dose of study drug.
20. Use of strong inducers or inhibitors of CYP3A4 within 2 weeks before the first dose of study drug (see Appendix 3 for a list of applicable drugs);
21. Surgery or invasive procedure (ie, a procedure that includes a biopsy; central venous catheter placement is allowed) within 60 days prior to the first dose of study drug or unhealed surgical incision;
22. Any unresolved toxicities from a previous antitumor treatment greater than National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE) v5.0 grade 1 (except for alopecia or neurotoxicity grade≤2).
23. Known human immunodeficiency virus (HIV) infection;
24. Known history of active viral hepatitis. For subjects with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated. Subjects with HCV infection who are currently on treatment are eligible if they have an undetectable HCV viral load.

25. Clinically uncontrolled active infection requiring IV antibiotics;
26. Tumor invasion of a large vascular structure (eg, pulmonary artery, superior or inferior vena cava);
27. Women who are pregnant or lactating;
28. Brain metastases and/or spinal cord compression untreated with surgery and/or radiotherapy, and without clinical imaging evidence of stable disease for 14 days or longer; subjects requiring steroids within 4 weeks prior to start of study treatment are excluded;
29. No other malignancy, except for non-melanoma skin cancer, *in situ* cervical ca or bladder ca (Tis and T1) that have been adequately treated during the 5 years prior to screening;
30. Inability to take medication orally, dysphagia or an active gastric ulcer resulting from previous surgery (eg, gastric bypass) or a severe gastrointestinal disease, or any other condition that investigators believe may affect absorption of the investigational product;
31. Other disease, metabolic disorder, physical examination anomaly, abnormal laboratory result, or any other condition (eg, current alcohol or drug abuse) that investigators suspect may prohibit use of the investigational product, affect interpretation of study results, or put the subject at undue risk of harm based on the investigator's assessment;
32. Known hypersensitivity to fruquintinib or any of its inactive ingredients.

6. STUDY CONDUCT

6.1. Study Procedures

6.1.1. Study Assessments

The following procedures will be performed according to the schedule in Table 1. All assessments must occur within ± 3 days (±1 day during cycle 1) from the scheduled date, unless otherwise noted.

6.1.1.1. Informed Consent

All subjects must sign the informed consent form (ICF) prior to any study-related examinations or protocol procedures. Tumor assessments completed as standard of care prior to signing the informed consent, but within 28 days of first dose of study treatment, may be used as baseline scans.

All subjects who sign ICF are to be entered into the IWRS system. The system will generate a subject identification number, which will be assigned to the subject.

6.1.1.2. Medical History

A complete medical history, including the subject's medical history, disease history and prior therapies for disease prior to signing of the ICF, should be recorded at screening. Comorbidities that began prior to signing the ICF should be recorded and followed as medical history.

6.1.1.3. Tumor Diagnosis and Treatment History

Tumor diagnosis should include the date of primary diagnosis of CRC and its type, disease stage, the date of first metastasis, type of previous treatment, start and end date/s, best overall response, date of PD, adverse reaction with severity ≥ grade 3. Prior use (yes/no) of trifluridine/tipiracil (Lonsurf®, TAS-102), regorafenib (Stivarga®), or both of these drugs, prior use of fluoropyrimidine-, oxaliplatin, and irinotecan-based chemotherapy. Prior use of a biological anti-VEGF therapy (yes versus no), prior RAS gene status (mutant versus wild type).

If the RAS gene test was not performed previously, it should be performed during screening. In subjects who are RAS wild type, anti-EGFR therapy must be offered unless medically contraindicated.

The subject's history of radiation therapy, including the start and end date/s and the site of radiation must be recorded. Surgical history, including operations and less-invasive diagnostic or therapeutic procedures (such as GI endoscopy, biopsy, etc.), the start and end date/s, name of each procedure and operation site must also be recorded at screening and in the appropriate eCRF.

6.1.1.4. Demographics

Demographic characteristics, including date of birth, sex, ethnic group/race, and any relevant lifestyle habits should be recorded at screening and in the applicable eCRF (as permitted by local regulations).

6.1.1.5. Concomitant Medication and Procedures

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a subject. All concomitant medications within 28 days before randomization must be recorded in the eCRF, including the generic name of the drug and daily dose, the reason/s for using the medication, as well as the start and stop date/s of the medication. Concomitant medications should be reviewed during the study according to the schedule in Table 1.

6.1.1.6. Comprehensive Physical Examination

A comprehensive physical examination includes subject height, weight and general condition, as well as an examination of the head, heart, chest (including the lungs), abdomen, extremities, skin, lymph nodes, nervous system and additional areas/systems as clinically indicated.

6.1.1.7. Limited Physical Examination

Limited physical examination includes vital signs and any change from baseline, any new abnormalities, examination of weight, thorax, abdomen, and additional areas/systems as clinically indicated. In order to assess changes from baseline and to evaluate for new abnormalities, the limited physical examination should assess for new or changed skin lesions, enlarged lymph nodes, palpable masses, and appropriate examination to address any subject-reported symptoms.

6.1.1.8. Eastern Cooperative Oncology Group (ECOG) Performance Status

Subject performance status will be graded according to the Eastern Cooperative Oncology Group (ECOG) performance status scale at study visits as detailed in Table 1. It is recommended that ECOG performance status scores be evaluated by the same investigator throughout the study. Details on the ECOG assessment and grading scale are available in Appendix 1.

6.1.1.9. Vital Signs

Vital signs include blood pressure, heart rate, respiration rate and temperature. For subjects with a baseline history of hypertension or hypertension that develops on study, blood pressure should be monitored per institutional standard practice.

6.1.1.10. Hematology

Hematology assessments include red blood cell count, hemoglobin, hematocrit, platelet count, white blood count with differential (absolute counts).

Note: If neutrophil count $\leq 1.0\times10^9$/L or platelet count$\leq 25\times10^9$/L, hematology assessments should be conducted per institutional standard practice.

6.1.1.11. Blood Chemistry

The blood chemistry panel includes sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, magnesium, phosphorus, total bilirubin, ALT, AST, ALP, lactate dehydrogenase, non-fasting total cholesterol, triglycerides, uric acid, total protein and albumin.

Blood chemistry tests for subjects with ALT or AST increase by >3x ULN, or increase by >2x baseline value should performed per institutional standard practice.

Creatinine clearance (CrCl) rate (units, mL/min) should be calculated using the baseline serum creatinine (Scr) value according to the Cockroft-Gault formula: for males: Ccr = [(140 - age) × weight (kg)] / [72 × Scr (mg/dL) x ideal body weight (IBW)]. For females, the same formula should be calculated and multiplied by 0.85.

6.1.1.12. Coagulation

Coagulation tests include prothrombin time (PTT), international normalized ratio (INR), and activated partial thromboplastin time (APTT).

6.1.1.13. Thyroid Function

Thyroid function tests include serum free triiodothyronine (fT3), serum free thyroxine (fT4) and thyroid stimulating hormone (TSH).

6.1.1.14. Urinalysis

Urinalysis parameters include urine pH, protein, glucose, and blood; microscopic for white blood cell and red blood cell count. A 24-hour urine for quantitative protein must be collected from all subjects with ≥ 2+ proteinuria. For conversions between quantitative and qualitative results, please see Appendix 8.

6.1.1.15. Pregnancy Test

All female subjects of childbearing potential must complete a blood pregnancy test at screening and within 30 days at the Safety Follow Up Visit, and a urine pregnancy test on day 1 of every cycle starting at cycle 2. Serum pregnancy test should be repeated for women with suspected pregnancy. This is not applicable for postmenopausal female subjects (ie, no menses for 12 months without an alternative medical cause), and the date of menopause should be recorded instead. Pregnancy testing and contraception are not required for women with documented permanent sterilization (eg, hysterectomy, bilateral salpingectomy and bilateral oophorectomy, or tubal ligation).

6.1.1.16. Electrocardiograms Monitoring

Single 12-lead electrocardiograms (ECG) will be collected in all subjects using standardized equipment, as described in Table 1, Table 2, and Table 3 during cycles 1 to 3. ECGs from standard equipment will be evaluated for safety by the principal investigator. In addition, continuous 12-lead Holter monitor will be used for QTc evaluation during cycle 1 in a subset of subjects and will be sent for central reading (see below in Continuous 12-Lead Holter Monitor for QTc Evaluation for details). From cycle 4 onward, ECG will only be performed as clinically indicated. Vital signs will be measured, a symptom-directed physical exam will be conducted, and safety related blood samples will be collected as per the time points in Table 1. These assessments should be completed before the start of any ECG recordings.

Continuous 12-Lead Holter Monitor for QTc Evaluation

Continuous ECG recordings using 12-lead Holter monitoring will be collected from the first approximately 120 patients (80 fruquintinib, 40 placebo) enrolled in the study to evaluate the effects of fruquintinib on ventricular repolarization. The assessments will be conducted at pre-

dose and post-dose on cycle 1 day 1 and cycle 1 day 21 at specific time points summarized in Table 2.

Subjects should reside in a quiet setting without distractions (eg, television, cell phones and staff talking) at each scheduled time point for ECG measurements. Subjects should rest in a supine position for at least 10 minutes before and 5 minutes after the scheduled time point and should refrain from talking or moving arms or legs. Skin preparation should be optimal to obtain high quality ECGs; if deemed appropriate, the chest should be shaved and prepared with light abrasion.

Continuous digital 12-lead Holter ECGs will be recorded as described in the ECG/Holter manual. Good quality 12-lead ECG selection and extraction will occur during a 10-minute timeframe starting 5 minutes before and ending 5 minutes after the scheduled ECG time point. All Holter recorder devices (as supplied by the central ECG laboratory) will be of the same brand and model with the same software, and would have been recently serviced and calibrated. Documentation describing the brand, type, software and service/calibration history of Holter recorders will be provided by the central ECG laboratory and archived at the site as well as in the sponsor's study file. Transfer of the Holter recordings and extraction of the ECG tracings will be performed as described in the ECG/Holter manual.

Ten-second digital ECG tracings will be extracted from the Holter device in triplicate by the central ECG laboratory according to the following principles:

- The actual time of dosing will be communicated to the central ECG laboratory on the Holter acquisition form completed by the site.
- Using visual inspection or automated tools as appropriate, the central ECG laboratory will identify a period of stable HR on the continuous Holter tracing within ±5 minutes of the nominal ECG time point (determined relative to the actual dosing time for an individual subject). Three 10-second ECGs will be extracted in close succession from this identified segment.
- The scheduled time points for triplicate ECG extraction are summarized in Table 2.

Unless warranted by a specific safety endpoint of the study, the Holter tracings will not be routinely analyzed for rhythm and conduction abnormalities. These analyses will only be performed on individual subject's Holter if warranted by TEAEs (eg, syncope).

6.1.1.17. Echocardiogram

An echocardiogram should be done at Screening, cycle 2 day 1, and on day 1, every 3 cycles thereafter. Assessment parameters include left ventricular ejection fraction and general assessment of cardiac function. MUGAs are permitted if echocardiograms cannot be performed.

6.1.1.18. Tumor Evaluation/Imaging

Tumor assessments will be performed at study visits specified in Table 1.

All measurable and evaluable lesions should be assessed and documented using image-based evaluation. All subjects are to be evaluated utilizing contrast-enhanced computed tomography (CT) scan of the chest, abdomen, and pelvis, or other acceptable cross-sectional imaging per RECIST v1.1. Evaluations should include other areas of the body, as clinically indicated. Disease status will be assessed by the investigator or designated site staff using RECIST v1.1. The same

imaging procedure used to define measurable lesions at baseline must be used throughout the study for each subject, unless medically contra-indicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

Tumor assessments completed as standard of care prior to signing the informed consent, but within 28 days of first dose of study treatment, may be used as baseline scans.

Imaging for all subjects will also be collected for central storage. Please refer to the study-specific central imaging manual for collection and shipping instructions.

6.1.1.19. Tumor Markers

Assessment of serum carcino-embryonic antigen (CEA) levels will be performed according to the schedule in Table 1. The dates of blood sampling must be recorded in the eCRF.

6.1.1.20. Circulating Tumor DNA

Collection of circulating tumor DNA (ctDNA) will be collected according to the schedule in Table 1. For collection and shipping instructions please refer to study specific laboratory manual. The dates of blood sampling must be recorded in the eCRF.

6.1.1.21. Subject Randomization

On day -2 to day 1, after verifying the subject's eligibility, the site will log into the IWRS and the subject will be randomized by the system. The system will generate a serial number matching a bottle of investigational product in the site's inventory. The site will take investigational product with the serial number assigned by IWRS from inventory and dispense it to the subject. The first dose should be administered on cycle 1 day 1.

6.1.1.22. Quality of Life Assessment

A quality of life assessment, using QLQ-C30: cancer-specific; and EQ-5D-5L: general, must be performed during the screening visit as well as day 1 of each cycle until treatment is discontinued.

6.1.2. Pharmacokinetics Evaluations

6.1.2.1. Sample Collection and Handling

Samples for PK analysis will be collected in all subjects according to the schedule in Table 2 and Table 3. The actual dates and times of PK sampling should be recorded in appropriate eCRF. In addition, the dates and times of the dose administered on the day of PK collection and one day before PK collection must be recorded in the eCRF.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided to the sites. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

6.1.2.2. Analytical Procedures

Plasma samples will be analyzed to determine concentrations of fruquintinib and its active metabolite M11 using a validated, specific, and sensitive Liquid Chromatography-Tandem Mass Spectrometry (LC MS/MS) method.

If required, then plasma samples may be analyzed to document the presence of circulating metabolites using a qualified research method.

6.1.3. End of Treatment Visit

Subjects who have completed the study or have discontinued study treatment will be asked to return to the investigational site to receive safety examinations and assessments within 7 (±3) days after the last dose of study drug.

6.1.4. Safety Follow-Up Visit

All subjects who have completed an End of Treatment Visit will have a Safety Follow-Up Visit. The Safety Follow-Up Visit will be conducted at 30 (±7) days from the EOT Visit.

6.1.5. Efficacy Follow-Up

Any subject who discontinues study treatment for any reason other than disease progression should be followed until progression is documented or until a new anti-cancer treatment is initiated for PFS assessment and until death for OS assessment.

6.1.6. Survival Follow-Up

Every 12 (±2) weeks after the End of Treatment Visit the investigator or their designee should call the subject to collect information related to survival status and their use of other anti-cancer treatments, including drug name, dosage, treatment start and end dates, and efficacy. Information related to radiotherapy received after disease progression is also needed, including radiotherapy location, radiation dose, start date, and end date.

6.1.7. Long-term Extension

Subjects who are still on study treatment at the time of study completion may continue to receive study treatment if they are experiencing clinical benefit and no undue risks.

Continued access will apply to this study only if at least 1subject is still on study treatment when study completion occurs. The sponsor will notify investigators when the continued access period begins.

6.2. Discontinuation or Withdrawal

6.2.1. Permanent Discontinuation of Treatment

The investigator has the right to discontinue a subject from the study for any medical condition that the investigator determines is in the best interest of the subject, reasons of non-compliance (eg, missed doses, visits), or pregnancy.

Any subject who discontinues treatment should be encouraged to return to the study site for an End of Treatment Visit and continue with the remaining study visits outlined in Table 1. The primary reason for discontinuation must be recorded on the appropriate eCRF.

Subjects may be discontinued from treatment for any of the following reasons:

1. Disease progression (according to RECIST 1.1), unless there is reasonable evidence of clinical benefit to justify continuation on the study treatment. The continuation decision should be made by the investigators in consultation with the sponsor. The disease progression date is the date when radiological disease progression is first reported according to RECIST 1.1 criteria.
2. Withdrawal of consent;
3. Intolerable toxicity;
4. Poor subject compliance;
5. Use of other antitumor treatment during the study;
6. Pregnancy;
7. Subject is lost to follow-up;
8. The investigator or sponsor determines it is in the best interest of the subject;
9. Study is terminated by the sponsor;
10. Death;
11. End of this study.

6.2.2. Withdrawal from Study

All study participants have the right to withdraw from the study at any time. During the treatment period and follow-up period, a subject who withdraws consent to continue participation in the study will not be followed for any reason after consent has been withdrawn. Every effort should be made to obtain information on subjects who discontinue study treatment but who do not withdraw consent to continue participation in the study. If a participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

6.2.3. Replacement of Subjects

Subjects will not be replaced in this study.

6.2.4. Subjects Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a

certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

Should the participant continue to be unreachable, he/she will be considered to be withdrawn from the study.

6.3. Study Termination

The sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

6.4. End of Study

The end of the study defined as the last visit of the last subject in the study.

7. STUDY DRUGS

7.1. Study Drug Administration

Fruquintinib (at a dose of 5 mg) or matching placebo will be administered PO, QD, on a 3 weeks on, 1 week off schedule. One treatment cycle is 4 weeks. The administration time should be recorded accurately. Study drug may be given either in the fasting state or after meals. If dose adjustment is required, 1 mg fruquintinib or matching placebo capsules will be used.

On days with PK collection, treatment should be administered at the site by a delegated study staff member.

7.2. Description of Products

Fruquintinib will be provided as 1 mg or 5 mg capsules for oral administration. Matching placebo capsules for each strength will also be provided.

7.2.1. Formulation, Storage, Preparation and Handling

The investigational drugs are formulated as capsules, which are packaged in labeled bottles. The drug information is provided in Table 5. Additional information is available in the pharmacy manual.

Table 5 Information on Investigational Products

Name	Dosage	Specification	Administration Method
Fruquintinib	Capsule	5 mg	Oral
Fruquintinib	Capsule	1 mg	Oral
Matching placebo*	Capsule	5 mg	Oral
Matching placebo *	Capsule	1 mg	Oral

* The appearance of the matching placebo is identical to that of the study drug.

All the investigational drugs should be sealed and stored in a secure, limited access area under appropriate conditions. The storage temperature should be between 10℃ to 30℃. Investigational drugs should not be used beyond expiration date provided by the manufacturer.

The temperature-monitoring log should be recorded and filed in the study binder.

7.2.2. Drug Accountability

7.2.2.1. Assignment/Disposal (Study Site)

All study drug required for this study will be provided by Hutchison MediPharma Limited. The recipient will acknowledge receipt of the drug by returning the appropriate documentation form indicating shipment content and condition. Damaged supplies will be replaced.

Accurate records of all study drug received at, dispensed from, returned to and disposed of by the study site should be recorded by using the Drug Inventory Log.

Study drug will be disposed of at the study site according to the study site's institutional standard operating procedure or returned to Hutchison MediPharma Limited or a Hutchison identified entity with appropriate documentation, as determined by the study site. If the study site chooses to destroy study drug, the method of destruction must be documented.

7.2.2.2. Drug Return (Subject)

On day -2 to day 1, only subject randomization and drug assignment will be performed. The first dose of study drug should be administered on C1D1. Subjects will be provided with a pill diary at randomization and be instructed on how to account for each day's dose appropriately. Subjects should return all unused study drug and containers from the previous cycle on day 1 (date of scheduled visits) of each subsequent cycle, and new study drug will be dispensed on the same day. Site study staff should review subjects pill diary and provide a new diary if necessary at the day 1 visit of each cycle.

If a dose adjustment is required (eg, decrease from 5 mg QD to 4 mg QD), the subject must return to the investigational site and return all unused study drug. The site must log into the IWRS, adjust the dose, reassign the drug serial number, and dispense new study drug dose (in 1 mg capsules) to the subject. If the dose is adjusted a second time, ie, from 4 mg QD to 3 mg QD, the site must log into the IWRS and record the second dose adjustment. On this occasion, it is not necessary to reassign a new drug serial number. If tumor evaluation shows PD during the previous cycle and new drug has been dispensed, the subject must return all unused study drug on the 30-day safety visit after EOT.

7.3. Treatment Assignment and Bias Minimization

7.3.1. Treatment Allocation

Treatment will be allocated using IWRS randomization strategy and procedure (refer to the IWRS manual). After screening, subjects who meet the eligibility criteria will be randomized into the fruquintinib or placebo group in a 2:1 ratio. Randomization will be stratified by:

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

7.3.2. Extent and Maintenance of Blinding

The study subject, investigators, and study site personnel will remain blinded to all randomization assignments throughout the study except for the specific circumstances described in Section 7.3.3. The sponsor's study director, study monitor, and any other sponsor and contract research organization (CRO) personnel who are in regular contact with the study site will remain blinded to all subject randomization assignments, except sponsor pharmacovigilance personnel for the purpose of IND safety reports.

7.3.3. Unblinding Procedures

7.3.3.1. Emergency Unblinding

Unblinding can occur in emergency cases. If unblinding is required for treatment of a subject for an SAE, the investigator must first contact the sponsor's medical monitor before unblinding, and then unblind the subject using the IWRS. Once unblinded, the subject should discontinue the treatment but will continue to be followed for safety and efficacy. The investigator should record the event in the source document.

7.4. Assessment and Verification of Compliance

The investigator is responsible for ensuring the subject's treatment compliance. The sponsor will provide supervision through on-site monitoring visits made by its representatives. The investigators should maintain complete and accurate records of drug use. The dosing regimen and subject's actual dosing should be recorded in the original treatment records as well as eCRF. At each treatment visit, the investigators or study staff should comprehensively assess the subject's treatment compliance according to the drug dispensing and return status at each visit and the actual dosing conditions, such as missed doses and overdosing reported by the subject. The subjects must return all drug bottles and remaining capsules at the end of the study. The investigational sites must return all remaining supplies and drugs to the sponsor or provide evidence of destruction at the conclusion of the study.

7.5. Prior and Concomitant Therapies

7.5.1. Prohibited Therapies

Any therapy intended for the treatment of cancer (with the exceptions as noted in Section 7.5.2, whether currently marketed or experimental, is prohibited. This includes, but is not limited to, the following: chemotherapy, hormonal therapy, biologic therapy, radiotherapy, or herbal therapy.

Concomitant use of medications that have a known risk of causing QT prolongation and/or torsades de pointes (see "combined" list at http://www.crediblemeds.org, with attention to those drugs listed as KR ("known risk").

7.5.2. Permitted Therapies

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a subject. All concomitant therapy within 28 days prior to randomization and the Safety Follow Up visit. All concomitant medications should be reported to the investigator and recorded on the appropriate eCRF.

Subjects who use oral contraceptives, hormone-replacement therapy, or other allowed maintenance therapy may continue their use if indicated.

Prophylactic use of anticoagulation for the maintenance of patency of permanent indwelling central venous access devices or for subjects at high risk of venous thromboembolism is permitted during study treatment. If subjects are receiving anti-coagulation, they should be very closely monitored for potential hemorrhage, and:

The investigator should closely monitor subjects receiving anti-platelet and/or anti-thrombotic drugs during study drug treatment and make a timely decision on whether to continue or stop such drugs in subjects that report grade ≥2 hemorrhagic events at any site, based on an individual assessment of the risk-benefit balance (See Appendix 6 for additional information on the clinical management of severe or serious hemorrhagic AEs).

Subjects that develop arterial thromboembolic events should discontinue the study drug. If a subject suffers a venous thromboembolic event while still receiving study drug, it may still be possible for him or her to remain on study treatment under close monitoring and dose modification of study drug.

Prophylactic antiemetic, granulocyte colony stimulating factors, granulocyte macrophage colony-stimulating factors, platelet simulating factors or erythropoietin are permitted as clinically indicated.

Palliative radiation for symptom control is allowed provided it does not compromise tumor assessments of target lesions. However, fruquintinib treatment should be suspended during the radiation period and not resumed until at least 7 days after radiation only after meeting the following criteria:

- Radiation related toxicities resolves to grade ≤2;
- No disease progression observed.

All supportive measures consistent with optimal subject care will be given throughout the study.

7.5.3. Drug-Drug Interactions

In vitro metabolism data indicate that CYP3A plays an important role in the metabolism of fruquintinib. The potential effects of medications that can affect the PK of fruquintinib via the CYP3A pathway have not been tested in the clinic. Therefore, medications that are strong inhibitor or strong inducer of CYP3A should not be administered concomitantly with fruquintinib. Examples of these medications to avoid are listed in Appendix 3.

In vitro, fruquintinib is shown to have the potential to inhibit P-gp and BCRP (see Section 2.1.3.2). Avoid concomitant use with medications that are sensitive substrates of P-gp or BCRP where possible. If used together, monitor subjects more frequently for adverse reactions, and consider dose reduction of the P-gp or BCRP substrate medication. Examples of the medications that are sensitive substrates of P-gp and BCRP are listed in Appendix 3.

Fruquintinib shows pH-dependent solubility (ie, solubility at pH 6.0–6.5 < solubility at pH 1–2) and is less well absorbed as gastrointestinal pH increases. Subjects should avoid using proton pump inhibitors (eg, esomeprazole, lansoprazole, pantoprazole) during the study. If concomitant use of an acid-reducing agent is unavoidable, H_2-antagonist (eg famotidine, ranitidine, nizatidine) may be used but should be administered approximately 10 hours before or 2 hours after fruquintinib dosing. Antacid may be used, but the antacid dose should be administered at least 2 hours before or 2 hours after fruquintinib dosing.

7.5.4. Rescue Therapies

Not applicable.

7.5.5. General Dose Adjustment Note

The severity of AEs will be graded according to the NCI CTCAE v5.0. Reasons for dose modifications or delays, the supportive measures taken, and the outcome should be documented in the subject's chart and recorded in the eCRF.

- For any concomitant conditions already apparent at baseline, the dose modifications will apply according to the corresponding shift in toxicity grade, if the investigator feels it is appropriate. For example, if a subject has grade 1 asthenia at baseline that increases to grade 2 during treatment, this will be considered a shift of one grade and treated as grade 1 toxicity for dose-modification purposes.
- For toxicities that are considered by the investigator to be unlikely to develop into serious or life-threatening events, treatment can be continued at the same dose.
- To recover from acute toxicity, unless otherwise indicated, the treatment can be delayed for up to 14 days. If a treatment delay longer than 14 days is required, treatment should be discontinued. Continuation/resumption of fruquintinib treatment after an interruption of more than 14 days must be discussed with the medical monitor or his or her designee.
- Where several toxicities with different grades or severity occur at the same time, the dose modifications should be according to the highest grade observed.

7.5.6. Dose Modification Guidance

7.5.6.1. Dose Modification Sequence by Starting Dose and for General Hematologic and Non-Hematologic Toxicity

The dose reduction sequence by starting dose is shown in Table 6. Subjects are allowed to have no more than 2 dose reductions: one reduction from 5 mg QD to 4 mg QD, and if not tolerated, then a second reduction from 4 mg QD to 3 mg QD (see Table 6). Once a dose has been reduced, it cannot be re-escalated.

Table 6 Dose Modification Sequence by Starting Dose

Dose Level 0* (Original dose)	5 mg QD 3 weeks on, 1 week off	Fruquintinib of 5 mg, 1 capsule, or 1 capsule of the matching placebo
Dose Level -1* (the 1st dose reduction)	4 mg QD 3 weeks on, 1 week off	Fruquintinib of 1 mg, 4 capsules, or 4 capsules of the matching placebo
Dose Level -2* (the 2nd dose reduction)	3 mg QD 3 weeks on, 1 week off	Fruquintinib of 1 mg, 3 capsules, or 3 capsules of the matching placebo

* Doses are daily, on days 1-21 each 28-day cycle (3 weeks on, 1 week off)

Dose reduction guidelines for haematologic and non-haematologic toxicities, other than Palmar-plantar erythrodysesthesia (PPE), Proteinuria, Hypertension, Decreased platelet count, Hemorrhage, and liver function impairment, are shown in are shown in Table 7. Treatment should be held until AE/toxicity resolves or improves to ≤ grade 1. If a subject has a grade 3 toxicity that

is expected to be manageable and reversible with a dose reduction, treatment should be held until toxicity resolves to ≤grade 1. Subjects with grade 3 non-haematologic toxicity not described below that does not resolve to ≤grade 1 within 14 days should permanently discontinue the study drug unless approval to continue is obtained in writing from the sponsor.

Table 7 Dose Modification Recommendations for Hematologic and Non-Hematologic Toxicity

NCI CTCAE v5.0 Toxicity Grading	Action
Grade 1 or 2[a]	None
Grade 3[b]	Interrupt the dose until the toxicity resolved to ≤grade 1 or baseline level within 14 days, then reduce the dose to lower a dose level
Grade 4	Discontinue treatment permanently

a Should any arterial thrombosis occur the treatment should be terminated.

b Including grade 3 diarrhea and stomatitis, etc. that are ineffectively treated by drug therapies, but excluding grade 3 menstrual cycle extension.

7.5.6.2. Dose Modification for Important Identified Risks

The dose modification and treatment suggestions for specific identified risks are provided in Table 8(PPE), Table 9 (proteinuria), Table 10 (hypertension), Table 11 (decreased platelet count), Table 12 (hemorrhage at any site), and Table 13 (abnormal liver function).

Table 8 Dose Modification for Palmar-Plantar Erythrodysethesia

AE Grading Standard	Dose Adjustment	Treatment Suggestions
Grade 1: numb, paresthesia, dysesthesia, erythema, painless edema, desquamation, thicken skin and hand and foot discomfort which does not affect the normal activities; without any pain	None.	Active supportive treatment can be adopted to relieve the symptoms; for example, moisturizing skin cream, lotion, or hydrophilic urea ointment can be used.
Grade 2: erythema with pain accompanied by hand and foot swelling and /or discomfort, which affects normal activities	Hold treatment. Resume at the same dose if the AE recovers to grade 1 or baseline level within 14 days.	Active supportive treatment can be adopted to relieve the symptoms; for example, moisturizing skin cream, lotion, or hydrophilic urea ointment can be used.
Grade 3: wet desquamation, ulcer, blister or severe hand and foot pain or severe discomfort, which affects work or normal activities.	Hold treatment. Dose reduce and resume treatment at the next lowest dose level if the AE recovers to grade 1 or baseline level within 14 days.	Active supportive treatment can be adopted to relieve the symptoms; Should the same AE occur for 3 times or still occurs after 2 times of dose reduction, the drug should be terminated.

Table 9 Dose Modification for Proteinuria[a]

AE Grading Standard	Dose Adjustment	Treatment Suggestions
Grade 1: Proteinuria 1+ by urinalysis; 24-hour urine protein quantitation <1.0 g	None	Follow up at scheduled study visits.
Grade 2: Proteinuria 2+ by the urinalysis; 24-hour urine protein quantitation is between 1.0 to <2.0 g	None	Provide supportive treatment and increase the frequency of urine monitor to once a week; consult nephrologist if necessary.
Grade 2: Proteinuria 2+ or above by urinalysis; 24-hour urine protein quantitation is between 2.0 to <3.5 g (excluding 3.5 g)	Hold treatment. Dose reduce and resume treatment at the next lowest dose level if the AE recovers to grade 1 or baseline level within 14 days.	Provide supportive treatment and increase the frequency of urine monitor to once a week; consult nephrologist if necessary.
Grade 3: 24-hour urine protein quantitation ≥3.5 g	Hold treatment. Dose reduce and resume treatment at the next lowest dose level if the AE recovers to grade 1 or baseline level within 14 days.	Provide supportive treatment and increase the frequency of urine monitor to once or twice a week; consult nephrologist if necessary. Should the same AE occur for 3 times or still occurs after 2 times of dose reduction, the drug should be terminated.
a: If protein ≥ 2+ on urinalysis during the study, a 24-hour urine test should be conducted within 1 week, and dose modification will be done by the result of 24-hour urine protein quantitation.		

Table 10 Dose Modification for Hypertension

AE Grading	Dose adjustment	Treatment Suggestions
Grade 1: prehypertension (systolic BP 120-139 mmHg or diastolic BP 80-89 mmHg)	None.	Follow up as planned schedule
Grade 2: SBP 140-159 mmHg or DBP of 90-99 mmHg; or DBP symptomatic increase >20 mmHg	None.	Treatment objective: lower the blood pressure to <140/90 mm Hg (or <130/80 mm Hg in subjects with chronic renal disease and/or diabetes). Refer to Appendix 7.
Grade 3: SBP ≥ 160 mmHg or DBP ≥100mmHg; or more than one drug or more intensive therapy are used	If BP >160/100mmHg lasts for >7 days after initiation of anti-hypertensive treatment or modification of current anti-hypertensive treatment, treatment should be held. If hypertension resolves to grade 1 or baseline level within 14 days, treatment should be resumed at the next lowest dose level.	Treatment objective: lower the blood pressure to <140/90 mmHg (or <130/80 mm Hg in subject with chronic renal disease and/or diabetes). Refer to Appendix 7.
Grade 4: Life threatening (eg, malignant hypertension, temporary or permanent neurological deficits and hypertensive crisis)	Permanently discontinue study treatment.	Emergent medical treatment.

Table 11 Dose Adjustment for Decreased Platelet Count

AE Grading	Dose Adjustment	Treatment Suggestions
Grade 1: Platelet count <LLN - 75,000/ mm^3; <LLN - 75.0 $\times 10^9$/L	None.	Perform follow up visit as scheduled.
Grade 2: Platelet count <75,000-50,000/mm^3; <75.0 - 50.0 $\times 10^9$/L	Hold treatment. Resume at the same dose if the AE recovers to grade 1 or baseline level within 7 days.	Hematology test should be monitored every 2-3 days; active treatment for platelet elevation is recommended.
	Hold treatment. Dose reduce and resume treatment at the next lowest dose level if the AE recovers to grade 1 or baseline level within 7-14 days.	Hematology test should be monitored every 2-3 days; active treatment for platelet elevation is recommended.
Grade 3: Platelet count <50,000 - 25,000/mm^3; <50.0 - 25.0 $\times$ 10^9/L	Hold treatment. Dose reduce and resume treatment at the next lowest dose level if the AE recovers to grade 1 or baseline level within 14 days.	Hematology test should be monitored every 2-3 days; active treatment (platelet transfusion) to elevate the platelet count is recommended. Hematology examination should be performed once every week in the follow up visit.
Grade 4: Platelet count <25,000/mm^3; <25.0 $\times$ 10^9/L	Permanently discontinue study treatment.	Hematology test should be performed once daily until the AE recovers to grade 2 or a lower grade; platelet transfusion or other active treatment should be provided

Table 12 Dose Adjustment for Hemorrhage at any Site

AE Grading	Dose Adjustment	Treatment Suggestions
Grade 1	None	Perform follow up visit as scheduled.
Grade 2	The drug can be interrupted and then reduced to the lower dose level should the AE recovered to grade 1 or baseline level within 14 days.	Provide active treatment[b]
Grade 3 or above[a]	Permanently discontinue study treatment.	Emergent medical intervention[b]

a Refer to Appendix 6 for clinical management of severe or serious hemorrhage.
b The investigator should closely monitor subjects receiving anti-platelet and/or anti-thrombotic drugs during study drug treatment and make a timely decision on whether to continue or stop such drugs in subjects that report grade ≥2 hemorrhagic events at any site, based on an individual assessment of the risk-benefit balance (See Section 7.5.2).

Table 13 Dose Adjustment for Abnormal Liver Function

AE Grading[a]	Dose Adjustment	Treatment Suggestions
Grade 1	None.	Follow up per planned schedule.

Table 13 Dose Adjustment for Abnormal Liver Function

AE Grading[a]	Dose Adjustment	Treatment Suggestions
Grade 2 or 3 (Liver function is abnormal but the biochemical criteria for Hy's Law[b] are not met)	1. Drug interruption can be considered; 2. The dose should be reduced to the lower dose level if the AE recovers to grade 1 or baseline within 14 days.	Provide supportive care and increase the frequency of liver function monitoring to 1-2 times a week.
Grade 2 or 3 (Liver function is abnormal and the biochemical criteria for Hy's Law[b] are met)	The study drug should be terminated immediately.	Provide supportive care and increase the frequency of liver function monitoring to 2-3 times a week. Urgent medical intervention indicated.
Grade 4	The study drug should be terminated.	Urgent medical intervention indicated.

a Including increasing of ALT, AST, and total bilirubin, whether or not the biochemical criteria for Hy's Law have been met.

b Hy's Law is an increase in serum AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN, and no other reason can be found to explain the biochemical changes, for example, new or worsening hepatobiliary metastases, elevated serum alkaline phosphatase indicating cholestasis, viral hepatitis, another suspect drug, or any other specific cause of severe hepatocellular injury. The elevation in transaminases must precede or be coincident with (ie, on the same day as) the elevation in total bilirubin, but there is no specified timeframe within which the elevations in transaminases and total bilirubin must occur. See Section 8.2.2 for special reporting requirements and Appendix 5 for additional information regarding Hy's Law.

8. SAFETY MONITORING

8.1. Definitions

8.1.1. Adverse Event

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product or other protocol-imposed intervention, whether or not considered related to the medicinal product. Adverse events will be assessed according to the NCI CTCAE v5.0.

8.1.2. Serious Adverse Event

An AE is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE. An event is considered ″life-threatening″ if, in the view of the investigator, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction (AR) that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject or patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.2. Adverse Event Reporting

8.2.1. Adverse Event Reporting Period

After informed consent, but prior to initiation of study drug, all serious adverse events (SAEs) regardless of attribution will be collected. After initiation of study drug, all SAEs and AEs regardless of attribution will be collected until 30 days after the last dose of study drug or a new treatment of anti-tumor therapy, whichever is earlier. After this period, investigators should report only SAEs that are considered to be related to the study drug.

8.2.2. Expedited Reporting

Certain events require immediate reporting to allow the sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events (both initial

and follow-up) to the sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the sponsor within 24 hours after first learning of the event, regardless of relationship to study drug:

- SAEs (from informed consent to 30 days following the last dose of study drug or a new treatment of anti-tumor therapy),
- Abnormal hepatic function is defined as serum AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN, regardless of seriousness.
    - For management for hepatic function abnormal event, refer to Table 13 (Dose Adjustment for Abnormal Liver Function). Hy's Law is an increase in serum AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN, and no other reason can be found to explain the biochemical changes, for example, new or worsening hepatobiliary metastases, elevated serum alkaline phosphatase (ALP) indicating cholestasis, viral hepatitis, another suspect drug, or any other specific cause of severe hepatocellular injury. The elevation in transaminases must precede or be coincident with (ie, on the same day as) the elevation in total bilirubin, but there is no specified timeframe within which the elevations in transaminases and total bilirubin must occur. See Appendix 5 (Clinical Evaluation of Possible Drug-Induced Liver Injury (DILI) for additional information regarding Hy's Law.
- CTCAE grade ≥3 hemorrhagic event,
    - When there is a grade ≥3 hemorrhagic event per NCI CTCAE (Version 5.0). The management of severe or serious hemorrhagic events will be conducted according to Appendix 6 (Clinical Management of Severe or Serious Hemorrhagic Events).
- Pregnancy,

8.3. Eliciting Adverse Events

A consistent methodology of non-directive questioning for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinic visit?"
- "Have you had any new or changed health problems since you were last here?"

8.4. Assessment of Severity

Investigators will seek information on AEs and SAEs at each subject contact. All AEs and SAEs, whether reported by the subject or noted by authorized study personnel, will be recorded in the subject's medical record and on the appropriate AE/SAE form.

For each AE and SAE recorded on the applicable eCRF, the investigator will make an assessment of severity through clinical description by referring to the five-grade determination standard in the NCI CTCAE v5.0. Please use the guideline below for the assessment of severity when the observed or reported AE is not listed in the NCI CTCAE v5.0:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
- Grade 3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

Note:
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

8.5. Causality assessment

Investigators should use their knowledge of the subject, the circumstances surrounding the AE, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the study drug. To ensure consistency of causality assessments, investigators should apply the general guidelines in provided as below:

- **Related:** There is a reasonable possibility that the event may have been caused by the product under investigation. Factors that point toward this assessment include but are not limited to: a positive re-challenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation or dose reduction, a biologically plausible relationship between the drug and the AE, or a lack of an alternative explanation for the AE.

- **Not Related:** There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

8.6. Documenting Adverse Events

When an AE or SAE is recorded, the preferred medical terminology or concept should be used. Abbreviations and colloquialisms (eg, jargon or slang) should be avoided.

All AEs (including SAEs) should be recorded on the AE eCRF, and the check box for "Serious" should be ticked for entries that fit the criteria for SAEs. The investigator should also complete an SAE report and submit this to the sponsor or its designee within 24 hours of knowledge of the event.

Only one medical concept should be recorded in the event field on the eCRF.

8.6.1. Diagnosis versus Symptoms and Signs

If known, a diagnosis should be recorded on the eCRF rather than individual signs and symptoms (eg, hepatic failure should be recorded instead of jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the eCRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

8.6.2. Adverse Event Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (eg, cascade events or clinical sequelae) should be identified by their primary cause with the exception of severe or serious secondary events. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the eCRF if the dehydration is mild.

However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the eCRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the eCRF.

8.6.3. Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution between subject evaluation time points. Such events should only be recorded once in the eCRF. The event's initial severity should be recorded and updated when it increases so as to record to highest severity.

A recurrent AE is one that occurs and resolves between subject evaluation time points and subsequently recurs. All recurrent AEs should be recorded on the eCRF respectively.

8.6.4. Abnormal Laboratory Values or Abnormal Vital Signs

Not every laboratory abnormality/abnormal vital sign qualifies as an AE. A laboratory test result/abnormal vital sign must be reported as an AE if it is a change from baseline and meets any of the following criteria:

- Accompanied by clinical symptoms,
- Results in a change in study treatment (eg, dosage modification, treatment interruption, or treatment discontinuation),
- Results in a medical intervention (eg, potassium supplementation for hypokalemia) or a change in concomitant therapy,
- Clinically significant in the investigator's judgment.

Investigators are responsible for reviewing all laboratory findings and abnormal vital signs and determining whether or not each abnormality should be reported as an AE.

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (eg, ALP and bilirubin 5 × ULN associated with cholecystitis), only the diagnosis (eg, cholecystitis) needs to be recorded on the eCRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the eCRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7.0 mmol/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the eCRF, unless their severity, seriousness, or etiology changes.

8.6.5. Preexisting Medical Condition

A preexisting medical condition is one that is present at screening. Such conditions should be recorded on the eCRF as medical history. A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study (excluding deterioration of the study disease conditions). When such events are recorded on the eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (eg, "more frequent headaches").

8.6.6. Pregnancy

A female subject must be instructed to stop taking the study drug and immediately inform the investigator if she becomes pregnant during the study. The investigator should report all pregnancies within 24 hours of awareness to the sponsor (the reporting period for pregnancy continues up to 30 days after completion of the study drug). The investigator should counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the subject should continue until outcome of the pregnancy. Pregnancies occurring up to 30 days after the completion of the study drug must also be reported to the investigator.

Male subjects must also be instructed to inform the investigator immediately if their partner becomes pregnant during the study or within 90 days after the last dose of study drug. If such an event occurs, it should be reported as described above.

Pregnancy loss of any kind should always be classified as serious AE (as the sponsor considers these medically significant), recorded on the eCRF, and expeditiously reported to sponsor.

Any congenital anomaly/birth defect in a child born to a female subject or female partner of a male subject exposed to the investigational product should be recorded and reported as an SAE.

8.6.7. Worsening of Solid Tumor

Worsening and/or progression of the subject's solid tumor should not be recorded as an AE or SAE. These data will be captured as efficacy assessment data only. If there is any uncertainty about an AE being related only to the disease under study, it should be reported as an AE or SAE.

8.6.8. Death

All deaths that occur during the protocol-specified AE reporting period must have the underlying cause reported to the sponsor as an SAE with death listed as the outcome. Deaths due solely to the progression of disease must also be reported to the sponsor as an SAE. Death events that occur after 30 days following last dose of study drug must be reported to the sponsor as an SAE only if it is confirmed as related to study drug. If the primary cause of death is unknown and cannot be ascertained at the time of reporting, please record "Unknown cause death" on the eCRF, and the "unexplained/unknown death" should be reported expeditiously as an SAE. The SAE should be reported before the specific cause of death has been determined.

8.7. Duration of Follow-up for Adverse Events

The investigator will follow all unresolved AEs and SAEs until the events are resolved or stabilized, the subject is lost to follow-up, subject death, or end of study. Resolution of AEs and SAEs (with dates) should be documented on the appropriate eCRF and in the subject's medical record to facilitate source data verification (SDV). For SAEs, if, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded in the additional case details section of the eCRF.

For some SAEs, additional case details deemed necessary to appropriately evaluate the SAE report (eg, hospital discharge summary, consultant report, or autopsy report) may be followed-up by telephone, fax, email, and/or a monitoring visit.

All pregnancies that occur during the study should be followed until pregnancy outcome.

9. STATISTICAL ANALYSIS

9.1. Statistics and Analysis Method

A separate statistical analysis plan (SAP) will provide specific details on analytical methods.

9.1.1. Statistical Hypothesis

This study is designed to demonstrate superiority of fruquintinib plus BSC (treatment arm) over placebo plus BSC (placebo arm) in prolonging OS for subjects with refractory mCRC. The study is 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).

9.1.2. Sample Size Rationale

The total sample size and number of OS events required for efficacy assessment in the ITT population is calculated based on the following assumptions:

- A one-sided significance level of 0.025;
- Assuming an OS HR (treatment arm/placebo arm) of 0.73, this sample size yields approximately 80% statistical power to detect superiority of the fruquintinib arm over placebo arm. 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).
- An enrollment rate of 30 subjects per month during the first 3 months and 50 subjects per month thereafter;
- Yearly dropout rate of 10%;
- Randomization ratio = 2:1;
- Data maturity = 70%;
- One interim futility analysis when 1/3 of the total number of OS events (ie, 121 OS events) have occurred

Under the premise of these assumptions, approximately 522 subjects will be randomized to this study over approximately 13 months in this study. OS will be analyzed when 364 OS events are observed, which is expected to occur in approximately 7 months after the end of enrollment.

In clinical practice, TAS-102 is used more commonly than regorafenib. To ensure that the subject population is representative of clinical practice, post-regorafenib subjects will be capped at 262 subjects if there is an unanticipated enrichment of that population. This will ensure that at least 50% of the subjects will be post-TAS. Subjects are considered in post-TAS-102 or post-regorafenib populations if they have received at least one dose of either agent, respectively, prior to entering the study. Based on the similar mechanisms of action between regorafenib and fruquintinib, it will be of clinical interest to evaluate the magnitude of benefit in each of the populations when compared to the ITT population.

9.1.3. Analysis Sets

Intent-to-Treat (ITT) Population

All randomized subjects will be included in the ITT population. Subjects will be analyzed by treatment arm as randomized. The ITT population will be the primary population for evaluating all efficacy endpoints and patient characteristics.

Safety Analysis Population

All randomized subjects who received at least one dose of study treatment will be included in the safety analysis population. Subjects in this population will be analyzed according to the treatment they actually received. This population will be used for all safety analyses.

9.2. Primary and Secondary Endpoints

9.2.1. Primary Endpoint

The primary endpoint of the study is overall survival, defined as the time (months) from date of randomization to death from any cause. Subjects without report of death at the time of analysis will be censored at the date last known alive.

9.2.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints include PFS, ORR, DCR, and DoR.

9.2.2.1. Progression-free Survival

PFS is defined as the time (months) from randomization until the first radiographic documentation of objective progression as assessed by investigator using RECIST v1.1, or death from any cause. Subjects who did not die or progress will be censored at the date of last radiographic assessment. If no baseline or post-baseline radiologic assessment was available, the subject will be censored at the date of randomization. The use of new anticancer therapy prior to progression will result in censoring at the date of last radiographic assessment prior to initiation of new therapy. If death/PD occurred after two or more consecutive missed radiographic visits, subjects will be censored at the date of last radiographic assessment prior to missed visits.

9.2.2.2. Objective Response Rate

Objective response rate is defined as the proportion of subjects achieving a best overall response of confirmed complete response (CR) or partial response (PR), per RECIST v1.1, as determined by the investigator.

9.2.2.3. Disease Control Rate

Disease control rate is defined as proportion of subjects achieving a best overall response of confirmed CR, PR, or SD, per RECIST v1.1, as determined by the investigator. To be qualified for SD, the duration of SD should last for at least 6 weeks.

9.2.2.4. Duration of Response

Duration of response is defined as the time (months) from the first occurrence of PR or CR, whichever comes first, until the date of radiographic PD or death. The duration of response will be determined for subjects with best overall response of confirmed CR or PR.

9.2.3. Secondary Safety Endpoints

Safety endpoints include AE, laboratory tests, vital signs and weight, ECG, echocardiogram/MUGA (especially LVEF) and ECOG PS.

All AEs, whether related to the drug or not, will be recorded in the eCRF including the start/end date, measures taken, treatment affected (yes versus no) and the outcome. For all the events, the causality with the treatment and the severity will be determined by the investigator.

9.2.4. Other Endpoints

9.2.4.1. Patient Reported Outcomes

Quality of life will be assessed using EORTC QLQ-C30 and EQ-5D-5L questionnaires. Quality of life score, change from baseline, subjects achieving minimally important difference (MID) cut-off, and time to deterioration (TTD) will be assessed.

9.2.4.2. Assessment of Resource Utilization

Health care resource utilization assessments such as physician visits, emergency room visits, hospital care (eg, inpatient and outpatient), drug prescriptions etc. will be assessed.

9.2.5. Statistical Methods

9.2.5.1. Analysis of Efficacy Endpoints

Efficacy analyses will be based on ITT population. All secondary endpoints based on radiological assessments of tumor burden will be derived from investigator assessment using RECIST v1.1. Additional sensitivity analyses may be performed and will be outlined in the SAP.

9.2.5.1.1. Primary Endpoint - Overall Survival

A 1-sided stratified log-rank test will be used for the comparison of OS of the fruquintinib with placebo group at a significance level of 0.025. The same factors used for randomization will be used for stratification: prior therapy with TAS versus regorafenib versus both trifluridine/tipiracil (TAS-102) and regorafenib; RAS status (wild type versus mutant); and duration of metastatic disease (<18 months versus ≥18 months). Kaplan-Meier methodology will be used to estimate the median OS and its 2-sided 95% Confidence Interval (CI) for each treatment arm. Plots will be produced by treatment arm. The Hazard Ratio (HR) will be estimated by stratified COX model including a 2-sided 95% Confidential Interval (CI).

9.2.5.1.2. Secondary Efficacy Endpoints (PFS, ORR, DCR, DoR)

First secondary endpoint is to evaluate PFS in subjects with refractory mCRC treated with fruquintinib plus BSC versus placebo plus BSC. The Fixed-Sequence Method will be used to adjust for multiple comparisons of OS between the fruquintinib plus BSC arm and the placebo plus BSC arm (primary endpoint) and PFS (first secondary endpoint). If the primary endpoint analysis is significant at the 0.05 (two-sided) level, a superiority test of PFS in the first secondary endpoint will be done at the 0.05 (two-sided) significant level. Kaplan-Meier methodology will be used to estimate the median PFS and its 2-sided 95% confidence interval (CI) for each treatment arm. Plots will be produced by treatment arm.

The hazard ratio (HR) will be estimated by stratified COX model including a 2-sided 95% CI.

The estimates of DCR and ORR in each treatment group and their 2-sided 95% CIs will be presented. Comparison of DCR and ORR between treatment groups will be performed using stratified Cochran-Mantel-Haenszel test. The CI of difference in DCR and ORR between treatment groups will be calculated using the approximate normal distribution method of binomial distribution.

Duration of response (DoR) will only be determined for subjects who responded (confirmed best overall response of CR or PR). Statistical test will not be conducted, as subjects with response are not randomized. Descriptive analysis will be adopted for DoR. For each treatment group, results will be presented by Kaplan-Meier estimates and distribution curve.

9.2.5.1.3. Subgroup Analyses

Subset analyses may be conducted, for example, by age, performance status, prior lines of therapy, prior use of TAS-102, prior use of regorafenib, region, and others as deemed appropriate.

9.2.5.2. Analysis of Safety Endpoints

All safety parameters will be summarized and listed by using the safety population.

TEAEs will be summarized by MedDRA system organ class (SOC) and PT. The incidence and percentage of subjects with at least 1 occurrence of a preferred term will be included according to the most severe NCI-CTCAE version 5.0. Relationship to study therapy (causality) will be summarized separately. If more than one AE was recorded for a subject within a PT, the subject will be counted once in the most severe grade.

Laboratory data will be summarized by visit. All TEAEs and abnormal laboratory variables shall be evaluated by the NCI CTC AE Version 5.0 Classification System. Other safety data including vital signs, ECG, ECOG PS will be summarized using descriptive statistics.

9.2.5.3. Analysis of Other Endpoints

9.2.5.3.1. Subject Reported Outcomes

Subject reported outcomes will be assessed using EORTC QLQ-C30 and EQ-5D-5L questionnaires. The number and percentage of subjects who completed the questionnaires will be summarized for each treatment arm by visit. Reasons for non-completion will be presented. Quality of life scores and change from baseline scores will be compared between treatment arms using mixed model repeated measures approach adjusting for covariates. For each scale,

appropriate minimally important difference (MID) cut-off will be determined and number and percent of subjects achieving the MID will be presented. In addition, time to deterioration (TTD) will be summarized using Kaplan-Meier methodology.

9.2.5.3.2. Resource Utilization

Health care resource utilization data including number and percent of subjects hospitalized, reasons for hospitalizations, emergency room visits, drug prescriptions will be summarized.

9.3. Pharmacokinetic and Pharmacodynamic Analyses

9.3.1. Population PK and Exposure-Response Analyses

Descriptive statistics (including but not limited to arithmetic mean, standard deviation, coefficient of variation, median, minimum, maximum and geometric mean) will be provided for the observed concentrations for fruquintinib and metabolite M11.

Population PK analysis of plasma concentration-time data of fruquintinib and metabolite M11 will be performed using nonlinear mixed-effects modeling. The population PK modeling will include all subjects with sufficient and interpretable PK assessments. The data from the population PK samples may be combined together with the data from other studies for the population PK analysis. If relevant and sufficient data are available, the relationship of exposure to fruquintinib and M11 to measures of efficacy and AEs may also be analyzed. Details of the population PK and/or exposure-response analysis will be given in a population PK/pharmacodynamic analysis plan. The results of the population PK/pharmacodynamic analysis will be presented in a separate report.

9.3.2. Pharmacodynamic (ECG) Analysis

Subjects who 1) receive at least 1 dose of study drug, and 2) have baseline and at least 1 post-dose ECG measurement will be evaluable for pharmacodynamic (ECG) evaluation. Subjects who had reduced dosage, prolonged dose interruption of >2 days in cycle 1, or who had any dose interruption within 7 days before cycle 1 day 21, or were discontinued from the study prior to the completion of ECG data collection (cycle 1 day 21) will be excluded. For each of the ECG parameters, the average values from the 3 readings of a triplicate ECG set will be used in the analysis.

For all ECG parameters, the baseline will be defined as the mean values of the triplicate ECG measurements taken at pre-dose on cycle 1 day 1.

9.3.2.1. QTc Intervals

The terminology QTc is used in this section as a general notation for corrected QT intervals using any of the specified methods.

The QT interval data will be corrected for heart rate using 2 correction methods (Fridericia – QTcF and Bazett – QTcB). For each QTc correction method, the relationship between QTc and RR at baseline will be evaluated graphically by plotting the logarithm of baseline QTc values against the logarithm of corresponding RR intervals. Fridericia will be used as the primary correction method for statistical analysis. If the correlation between QTc and RR intervals remains significant using the Fridericia correction method, an alternative correction method may be considered for statistical analysis in addition to QTcF.

For the statistical analysis based on the primary correction method (QTcF), the mean changes from baseline (ΔQTc) at each time point will be summarized (mean, standard deviation, median and range, 2-sided 90% confidence interval). The difference in ΔQTc between fruquintinib and placebo (ΔΔQTc) for each individual will also be calculated at each time point (individual ΔQTc for fruquintinib – mean ΔQTc for placebo at the same time point). Mean values for the difference and 2-sided 90% CI for mean difference will be calculated at each time point.

The primary analysis will focus on the maximum mean change from baseline in QTc (ΔQTc) on cycle 1 day 21, which will be estimated by the mean QTc change at around T_{max}, the time when the maximum plasma concentration is reached (ie, steady state). The same analysis will be performed for ΔQT data using other correction methods if data warrant. The mean change from baseline in QTc (±standard deviation) over time will be plotted.

In addition, QTc will be categorized based on ICH E14 guidelines. Tables will present the number and percentage of subjects meeting or exceeding the following categories:

- QTc interval prolongation:
  - Absolute values > 450 to ≤ 480 msec
  - Absolute values > 480 to ≤ 500 msec
  - Absolute values > 500 msec
- QTc interval change from baseline:
  - Increase from baseline > 30 to ≤ 60 msec
  - Increase from baseline > 60 msec

9.3.2.2. Heart Rate, QRS, and PR intervals

For each treatment and time point of measurement, heart rate (HR), QRS interval and PR interval, as well as the change from baseline in HR, QRS and PR (ΔHR, ΔQRS, ΔPR), will be summarized using descriptive statistics (mean, standard deviation, median, range, and 90% CI). The number and percentage of subjects with HR >100 bpm will be tabulated for each time point. The number and percentage of subjects with QRS >110 msec will be tabulated for each time point. The number and percentage of subjects with PR >200 msec will be tabulated for each time point.

9.3.2.3. T-wave and U-wave Morphology

The number and percentage of subjects having T-wave morphology changes from baseline and/or the occurrence of abnormal U-waves that represent the appearance or worsening of the morphological abnormality will be summarized. Subjects with abnormal ECG findings will be listed. Additional analyses will be performed if deemed necessary.

9.3.3. QTc-PK Analysis

The potential relationship between QTc and PK will be evaluated using data from all subjects who have data from baseline and at least 1 post-dose ECG measurement following the first dose. QTc change from baseline before and after correction for placebo (ΔQTc and ΔΔQTc) using the primary correction method (see Section 9.3.2.1) at each time point of measurement will be plotted against

the corresponding plasma concentrations of fruquintinib and M11 separately. Additional plots will be produced, if deemed necessary.

A linear mixed effects model will be fitted to the ΔQTc and ΔΔQTc data from cycle 1 day 1 and cycle 1 day 21 with either parent or metabolite concentration as a predictor and subject as a random effect; if the intercept term is not significant, the model will be re-fitted with a zero intercept term. Based upon these relationships, the predicted population average ΔQTc and ΔΔQTc as well as their corresponding upper 90% 2-sided confidence interval bound will be computed at the mean maximum plasma concentrations (ie, C_{max}) of fruquintinib and M11, or other concentrations of interest.

9.4. Interim Analysis

An independent data monitoring committee (IDMC) will be convened to review accumulating safety data. During the study, safety interim analyses will be performed approximately every 6 months. The frequency of safety interim analysis may be modified upon IDMC recommendation.

One interim futility analysis will be performed when approximately 1/3 of the total number of OS events (ie, 121 OS events) had occurred. This interim analysis is for futility only. The IDMC will be instructed to recommend stopping the study for futility if the 1-sided p-value from a stratified log-rank test is at least 0.622 (corresponding to an observed HR of 1.062). Otherwise, the study will continue with full enrollment. There is a 37.8% chance of terminating the study for futility at the interim analysis if the true median OS in fruquintinib arm is 5 months, ie, fruquintinib is ineffective. There is a 2.6% chance of stopping for futility, declaring fruquintinib ineffective at the interim if the true median OS in fruquintinib arm is 6.8 months, ie, fruquintinib is effective in our study population.

10. ETHICAL CONSIDERATIONS

10.1. Quality Control and Quality Assurance

The clinical study will be executed and reported following GCPs, all applicable regulatory requirements and applicable SOPs, including quality control of documents. Deviations will be documented. To ensure compliance, the sponsor may conduct one or several quality assurance audit(s).

10.2. Ethics Review

The Independent Ethics Committee (IEC) / Institutional Review Board (IRB) must review the protocol and amendments, investigator's brochure, informed consent form, study-relevant materials (such as advertisements for subject recruitment) and any other essential documents. IEC/IRB approval is to be obtained prior to the study.

All amendments are to be reviewed and approved by the IEC/IRB, applicable regulatory authorities (as required) and documented. All unexpected SAEs should be reported to the sponsor, IEC/IRB and applicable regulatory authorities as required. During the study, protocol deviations that may increase a subject's risk should be reported to the IEC/IRB in a timely manner.

10.2.1. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

10.3. Informed Consent

Investigators or designees must obtain the signed informed consent form from subjects prior to conducting any study-related procedures. The nature, objectives, and potential risks and benefits of participating in the study must be explained to subjects. Subjects must be informed that they may withdraw consent to participate in the study without any limitations. If the subject cannot sign the informed consent form, a legally acceptable representative of the subject must sign the informed consent form. If the subject and the legally acceptable representative are not able to read and write, an impartial witness should be present throughout the whole process of providing informed consent. Once the subject and the legally acceptable representative give their oral consent, the informed consent form should be signed by the impartial witness to confirm that the subject and the legally acceptable representative fully understand the study and their right to withdraw informed consent without any limitations. Informed consent should be recorded in the CRF. If the risk and benefit assessment changes after the safety analysis, the informed consent form needs to be reviewed and updated and all updated information should be provided to subjects (including subjects who have already received the study drug).

10.4. Data Privacy

All information about fruquintinib (such as patent application, formulation, manufacturing process and basic study information) is considered confidential as long as it is unpublished.

All information obtained in the study is considered confidential. Hutchison MediPharma Limited will open the information to investigational personnel, the NMPA (National Medical Products Administration), and any other regulatory authority when necessary. To ensure the completeness of the study analysis data, investigational personnel are accountable for providing all results and data to the sponsor.

Investigators must guarantee the privacy of subjects by not disclosing subject-related information to third parties without authorization. eCRFs and other documents submitted to the sponsor should not contain the subject's name. Subjects are identified only by Patient Code. Investigators may retain the identification forms, which include subject numbers, names, and addresses. Informed consent forms and other documents should be documented properly, and should not be given to the sponsor.

10.5. Disclosure

Final study results will be published on a public clinical trial website according to applicable local guidelines and regulations.

10.6. Biological Specimens and Data

Subjects who agree to participate in a future biomedical research sub-study will be required to consent to this optional sub-study before samples are collected for long-term storage. No additional samples will be collected for future biomedical research. Samples will be single/double-coded as defined by ICH guideline E15.

The unused samples for study-related research, as well as unused PK samples, will be stored for up to 15 years after the final date of the database lock. The unused samples may be utilized for future biomedical research. After 15 years, any residual samples will be destroyed. The results of these future biomedical research analyses will not be shared with subjects and will not be presented in the CSR.

If there are specific site or country requirements involving the pharmacogenomic analyses that the sponsor is unable to comply with, samples will not be collected at those sites.

11. OVERSIGHT

11.1. Independent Monitoring

11.1.1. Independent Data Monitoring Committee

An IDMC will be established in this study. The IDMC will consist of at least 4 independent clinical oncology physicians and 1 independent statistician with no conflicts of interest with the sponsor. The IDMC will evaluate the safety data regularly, and the patients' safety will be determined by the evaluation of the risk/benefit at a regular review meeting. The responsibilities of the IDMC will include:

- Regular (approximately every 6 months) blinded review of the study data to provide suggestions such as "continue as planned, suspend, protocol amendment, terminate study" so as to prevent patients from being exposed to unsafe dose and treatment regimes.
- Review of interim analysis data to provide suggestions such as "continue as planned, suspend, protocol amendment, terminate study."

Upon completion of the data review, the IDMC will provide suggestions on whether or not to continue the study, if modification of the protocol is recommended or if study termination is required. The final decision shall be made by Hutchison MediPharma Limited. The IDMC membership and governance is outlined in a separate IDMC charter.

11.2. Quality Control and Assurance

In accordance with ICH, the sponsor is responsible for quality assurance to ensure that the study is conducted, and the data are generated, recorded, and reported in compliance with the protocol, GCP, and any applicable regulatory requirement(s). The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site. The sponsor and investigator ensure that any individual or party who performs trial-related duties or functions on behalf of the sponsor/investigator is qualified to perform the trial-related duties or functions.

The overall procedures for quality assurance of clinical study data are described in the sponsor or designee's standard operational procedures. The planned quality assurance and quality control procedures for the study are described in the following sections.

11.3. Monitoring

Monitors designated by the sponsor will contact and visit investigators at regular intervals to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of subjects are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, GCP, and all applicable regulatory requirements. During regular visits, the monitors may verify CRFs for protocol compliance, data completeness, consistency, and accuracy. Monitors may also obtain laboratory test results and other records for verifying CRF accuracy. Investigators (or their designee) should cooperate with monitors to resolve questions raised during monitoring.

The investigator must allow study-related monitoring.

11.3.1. Audits

Authorized representatives of Hutchison MediPharma Limited, a regulatory/competent authority, and/or an IRB/IEC representative may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to examine all study-related activities and documents systematically and independently to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines, and any applicable regulatory requirements. The investigator should notify the sponsor (eg, CRA) listed within the protocol or other contacts provided immediately if contacted by a regulatory agency about an inspection.

11.3.2. Protocol Deviations

This protocol is monitored at several levels, as described elsewhere in this section. The study principal investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, subject-specific clinical and laboratory data, and routine and SAEs; reporting of expedited AEs; and accumulation of reported AEs from other trials testing the same drug(s). The sponsor and statistician have access to the data at all times.

All study investigators at participating sites who register/enroll subjects on a given protocol are responsible for timely submission of data via the mechanism described elsewhere in this section. All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

11.3.3. Records

11.3.3.1. Data Capture and Management

The term case report form (CRF) or electronic case report form (eCRF) should be understood to refer to electronic data capture (EDC) system. The EDC system is the database where pertinent study data are collected. For all subjects, including screen failures, data will be collected on source documents first. The principal investigator is responsible for assuring that the data entered into eCRFs is complete, accurate, and that entry and updates are performed in a timely manner. Blood and tumor samples for PK and biomarkers assessments will be collected by study sites and sent to the designated central laboratory for processing. Data from ECG will be collected at the study sites, and the data will be transmitted to a designated CRO for centralized analysis, as well as for further processing and data reconciliation. Imaging data will be collected at the study sites, and a designated CRO will perform further processing, data reconciliation, and holding.

At all times, the principal investigator has final responsibility for the accuracy and authenticity of all clinical and laboratory data entered in the EDC. Subject source documents are the investigator's/physician's subject records maintained at the study site. In cases where the source documents are the hospital or the physician's chart, the information collected in the EDC must match those charts. All final data recorded in EDC system will be copied onto CDs and kept by the sponsor. A copy of these CDs will also be kept at the clinical site. All data recorded on source documents will be kept at the clinical site.

The completed pages of the EDC system are the sole property of the sponsor and should not be made available in any form to third parties without written permission from the sponsor, except for authorized representatives of the sponsor or appropriate regulatory authorities.

11.3.3.2. Source Documentation

The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's study subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable and not obscure the original entry. Any changes should be explained if necessary (eg, via an audit trail).

11.3.3.3. Study Files

For studies using eCRFs, Hutchison MediPharma Limited personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff is required to respond promptly to queries and to make any necessary changes to the data. Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs will be coded using the MedDRA terminology. Samples collected for all third party data such as ECG, PK and biomarker will be processed centrally and the results will be sent electronically to HMP (or a designated CRO). At the conclusion of the study, the occurrence of any protocol deviations will be determined. After these actions have been completed and the data has been verified to be complete and accurate, the database will be declared locked.

Authorization is required prior to making any database changes to locked data, by joint written agreement between the Head of Biostatistics and Data Management and the Head of Clinical Development. For EDC studies, after database lock, the investigator will receive a CD-ROM or paper copies of the subject data for archiving at the investigational site.

11.3.3.4. Records Retention

The study should be recorded accurately by investigators so that study data can be verified. The study documents can be divided into two types: investigator documents and subject source data. Investigator documents include protocol and amendments, the eCRF and data clarification forms, approvals and correspondence with the IEC and regulatory authorities, ICF, study drug records, study personnel curriculum vitae and authorization forms, and any other essential documents.

Subject source data documents (recording primary efficacy/safety data) include clinic/hospital medical history, scheduled visit dates, original laboratory test results, ECG, electroencephalogram, radiological imaging, pathological and specific assessment reports, signed ICF, medical records, and subject screening forms. The documents mentioned above should be properly stored by the investigator for 5 years after the study is completed. If investigators need to transfer the documents to another party or place, the sponsor must be notified in advance.

If the documents cannot be stored properly at the investigational site, the documents can be transferred by the investigator and sponsor to an approved storage facility. The documents must be sealed for storage and easily found for review in the case of a regulatory authority audit. If the documents are still in use, they can be copied and stored elsewhere.

11.4. Study Termination or Study Site Closure

The sponsor and the investigator have the right to close out a site prematurely.

Investigator's Decision

The investigator must notify the sponsor of a desire to close out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close out procedures after review and consultation

Sponsor's Decision

The sponsor will notify the investigator(s) of a decision to close out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any subject within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of subjects required for the study are enrolled earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CROs used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

12. PUBLICATION POLICY

The study results may be published in scientific journals. The names of investigators who make an important contribution to the study implementation and management, and personnel who make an important contribution to the study design, analysis, and interpretation (such as staff or consultants from Hutchison MediPharma Limited) will be listed in the publication. Hutchison MediPharma Limited agrees to provide the article to investigators for review prior to publishing any study results. Investigators must obtain approval from the sponsor before contributing to any related articles or abstracts.

The property of confidential information belongs to Hutchison MediPharma Limited. Without permission from Hutchison MediPharma Limited, the information cannot be used for any purpose other than this study.

13. FINANCING AND INSURANCE

Financing and insurance information will be addressed in a separate agreement.

14. REFERENCES

American Cancer Society, Key Statistics for Colorectal Cancer, 2019. URL: www.cancer.org/ cancer/ colon-rectal-cancer/about/key-statistics.html; accessed February 12, 2019.

Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018 Nov;68(6):394-424

Duda DG, Batchelor TT, Willett CG, Jain RK. VEGF-targeted cancer therapy strategies: current progress, hurdles and future prospects. *Trends Mol Med*. 2007 Jun;13(6):223-30.

Grothey A, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, Humblet Y, Bouché O, Mineur L, Barone C, Adenis A, Tabernero J, Yoshino T, Lenz HJ, GoldbergRM, Sargent DJ, Cihon F, Cupit L, Wagner A, Laurent D; CORRECT Study Group. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013 Jan 26;381(9863):303-12.

Izzedine H, Ederhy S, Goldwasser F, Soria JC, Milano G, Cohen A, Khayat D, Spano JP. Management of hypertension in angiogenesis inhibitor-treated patients. *Ann Oncol*. 2009 May;20(5):807-15.

Jayson GC, Kerbel R, Ellis LM, Harris AL. Antiangiogenic therapy in oncology: current status and future directions. *Lancet*. 2016 Jul 30;388 (10043):518-29.

Koopman M, Kortman GA, Mekenkamp L, Ligtenberg MJ, Hoogerbrugge N, Antonini NF, Punt CJ, van Krieken JH. Deficient mismatch repair system in patients with sporadic advanced colorectal cancer. *Br J Cancer*. 2009 Jan 27;100(2):266-73.

Li J, Qin S, Xu R, et al. Effect of fruquintinib vs placebo on overall survival in patients with previously treated metastatic colorectal cancer. *JAMA*. 2018;319(24):2486-96.

LONSURF® (trifluridine and tipiracil) Prescribing Information. Taiho Pharmaceutical Co, Taiho Oncology, Inc. Princeton NJ, USA. Revised Feb 2019

Mayer R, Van Cutsem E, Falcone A, et al. Randomized Trial of TAS-102 for Refractory Metastatic Colorectal Cancer (RECOURSE). *N Engl J Med* 2015; 372: 1909-19.

National Comprehensive Cancer Network (NCCN), Version 2019.

STIVARGA® (regorafenib) Prescribing Information. Bayer HealthCare Pharmaceuticals, Inc, Whippany NJ, USA. Revised Apr 2017.

Sun Q, Zhou J, Zhang Z, Guo M et al., Discovery of fruquintinib, a potent and highly selective small molecule inhibitor of VEGFR 1, 2, 3 tyrosine kinases for cancer therapy. *Cancer Biol Ther*. 2014;15 (12):1635-45.

15. APPENDICES

APPENDIX 1 ECOG PERFORMANCE STATUS

Grade	Activity Level
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled, cannot carry on any self-care, totally confined to bed or chair
5	Death

APPENDIX 2 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST V1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1, are presented below.

1. Measurability of Tumor at Baseline

1.1 Definitions

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below.

1.1.1 Measurable Tumor Lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by CT or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray
- Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and follow-up, only the short axis will be measured and followed.

1.1.2 Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 but < 15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

1.1.3 Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

1.2 Specifications by Methods of Measurements

1.2.1 Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

1.2.2 Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested.

Chest X-Ray. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the

study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

2. Tumor Response Evaluation

2.1 Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

2.2 Baseline Documentation of Target and Non-Target Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is >10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node

measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis of <10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then, as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as a reference to characterize further any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression."

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (eCRF) (eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

2.3 Response Criteria

2.3.1 Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

- Complete response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.
- Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

2.3.2 Special Notes on the Assessment of Target Lesions

Lymph Nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to < 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Target Lesions That Become Too Small to Measure. During the study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist

may not feel comfortable assigning an exact measure and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the eCRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and BML (below measurable limit) should be ticked. (BML is equivalent to a "less than" sign.) (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm, and in that case BML should not be ticked.

Lesions That Split or Coalesce on Treatment. When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

2.3.3 Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- Complete response (CR): Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- Progressive disease (PD): Unequivocal progression of existing non-target lesions. The appearance of one or more new lesions is also considered progression.

2.3.4 Special Notes on Assessment of Progression of Non-Target Disease

When the Patient Also Has Measurable Disease. In this setting, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Patient Has Only Non-Measurable Disease. This circumstance arises in some phase 3 trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large" or an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in therapy." If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

2.3.5 New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

(18) F-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET)

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly, possible "new" disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

A negative FDG-PET scan at baseline with a positive FDG-PET scan during the study is a sign of PD based on a new lesion.

In the case of no FDG-PET scan at baseline and a positive FDG-PET scan during the study:

- If the positive FDG-PET scan during the study corresponds to a new site of disease confirmed by CT, this will be considered PD.

- If the positive FDG-PET scan during the study is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine whether there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
- If the positive FDG-PET scan during the study corresponds to a preexisting site of disease on CT that is not progressing on the basis of the anatomic images, this will not be considered PD.

2.4 Evaluation of Response

2.4.1 Time Point Response (Overall Response)

It is assumed that at each protocol-specified time point, a response assessment occurs. Table 14 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 15 is to be used.

Table 14 Time Point Response: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table 15 Time Point Response: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

2.4.2 Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with 3 measured lesions and, during the study, only 2 lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be "unable to assess" since the patient is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be "unable to assess" except where there is clear progression. Overall response would be "unable to assess" if either the target response or the non-target response is "unable to assess" except where this is clear evidence of progression, as this equates with the case being not evaluable at that time point.

2.4.3 Best Overall Response: All Time Points

The best overall response is determined once all the data for the patient is known. Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 16.

Table 16 Best Overall Response When Confirmation of Complete Response and Partial Response is Required

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD，PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD =progressive disease, and NE = inevaluable.

a: If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 0 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the eCRF.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic

deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Table 14 and Table 15.

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

In studies for which patients with advanced disease are eligible (ie, primary disease still or partially present), the primary tumor should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of complete response if the primary tumor is still present but not evaluated as a target or non-target lesion.

2.5 Frequency of Tumor Re-evaluation

Frequency of tumor re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of phase 2 studies where the beneficial effect of therapy is not known, follow-up every 6–8 weeks (timed to coincide with the end of a cycle) is reasonable. Smaller or greater time intervals than these could be justified in specific regimens or circumstances. The protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumor type under study) and how often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

After the end of the treatment, the need for repetitive tumor evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death). If 'time to an event' (eg, time to progression, disease-free survival, progression-free survival) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomized comparative trials in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6–8 weeks on treatment or every 3–4 months after treatment) and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

2.6 Confirmatory measurement/duration of response

2.6.1. Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials (see the paper by Bogaerts et al. in this Special Issue10). However, in all other circumstances, for example in randomized trials (phase 2 or 3) or in studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination

of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies that are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

2.6.2. Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

2.6.3. Duration of stable disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

APPENDIX 3 PROHIBITED MEDICATION

A series of strong inducers and strong inhibitors of CYP3A are listed in Table 17 and Table 18 below. Examples of sensitive substrates of P-gp and BCRP are listed in Table 19.

Patients who received a CYP3A strong inducer or strong inhibitor within 2 weeks (3 weeks for hyperforin perforatum/St. John's Wort treatment) prior to the first dose of the study drug will not be allowed to participate in the study. During the study, co-administration of strong inducers and inhibitors of CYP3A with fruquintinib should be avoided unless investigators consider it necessary. In this case, fruquintinib efficacy reduction or toxicity increases resulting from the interaction should be closely monitored.

Not all the medications are listed in the following tables. Other drugs known possibly to affect CYP3A activity and to be substrates of P-gp and BCRP should be used with caution. When combining fruquintinib with other drugs the prescription information of all concomitant medications should be reviewed.

Table 17 Typical Strong Inhibitors of CYP3A4

Strong Inhibitors of CYP3A4
Boceprevir
Clarithromycin
Conivaptan
Elvitegravir/Ritonavir
Fluconazole
Grapefruit juice[a,b]
Indinavir
Itraconazole
Ketoconazole
Lopinavir/Ritonavir
Mibefradil
Nelfinavir
Posaconazole
Ritonavir
Saquinavir
Telaprevir
Telithromycin
Tipranavir/Ritonavir
Troleandomycin
Voriconazole

a Super-concentrated grapefruit juice

b During the study, patients should not consume large amounts of grapefruit or lime (or products that include these fruits, such as grapefruit juice, Seville oranges, and orange jam). No more than one cup (120 mL) of grapefruit juice, half a grapefruit or a spoon full (15 g) of orange jam should be consumed each day.

Table 18 Typical Strong Inducers of CYP3A4

Strong Inducers of CYP3A4
Apalutamide
Avasimibe
Carbamazepine
Enzalutamide
Mitotane
Phenobarbital
Phenytoin
Rifabutin
Rifampin (or rifampicin)
St. John's wort

Table 19 Sensitive Substrates of P-gp or BCRP

Substrates of P-gp	Substrates of BCRP
Aliskiren	Methotrexate
Ambrisentan	Mitoxantrone
Colchicine	Imatinib
Dabigatran etexilate	Irrinotecan
Digoxin	Lapatinib
Everolimus	Rosuvastatin
Fexofenadine	Sulfasalazine
Imatinib	Topotecan
Lapatinib	
Maraviroc	
Nilotinib	
Posaconazole	
Ranolazine	
Saxagliptin	
Sirolimus	
Sitagliptin	
Talinolol	
Tolvaptan	
Topotecan	

APPENDIX 4 STUDY PLAN

Table 20 Summary of Clinical Trial Program of Fruquintinib in China and the US

Study Number (Name) NCT# and Indication	Study Title	Study Objectives and Phase	Study Subjects	Study Design	Current* Status
Studies in Cancer Patients					
2013-013-00CH1 NCT01645215 (FRESCO) 3rd+ line mCRC	A Phase III clinical trial of Fruquintinib or placebo in treatment of advanced colorectal cancer patients who have progressed after second-line chemotherapy	Confirmatory safety/efficacy. Phase 3	Fruquintinib: N=278; Placebo: N=138 (Tot. 416)	Randomized, double-blind, placebo-controlled, multicenter Phase III clinical trial	Completed
2015-013-00US1 NCT03251378 Advanced solid tumors; Refractory mCRC	A Multi-Center, Open-Label, Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Anticancer Activity of Fruquintinib in Patients with Advanced Solid Tumors of any Type, and in Patients with Refractory Metastatic Colorectal Cancer	Safety, Tolerability, PK Phase 1/1b	Planned: N=18; Current: N=14	Two-phase, open-label multi-center study. Phase 1/1b: dose escalation phase (completed). Phase 2: expansion phase (ongoing)	Ongoing
2009-013-00CH1 NCT01645215 Advanced solid tumors	A single center, open label, and dose escalation study to determine the maximal tolerated dose (MTD) and safety of Fruquintinib in patients with advanced malignant solid tumors	Dose escalation: safety, tolerability, and PK Dose expansion: safety, tolerability, PK and preliminary efficacy; Phase 1	Fruquintinib N=40	Two stages: Open-label, single center study Stage 1: dose escalation Stage 2: selected dose regimen expansion	Completed

Table 20 Summary of Clinical Trial Program of Fruquintinib in China and the US

Study Number **(Name)** **NCT# and Indication**	**Study Title**	**Study Objectives and Phase**	**Study Subjects**	**Study Design**	**Current* Status**
2012-013-00CH3 NCT01975077 3rd or above line mCRC	A Phase Ib, Randomized, Open-Label Study for Comparing Two Different Dosing Regimens of Fruquintinib as Third-Line or up Therapy for Advanced Colorectal Cancer in Patients Who Had Failed with Standard Therapy	Compare two dosing regimens of fruquintinib. (Safety, tolerability, PK, preliminary efficacy) Phase 1b	Fruquintinib N=62	Randomized, two-stage, open-label, multicenter study. Stage 1: two arms, two dose regimens, randomized Stage 2: selected dose regimen expansion	Completed
2012-013-00CH1 NCT02691299 3rd line mCRC	A Randomized, Double-blind, Placebo-controlled, Multi-center Phase II Clinical Trial to Evaluate the Efficacy and Safety of Fruquintinib Plus Best Supportive Care in advanced colorectal cancer patients who have progressed after second-line chemotherapy	PFS (Fruquintinib versus PBO), OS, ORR, safety Phase 2	Fruquintinib: N=47; Placebo: N=24 (Tot. 71)	Randomized, double-blind, placebo-controlled, multicenter study	Completed
2014-013-00CH1 NCT02590965 3rd line NSCLC	A Randomized, Double-blind, Placebo-controlled, Multi-center Phase II Clinical Trial to Evaluate the Efficacy and Safety of Fruquintinib Plus Best Supportive Care in Patients With Advanced Non-squamous Non-small Cell Lung Cancer	(Fruquintinib versus PBO), OS, ORR, safety Phase 2	Fruquintinib N=61. Placebo: N=30 (Tot. 91)	Randomized, double-blind, placebo-controlled, multicenter study	Completed

Table 20 Summary of Clinical Trial Program of Fruquintinib in China and the US

Study Number **(Name)** **NCT# and Indication**	**Study Title**	**Study Objectives and Phase**	**Study Subjects**	**Study Design**	**Current* Status**
2015-013-00CH1 NCT02691299 (FALUCA) 3rd line NSCLC	A Randomized, Double-blind, Placebo-controlled, Multi-center Phase III Clinical Trial in Patients With Advanced Non-squamous Non-small Cell Lung Cancer Treated With Fruquintinib	Confirmatory efficacy and safety NSCLC. Phase 3	Fruquintinib N=352 Placebo N= 171 (Total N=523)	Randomized, double-blind, placebo-controlled, multicenter study	Ongoing (Enrollment completed)
2017-013-00CH1 NCT03223376 2nd line gastric cancer	A Phase III Study to Evaluate the Efficacy and Safety of Fruquintinib in Combination With Paclitaxel Versus Paclitaxel Alone in Second Line Gastric Cancer	Phase 3	Planned: 544 Current: N=120	Randomized, double-blind, placebo-controlled, multicenter study	Ongoing
2014-013-00CH3 NCT02415023 2nd line gastric cancer	A Phase Ib/2 Clinical Study to Evaluate the Safety, Pharmacokinetic Characteristics and Preliminary Efficacy of Fruquintinib Combined With Paclitaxel in Patients With Advanced Gastric Cancer	(Fruquintinib + paclitaxel combo), safety, tolerability, PK, preliminary efficacy Phase 1b/2	Fruquintinib N=34	Two-stage, open-label, multicenter study. Stage 1: dose escalation. Stage 2: selected dose regimen expansion (combo + paclitaxel)	Completed

Table 20 Summary of Clinical Trial Program of Fruquintinib in China and the US

Study Number (Name) NCT# and Indication	Study Title	Study Objectives and Phase	Study Subjects	Study Design	Current* Status
2016-013-00CH1 NCT02976116 1st line NSCLC, EGFR+ sensitive EGFR+ (combo with gefitinib)	Fruquintinib in Combination With Gefitinib as First-line Therapy in Patients With Advanced Non-squamous Non-small-cell Lung Cancer Harboring Activating EGFR Mutations : a Single-arm, Multicenter, Phase II Study	Phase 2	Planned: N=40 Current: N=50	Randomized, double-blind, placebo-controlled, multicenter study	Ongoing
2017-013-00CH2 NCT03684967	Study of Fruquintinib (HMPL-013) in High Risk Patients With Advanced NSCLC	Phase 2	Planned: Cohort 1: N=25 Cohort 2: N=75 Current: N=0	Open-label, single arm, 2 cohorts, multi-center Cohort 1: patients of ≥75 years of age and ECOG PS of 0 to 2; Cohort 2: patients of 18 to 75 years of age and ECOG PS of 0 to 2	Ongoing
Studies in Healthy Volunteers					
2012-013-00CH2 NCT01955304	A Single-Center, Randomized, Open-Label, Single-Dose, Two-Cycle, and Cross-over Clinical Trial to Investigate the Effect of Food on Pharmacokinetics of Fruquintinib Capsule in Healthy Subjects	Primary: to determine the effect of food on the PK Secondary: to assess the safety and tolerability; to verify the major metabolites; and to explore the excretion of fruquintinib Phase 1	Healthy males N=29	Randomized, open-label, two-period crossover, two-stage, single center, food effect study Stage 1: dose escalation. Stage 2: selected dose regimen expansion	Completed

Table 20 Summary of Clinical Trial Program of Fruquintinib in China and the US

Study Number (Name) NCT# and Indication	Study Title	Study Objectives and Phase	Study Subjects	Study Design	Current* Status
2013-013-00CH2	A Single Center, Open-label, Randomized, Two-period Crossover Study to Evaluate the Pharmacokinetics and Bioequivalence in Healthy Male Chinese Volunteers Following Single Doses of Fruquintinib Capsules Produced by Two Different Manufacturers	Primary: to determine the bioequivalence of fruquintinib produced at two manufacturing sites. Secondary: to assess the safety and tolerability Phase 1	Healthy males N=28	Randomized, open-label, two-period crossover, two-stage, single center study. Stage 1: Exploring preliminary study. Stage 2: Bioequivalence study	Completed
2014-013-00CH5	A Single Center, Open-label, Randomized, Two-period Crossover Study to Evaluate the Pharmacokinetics and Bioequivalence in Healthy Male Chinese Volunteers Following Single Doses of Fruquintinib Capsules Produced by Two Different Manufacturers	Primary: to assess the bioequivalence of fruquintinib produced at two manufacturers; Secondary: safety, explore metabolism and excretion Phase 1	Healthy Males (N=24)	Randomized, open-label, two-period crossover, two-stage, single center study.	Completed
2015-013-00CH2 NCT02689752	Absorption, Metabolism and Excretion of [^{14}C] Fruquintinib in Healthy Male Volunteers after a Single Oral Administration of 5mg/100 μCi/Subject of [^{14}C] Fruquintinib	Evaluate mass balance in healthy male volunteers following a single oral administration of 5 mg/100 μCi/Subject of [^{14}C] fruquintinib Phase 1	Healthy Males (N=6)	To investigate the absorption, drug biotransformation and mass balance and to evaluated the PK and safety of fruquintinib. To identify the compound's major metabolites	Completed

*Fruquintinib Investigator's Brochure, v11.0

APPENDIX 5 CLINICAL EVALUATION OF POSSIBLE DRUG-INDUCED LIVER INJURY (DILI)

If ALT or AST is elevated to higher than 3 x ULN **and** bilirubin is elevated to higher than 2 X ULN, fruquintinib treatment should be discontinued immediately, and supportive treatment should be given. This combination of lab abnormalities meets the biochemical criteria for Hy's law, which is associated with a markedly increased possibility of severe drug-induced liver injury (DILI), and may progress to liver transplantation or death (FDA Guidance for Industry - Drug-Induced Liver Injury: Premarketing Clinical Evaluation. FDA, 2009).

If the biochemical criteria for Hy's law are met, fruquintinib should be immediately discontinued, and patients need to be very closely monitored (bilirubin, ALP, AST, and ALT measured 2-3 times weekly until the results return to baseline or normal), and other causes of liver injury evaluated (eg, new or worsening hepatobiliary metastases; non-malignant biliary obstruction; viral hepatitis A, B, or C; alcoholic or autoimmune hepatitis; preexisting or acute liver disease; ischemic liver injury; right-sided congestive heart failure; new or worsening liver metastases; or concomitant medication that could cause the observed injury). Consultation with a gastroenterologist or hepatoligist should be considered.

If the biochemical criteria for Hy's Law have been met, expedited reporting is required (see Section 8.1.1), before waiting for the evaluation of other causes to be completed.

Recommended Data Collection for Suspected DILI

The investigator is recommended to obtain the following information, so as to further evaluate and follow up and complete the clinical data. Data should be recorded on eCRFs where possible, and supplemented by investigator reporting as text in the clinical database:

- Medical history of the patient
    - Detailed history of current symptoms, diagnosis of complications and medical history
    - Previous medical history (viral hepatitis, alcoholic hepatitis, autoimmune disease, biliary tract disease and cardiovascular disease, etc.)
    - History of concomitant medication (including OTC and prescription drugs, herbal medicine and dietary supplements), alcohol consumption, recreational drugs and special diet
    - History of exposure to potentially hepatotoxic chemicals
- Complete the following laboratory tests:
    - Hematology
    - Clinical biochemistry: ALT, AST, bilirubin (including total bilirubin and direct bilirubin), ALP, albumin, PTT or INR, amylase, fasting blood glucose, cholesterol and triglycerides
    - Other Serum Tests: Hepatitis A (Anti-IgM and Anti-IgG), hepatitis B (HbsAg, Anti-HBs and HBV DNA), hepatitis C (Anti-HCV, and HCV RNA test is required for any patient with positive test result), hepatitis D (Anti-IgM and Anti -IgG), hepatitis E (Anti-HEV and Anti-HEV IgM).
- Complete appropriate auxiliary examination:

- Patients with confirmed elevation of ALT/AST combined with TBili are required to receive abdominal ultrasonography or other clinically applicable imaging examination within 48 hours (to exclude biliary tract, pancreatic, or intrahepatic causes, such as new or worsening hepatobiliary metastases or biliary calculi) and obtain the liver imaging result as soon as possible. If an alternative cause (such as biliary tract, pancreatic, or intrahepatic causes) of abnormal hepatic results cannot be confirmed by imaging, paracentesis is recommended for pathological examination after obtaining consent of the patient;
- If suspected cardiovascular causes exist, cardiac ultrasonography is recommended to exclude cardiovascular dysfunction (ie, right heart failure);

Long-term follow-up: Perform close monitoring on the patient through repetitive tests of ALT, AST and bilirubin (including total bilirubin and direct bilirubin) two to three times weekly until the laboratory ALT and/or AST abnormality becomes stable or recovers, and then proceed according to the protocol.

APPENDIX 6 CLINICAL MANAGEMENT OF SEVERE OR SERIOUS HEMORRHAGIC EVENTS

If hemorrhagic events are evaluated as severe (CTCAE grade ≥3) or SAEs, fruquintinib treatment should be discontinued or interrupted immediately, and appropriate treatment measures initiated to control bleeding (eg transfusion, radiologic, endoscopic, or elective operative intervention as indicated). When the patient is not well enough to tolerate an invasive procedure or operation, best supportive care is given (see Section 7.5.6.2). Patients need to be very closely monitored, both clinically (continuously), and by relevant laboratory testing (INR, aPTT, platelet count, hemoglobin) every 2-3 days until the results return to baseline or normal). During the initial assessment, a focused history and physical examination, with collection of vital signs and laboratory evaluation and imaging evaluation should be obtained, aimed at determining the time of onset, location, severity of bleeding, and whether bleeding is ongoing. Clinicians should be mindful of comorbidities and concomitant treatments (eg. anti-platelet therapy and/or thrombocytopenia, or liver disease) that could also contribute to bleeding and manage them as appropriate. Consultation with other department clinicians should be considered when necessary.

The investigator should closely monitor patients receiving anti-platelet and/or anti-thrombotic drugs during study drug treatment and make a timely decision on whether to continue or stop such drugs in patients that report grade ≥2 hemorrhagic events at any site, based on an individual assessment of the risk-benefit balance.

If a hemorrhagic event is evaluated as a severe (CTCAE grade ≥3) or SAE after taking fruquintinib, the investigator is required to report the event in an expedited fashion (within 24 hours of first awareness) to sponsor (see Section 8.2.2).

See Figure 2 below for guidance on the management of severe or serious hemorrhage at any site.

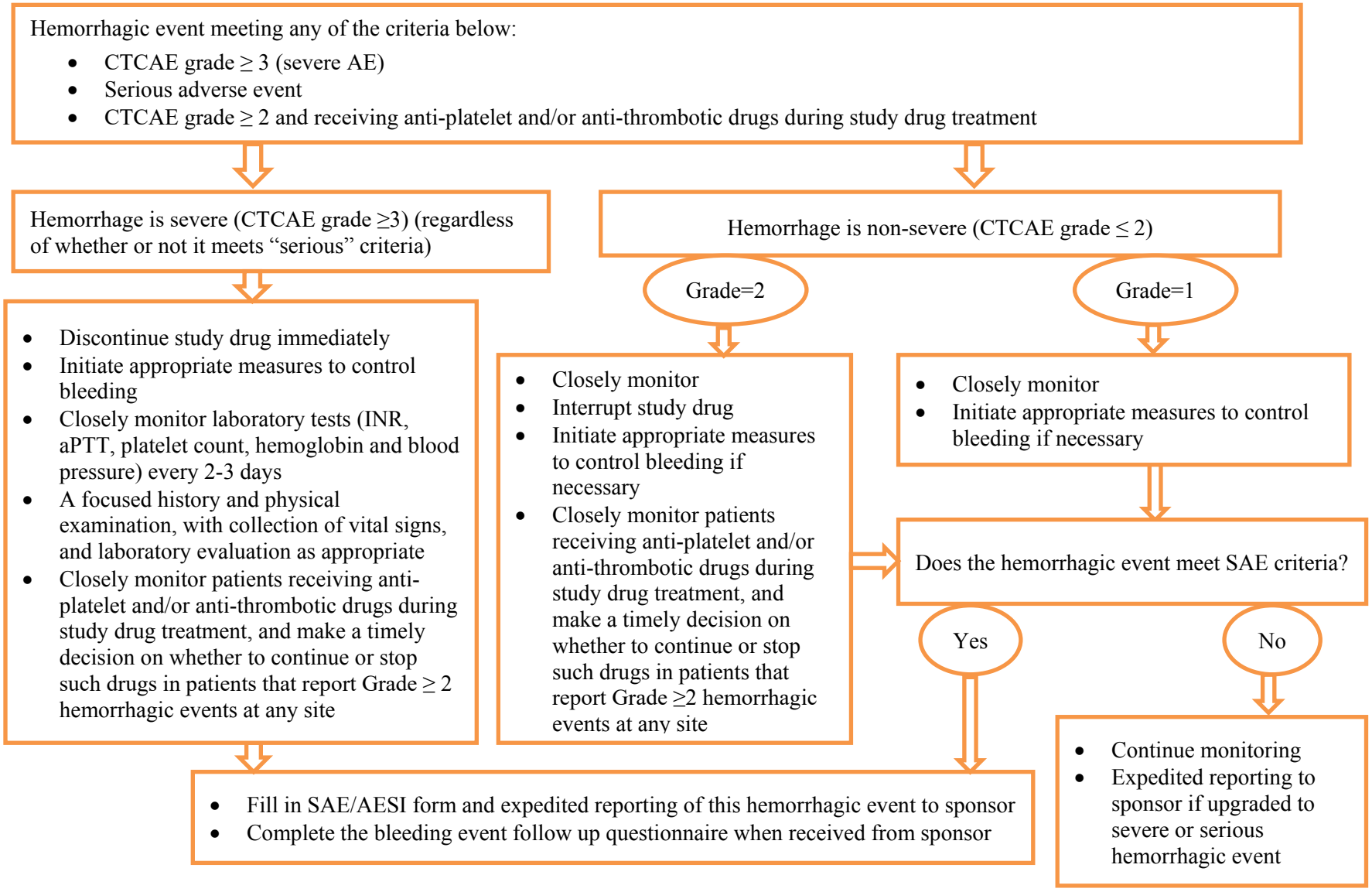
Recommended Data Collection for Severe or Serious Hemorrhagic Events:

The investigator is recommended to obtain the following information, so as to further evaluate and follow up and complete the clinical data. Data should be recorded on SAE/AESI report form where possible, and supplemented by Bleeding Event Follow-Up Questionnaire:

- Medical history of the patient
  - Detailed history of current symptoms, diagnosis of complications and medical history
  - Previous medical history
  - History of concomitant medication (
    - Vitamin K antagonists (eg warfarin)
    - NSAIDs (eg aspirin)
    - Anti-platelet drugs (eg, clopidogrel/glycoprotein GPIIb/IIIa inhibitors/dipyridamole)
    - Other anticoagulants (eg heparin/thrombolytics/SSRIs)
    - Food and herbal supplements with anticoagulant property
    - Immunosuppressants
    - Alcohol consumption
    - Recreational drugs and special diet
  - Family history of bleeding events
- Complete the following laboratory tests:
  - Hematology: hemoglobin, platelet, hematocrit, reticulocyte count

  - Clinical biochemistry: bleeding time, PTT, aPTT, INR
- Complete appropriate auxiliary examination:
  - Patients with confirmed bleeding are required to receive upper or lower GI endoscopy, bronchoscopy or other clinically applicable procedure or radiologic imaging within 48 hours, to confirm the site of bleeding.
  - If suspected cardiovascular causes exist, cardiac ultrasonography is recommended to exclude cardiovascular dysfunction (ie, right heart failure).

Figure 2 Severe or Serious Hemorrhagic Events Management Flow Chart



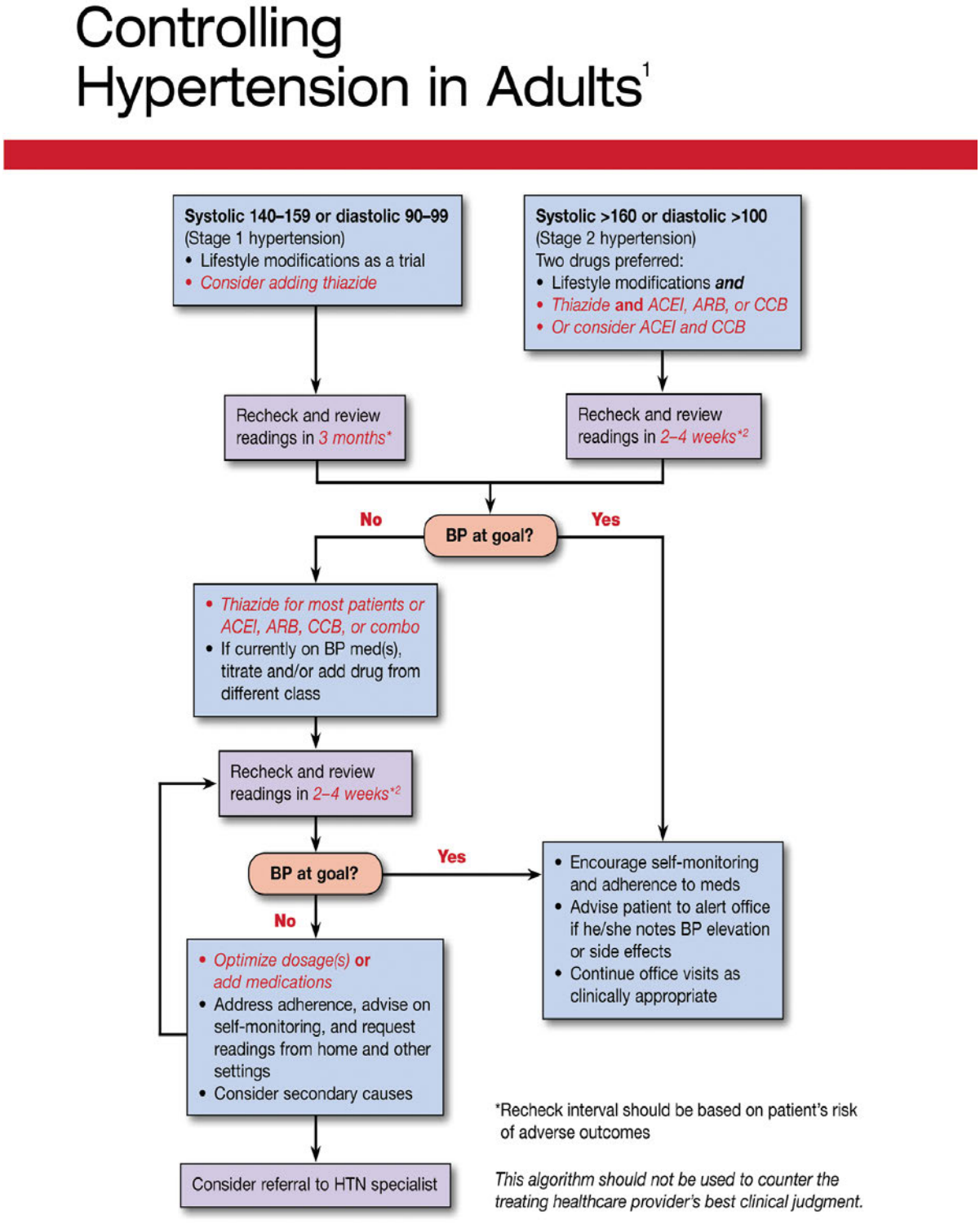
APPENDIX 7 MANAGEMENT OF HYPERTENSION IN PATIENTS RECEIVING FRUQUINTINIB

Hypertension is a common AE that has been reported in patients taking angiogenesis inhibitors (Izzedine 2009), including fruquintinib. Grade 3 AEs have been reported in 16% of patients treated with fruquintinib; no Grade 4 events have been reported to date. It appears that hypertension is a class-effect of VEGFR inhibitors (either antibodies or small molecules).

There is no standard therapy for angiogenesis inhibitor-induced hypertension because there have not been any published controlled clinical trials with specific agents. Therefore, one can take an approach based on the clinical characteristics of particular patients. Calcium channel blockers and angiotensin converting enzyme inhibitors (ACEI) are a reasonable first choice in most cases. For patients with proteinuria, chronic renal disease or metabolic disease, an ACE inhibitor or angiotensin II receptor blockers (ARB) may be preferred; for elderly patients, dihydropyridine calcium channel blockers may be preferred. In this appendix is a summary of the most recent American Heart Association (AHA)/American College of Cardiology (ACC) hypertension treatment guidelines. A cardiologist may be consulted if appropriate.

The objective of antihypertensive therapy in general is to control the blood pressure to a target level <140/90 mmHg. For high-risk populations, such as patients with chronic renal disease and/or diabetes, it may be appropriate to aim for a target blood pressure < 130/80 mmHg. On the following two pages (Figure 3), please see a summary of the most recent AHA/ACC hypertension treatment guidelines.

Figure 3 Schema from American Heart Association/ American College of Cardiology for Controlling Hypertension in Adults



Controlling Hypertension in Adults

The blood pressure (BP) goal for an individual is set by utilizing a combination of factors including scientific evidence, clinical judgment, and patient tolerance. For most people, the goal is <140 and <90;[3] however, lower targets may be appropriate for some populations such as African-Americans, the elderly, or patients with LV hypertrophy, systolic or diastolic LV dysfunction, diabetes mellitus or chronic kidney disease. Lifestyle modifications (LM) should be initiated in all patients with hypertension (HTN) and they should be assessed for target organ damage and existing cardiovascular disease. Self-monitoring[4] is encouraged for most patients throughout their care, and requesting and reviewing readings from home and community settings can help the provider assist the patient in achieving and maintaining good control. For patients with hypertension in combination with certain clinical conditions, specific medications should be considered first-line treatments.

Suggested Medications for Treatment of Hypertension in Presence of Certain Medical Conditions

- Coronary artery disease/Post MI: *BB, ACEI*
- Systolic heart failure: *ACEI or ARB, BB, ALDO ANTAG, thiazide*
- Diastolic heart failure: *ACEI or ARB, BB, thiazide*
- Diabetes: *ACEI or ARB, thiazide, BB, CCB*
- Kidney disease: *ACEI or ARB*
- Stroke or TIA: *thiazide, ACEI*

Lifestyle Modifications[3] (LM)

Modification	Recommendation	Approximate SBP Reduction (Range)**
Reduce weight	Maintain normal body weight (body mass index 18.5–24.9 kg/m^2)	5–20 mm Hg/10 kg
Adopt DASH*[5] eating plan	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat	8–14 mm Hg
Lower sodium intake[6]	a. Consume no more than 2,400 mg of sodium/day; b. Further reduction of sodium intake to 1,500 mg/day is desirable since it is associated with even greater reduction in BP; and c. Reduce intake by at least 1,000 mg/day since that will lower BP, even if the desired daily sodium intake is not achieved	2–8 mm Hg
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 min per day, most days of the week)	4–9 mm Hg
Moderation of alcohol consumption	Limit consumption to no more than 2 drinks (e.g., 24 oz beer, 10 oz wine, or 3 oz 80-proof whiskey) per day in most men, and to no more than 1 drink per day in women and lighter weight persons	2–4 mm Hg

*DASH, dietary approaches to stop hypertension
** The effects of implementing these modifications are dose and time dependent, and could be greater for some individuals

Abbreviations
ACEI, angiotensin-converting-enzyme inhibitor; ALDO ANTAG, aldosterone antagonist; ARB, angiotensin II receptor blocker; BB, β-blocker; BP, blood pressure; CCB, calcium channel blocker; HTN, hypertension; MI, myocardial infarction; SBP, systolic blood pressure; TIA, transient ischemic attack

References

1. Go AS, Bauman M, Coleman King SM, Fonarow GC, Lawrence W, Williams K, Sanchez E. An effective approach to high blood pressure control: a science advisory from the American Heart Association, the American College of Cardiology, and the Centers for Disease Control and Prevention. *Hypertension.* 2013: published online before print November 15, 2013, 10.1161/HYP.0000000000000003.
2. Jaffe MG, Lee GA, Young JD, Sidney S, Go AS. Improved Blood Pressure Control Associated with a Large-Scale Hypertension Program. *JAMA.* 2013;310(7);699-705.
3. National Heart, Lung, and Blood Institute, National Institutes of Health. *The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure — Complete Report.* National Heart, Lung, and Blood Institute, National Institutes of Health. NIH Publication No. 04-5230, 2004.
4. Centers for Disease Control and Prevention. *Self-Measured Blood Pressure Monitoring: Action Steps for Public Health Practitioners.* Atlanta, GA: Centers for Disease Control and Prevention, US Dept of Health and Human Services; 2013.
5. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med.* 2001;344:3-10.
6. Eckel RH, Jakicic JM, Ard JD, Hubbard VS, de Jesus JM, Lee I-M, Lichtenstein AH, Loria CM, Millen BE, Houston Miller N, Nonas CA, Sacks FM, Smith SC Jr, Svetkey LP, Wadden TW, Yanovski SZ. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013: published online before print November 12, 2013, 10.1161/01.cir.0000437740.48606.d1.

Hypertension Guidelines From: Go A, Bauman M, Coleman King S, et al. An Effective Approach to High Blood Pressure Control. A Science Advisory from the American Heart Association, the American College of Cardiology, and the Centers for Disease Control and Prevention. *J Am Coll Cardiol* 2014; 63:1230-8.

APPENDIX 8 CONVERSION TABLE FOR URINALYSIS RESULTS

Blood			**Leucocytes**		
Negative	0	0 cells/μL	Negative	0	<10 mg/dL
Trace	1+	1-24 cells/μL	Trace	1+	11-99 mg/dL
Small	2+	25-79 cells/μL	Small	2+	99-299 mg/dL
Medium	3+	80-199 cells/μL	Medium	3+	300-999 mg/dL
Large	4+	≥ 200 cells/μL	large	4+	>1000 mg/dL

Clinical Study Protocol

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 (FRESCO-2)

Short Title:	A global, randomized, placebo-controlled phase 3 study of fruquintinib in patients with refractory metastatic colorectal cancer
Acronym:	FRESCO-2
Investigational Product(s)	Fruquintinib
Protocol Number:	2019-013-GLOB1
Clinical Phase:	3
Date of Issue:	24 June 2021
Amendment:	4
Version Number:	1 *(for sponsor's use only)*
Sponsor	Hutchison MediPharma Limited Building 4, 720 Cailun Road, Zhangjiang Hi-Tech Park, Shanghai, China Post Code: 201203
Regulatory Agency Identifier Number(s)	IND: 131038 EudraCT 2020-000158-88

STATEMENT OF COMPLIANCE

The study will be conducted in compliance with this clinical study protocol, Good Clinical Practices (GCP) as outlined by ICH E6(R2), and all applicable local and national regulatory requirements. Enrollment at any clinical study site may not begin prior to that site receiving approval from the ethics committee of record for the protocol and all materials provided to potential participants.

Any amendments to the protocol or changes to the consent document will be approved before implementation of that amendment. Reconsent of previously enrolled participants may be necessary depending on the nature of the amendment.

The Principal Investigator will ensure that changes to the study plan as defined by this protocol will not be made without prior agreement from the Sponsor and documented approval from the ethics committee of record, unless such a change is necessary to eliminate an immediate hazard to the study participants.

All personnel involved in the conduct of this study have completed Human Patients Protection and GCP Training as outlined by their governing institution.

SPONSOR'S APPROVAL

Title	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 (FRESCO-2)
Protocol Number	2019-013-GLOB1
Amendment	4
Version Number *(for sponsor's use only)*	1

The design of this study as outlined by this protocol has been reviewed and approved by the sponsor's responsible personnel as indicated in the signature table below.

Name: [last name, first name]	**Title**:
[redacted]	Chief Medical Officer, Managing Director HUTCHMED International Corp
Signature: *See appended signature page*	**Date**: [DD Month YYYY]

Name: [last name, first name]	**Title**:
[redacted]	Chief Scientific Officer Hutchison MediPharma Limited
Signature: *See appended signature page*	**Date**: [DD Month YYYY]

INVESTIGATOR'S AGREEMENT

I have read the protocol, appendices, and accessory materials related to Study 2019-013-GLOB1 and agree to the following:

- To conduct this study as described by the protocol and any accessory materials
- To protect the rights, safety, and welfare of the participants under my care
- To provide oversight of all personnel to whom study activities have been delegated
- To control all investigational products provided by the sponsor and maintain records of the disposition of those products
- To conduct the study in accordance with all applicable local and national regulations, the requirements of the ethics committee of record for my clinical site, and Good Clinical Practices as outlined by ICH E6(R2).
- To obtain approval for the protocol and all written materials provided to participants prior to initiating the study at my site
- To obtain informed consent – and updated consent in the event of new information or amendments – from all participants enrolled at my study site prior to initiating any study-specific procedures or administering investigational products to those participants
- To maintain records of each patient's participation and all data required by the protocol

Name:	**Title:**	**Institution:**
Signature:		**Date:**

DOCUMENT HISTORY

All prior amendments of this study protocol are shown in the table below.

Amendment	**Date**
Original Protocol	25 Feb 2020
Amendment 1	08 Apr 2020
Amendment 2	30 Oct 2020
Amendment 3	16 Mar 2021
Amendment 3.1	25 Mar 2021

AMENDMENT SUMMARY

This 2019-013-GLOB1 Protocol Amendment 4 replaces 2019-013-GLOB1 Protocol Amendment 3.1. This amendment is considered non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The primary purpose of Protocol Amendment 4 is to provide clarity for select inclusion/exclusion criteria and the schedule of events, to remove instructions for concomitant proton pump inhibitors and H2-receptor antagonists, and to discontinue collection of circulating tumor DNA (ctDNA)due to supply chain issues related to COVID-19.

The major changes incorporated in Amendment 4 relative to Amendment 3.1 are summarized below. Editorial and formatting changes are not included in this summary. Summaries of prior amendments are available in Appendix 11.

Section	Summary of Change	Rationale for Change
Section 7.5.3 - Drug-Drug Interactions (Therapies to Avoid or Use with Special Caution)	Removed instruction that subjects should avoid proton pump inhibitor drugs and H2 blockers	Update made based on recent data indicating that concomitant use of proton pump inhibitors with fruquintinib had no effect on pharmacokinetic (PK) parameters
Section 1 - Synopsis Section 5.1 - Recruitment	Revised the planned estimated number of study sites from 140 to 160	Reflect potential increase in number of study sites
Section 1 - Synopsis, Inclusion Criterion #4 Section 5.3 - Inclusion Criteria, #4	For the inclusion criterion requiring patients must have received treatment with prior therapy, including anti-VEGF or anti-EGFR, examples of these treatments were added	Clarification
Section 1 - Synopsis, Exclusion Criterion #5 Section 5.4 - Exclusion Criteria, #5	Changed the protein level for which a 24-hour urine assessment is required.	Correction
Section 1 - Synopsis, Exclusion Criterion #6 Section 5.4 - Exclusion Criteria, #6	Added in details for blood pressure assessment process.	Clarification
Section 1.2 – Schedule of Events Table 1 Schedule of Events	Removed visit window day 21 of cycle 2 and cycle 3	Clarification for these particular study visits that have study drug administration and PK sampling, which preclude the use of visit window
Table 2 Schedule of Events for Dense Pharmacokinetic and Electrocardiogram Evaluations for the Subset of Approximately 120 Patients with Evaluable ECGs	Revised title	Added the requirement for 120 patients to have evaluable ECGs for PK/QTc evaluation.

Section	Summary of Change	Rationale for Change
Table 3 Schedule of Events for Sparse Pharmacokinetic and Electrocardiogram Evaluations for Patients Not Included in the Approximately 120 Evaluable Patients in the Subset in Table 2	Revised title	Changed the title to harmonize with change of title of Table 2.
Table 1 Schedule of Events Section 1.2.1 - Footnotes for Schedule of Events Table 1, #21 (footnote removed) Section 6.1.1.21 - Circulating Tumor DNA	Removed requirement for the collection of blood to evaluate ctDNA. Further noted that analysis of ctDNA samples collected would be performed according to the statistical analysis plan	Appropriate sample collection tubes are unable to be procured due to supply chain issues as a result of the COVID-19 pandemic.
Section 6.1.1.17 - Electrocardiograms Monitoring	Added that any subject with a pacemaker should undergo PK and safety ECG evaluations according to the schedule outlined in Table 3	Clarification to ensure subjects with pacemakers undergo sparse sampling
Section 6.1.1.18 - Echocardiogram	Added that echocardiograms completed as standard of care prior to signing the informed consent, but within 28 days of first dose of study treatment, may be used as baseline assessment.	Clarification
Section 1.2.2 - Footnotes for the Schedule of Events Tables 2 and 3, #4 (footnote added)	Added instruction to refer to the Holter Monitor instruction manual for appropriate timing of the start of the ECG recording.	Clarification
Appendix 9 Conversion Tables for Urinalysis Results	Added table to aid in conversion of proteins measured by urinalysis for assessment of proteinuria	Correct an oversight

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADL	Activities of daily living
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase/glutamic-pyruvic transaminase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AR	Adverse reaction
AST	Aspartate aminotransferase/glutamic-oxalacetic transaminase
AUC_{0-24}	Area under the concentration-time curve from 0 to 24 hours after drug administration
BCRP	Breast cancer resistance protein
BRAF	B-Raf proto-oncogene
BSC	Best supportive care
CAM	Chorioallantoic membrane
CDK	Cyclin-dependent kinase
CEA	Carcino-embryonic antigen
CFR	Code of Federal Regulations
CHL	Chinese Hamster Lung
CI	Confidence interval
C_{max}	Maximum plasma concentration
c-MET	Mesenchymal epithelial cells transforming factor
COVID-19	Coronavirus Disease 2019
CR	Complete response
CRC	Colorectal cancer
CrCl	Creatinine clearance
CRO	Contract research organization
CT	Computed tomography
ctDNA	Circulating tumor DNA
CTCAE	Common Terminology Criteria for Adverse Event
DCR	Disease control rate
dMMR	Deficient mismatch repair
DoR	Duration of response

Abbreviation	Definition
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of treatment
EC	Ethics Committee
EOT	End of Treatment
FDA	Food and Drug Administration
FD&C	The United States Federal Food, Drug and Cosmetic Act
FDG-PET	Fluorodeoxyglucose positron emission tomography
fT3	Serum free triiodothyronine
fT4	Serum free thyroxine
GCP	Good Clinical Practice
GI	Gastrointestinal
HA	Health Authority
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
IB	Investigator's brochure
IC_{50}	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonization
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intent-to-treat
IWRS	Interactive web response system
LDH	Lactic dehydrogenase

Abbreviation	Definition
LVEF	Left ventricular ejection fraction
mCRC	Metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MID	Minimally important difference
mL	Milliliter
MMR	Mismatch repair
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MSI-H	High levels of microsatellite instability
MTD	Maximum tolerated dose
MUGA	Multigated acquisition scan
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	The National Cancer Institute Common Terminology Criteria for Adverse Event
NE	Not evaluable
NOAEL	No observed adverse effect level
NSCLC	Non-small-cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PDGFR	Platelet-derived growth factor receptor
PFS	Progression-free survival
PK	Pharmacokinetic
PO	*Per os* (oral administration)
PPE	Palmar-plantar erythrodysesthesia
PR	Partial response
PS	Performance status
PT	Preferred term
PTT	Prothrombin time
QD	*Quaque die* (once daily)
QoL	Quality of life
RECIST	Response Evaluation Criteria In Solid Tumors

Abbreviation	Definition
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SMQ	Standardized MedDRA Query
SOC	System organ class
TEAE	Treatment-emergent adverse event
T_{max}	Time of observed maximum plasma concentration
TQT	Thorough QT
TSH	Thyroid stimulating hormone
TTD	Time to deterioration
TTP	Time to progression
ULN	Upper limit of normal
US	United States
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
WHO	World Health Organization

1 SYNOPSIS

Title	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 (FRESCO-2)
Short Title	A global, randomized, placebo-controlled phase 3 study of fruquintinib in patients with refractory metastatic colorectal cancer
Acronym	FRESCO-2
Phase	3
Study Design	This is a global, randomized, double-blind, placebo-controlled, multicenter phase 3 clinical trial to compare the efficacy and safety of fruquintinib plus best supportive care (BSC) versus placebo plus BSC in subjects with refractory metastatic colorectal cancer (mCRC). Approximately 687 subjects will be randomized in a 2:1 ratio to either the fruquintinib plus BSC treatment group or the placebo plus BSC treatment group. Randomization will be stratified by the following factors: • Prior therapy with trifluridine/tipiracil (TAS-102) versus regorafenib versus both trifluridine/tipiracil (TAS-102) and regorafenib • RAS status (wild type versus mutant) • Duration of metastatic disease (≤ 18 months versus > 18 months) Subjects will receive study treatment with each 4-week cycle consisting of 3 weeks of daily oral (PO) study medication and 1 week of study drug interruption (3 weeks on/1 week off). Tumor evaluation will be performed by imaging (computed tomography [CT] or magnetic resonance imaging [MRI] scan) every 8 weeks until there is progression of disease (PD), death, new anti-cancer treatment, or study completion, whichever comes first. Safety parameters will include adverse events (AE), and results from laboratory tests, vital signs, ECG, and echocardiogram. Post-discontinuation anti-tumor therapy and survival follow up after PD will also be recorded.
Rationale	Colorectal cancer (CRC) is the second most common malignancy in both men and women and the third most common cause of cancer-related death in the US, with an estimated 145,600 new cases and 51,020 deaths in 2019. Similarly, CRC is a major global health issue, with an estimated 1.8 million new cases and 880,000 deaths in 2018 worldwide (Bray 2018). There is no standard of care for patients who have progressed on approved standard-of-treatments, including chemotherapy, relevant biologics and TAS-102 and/or regorafenib. Patients who are well enough to receive additional therapy following all standard therapies either are considered for treatment on a clinical trial when available or are re-challenged with agents such as 5-FU or bevacizumab. Consequently, there is an unmet medical need for new medications that are safe and effective in patients with refractory mCRC who have progressed on, or had intolerable toxicity from, available standard systemic therapies, and for whom no effective therapy or standard of care exists. Fruquintinib is a novel, potent, and highly selective small molecule tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFR)-1, -2, and -3. In the FRESCO trial conducted in China, fruquintinib improved the median overall survival in patients with mCRC in a third-line or later setting when compared to placebo (median overall survival 9.3 months versus

	6.6 months; hazard ratio for death 0.65 (95% CI: 0.51-0.83; p < 0.001)(Li 2018). The results from this pivotal trial led to fruquintinib's approval in China. The safety profile of fruquintinib from an ongoing phase 1/1b study in the US is consistent with that of clinical studies performed in China, as well as published data for other small molecule VEGF inhibitors. The pharmacokinetic (PK) profile of fruquintinib in the US phase 1/1b study is also comparable to the PK profile in patients treated with fruquintinib in China at the same dose and dosing regimen (5 mg PO, QD, 3 weeks on, 1 week off, for each 4-week cycle). These data showing favorable efficacy and acceptable safety indicates fruquintinib is a promising candidate for development as a new treatment for patients with refractory mCRC and may address an unmet medical need globally. This global, multicenter, randomized, double-blind, placebo-controlled clinical trial will compare the efficacy and safety of fruquintinib in combination with BSC, to placebo in combination with BSC, in patients with refractory mCRC who have progressed on, or were intolerant to, TAS-102 and/or regorafenib. Patients must have also received prior standard therapies, including two lines of chemotherapy (fluoropyrimidine-, oxaliplatin-, and irinotecan-based), a biological VEGF inhibitor, and, if RAS wild type, an EGFR inhibitor. Patients with high microsatellite instability (MSI-H)/mismatch repair deficient (dMMR) tumors must have also received an immune checkpoint inhibitor if approved and available and if deemed appropriate.
Target Population	The study population will consist of subjects ≥18 years of age with histologically and/or cytologically documented metastatic colorectal adenocarcinoma who progressed on, or were intolerant to, all standard chemotherapies and relevant biologics and TAS-102 and/or regorafenib.
Inclusion/Exclusion Criteria	**Inclusion Criteria** Subjects may be enrolled in this study only if they satisfy all the following criteria: 1. Provide written informed consent; 2. Age ≥18 years; 3. Histologically and/or cytologically documented metastatic colorectal adenocarcinoma. RAS, BRAF, and microsatellite instability (MSI)/MMR status must be documented, according to country level guidelines; **4.** Subjects must have progressed on or been intolerant to treatment with either trifluridine/tipiracil (TAS-102) or regorafenib. 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 (eg, bevacizumab, aflibercept, ramucirumab) [*Please note that regorafenib is NOT an anti-VEGF biologic],* **and,** • if RAS wild-type, an anti-EGFR therapy (eg, cetuximab, panitumumab); 5. Subjects with microsatellite-high (MSI-H) or mismatch repair deficient (dMMR) tumors must have been treated with immune checkpoint

	inhibitors if approved and available in the subject's country unless the subject is ineligible for treatment with a checkpoint inhibitor; 6. Subjects who received oxaliplatin in the adjuvant setting and developed metastatic disease during or within 6 months of completing adjuvant therapy are considered eligible without receiving oxaliplatin in the metastatic setting. Subjects who developed metastatic disease more than 6 months after completion of oxaliplatin-containing adjuvant treatment must be treated with oxaliplatin-based therapy in the metastatic setting to be eligible; 7. Body weight ≥40kg; 8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1; 9. Have measurable disease according to RECIST Version 1.1 (RECIST v1.1), assessed locally. Tumors that were treated with radiotherapy are not measurable per RECIST v1.1, unless there has been documented progression of those lesions; 10. Expected survival >12 weeks; 11. For female subjects of childbearing potential and male subjects with partners of childbearing potential, agreement to use a highly effective form(s) of contraception, that results in a low failure rate (<1% per year) when used consistently and correctly, starting during the screening period, continuing throughout the entire study period, and for 90 days after taking the last dose of study drug. Such methods include: oral hormonal contraception (combined estrogen/ progestogen, or progestogen-only) associated with inhibition of ovulation, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal ligation, vasectomized partner, or true sexual abstinence in line with the preferred and usual lifestyle of the subject. Highly effective contraception should always be combined with an additional barrier method (eg, diaphragm, with a spermicide). The same criteria are applicable to male subjects involved in this clinical trial if they have a partner of childbirth potential, and male subjects must always use a condom; 12. Subjects with BRAF-mutant tumors must have been treated with a BRAF inhibitor if approved and available in the subject's country unless the subject is ineligible for treatment with a BRAF inhibitor. **Exclusion Criteria:** Subjects are not eligible for enrollment into this study if they have any of the following criteria: 1. Absolute neutrophil count (ANC) $<1.5\times10^9$/L, platelet count $<100\times10^9$/L, or hemoglobin <9.0 g/dL. Blood transfusion within 1 week prior to enrollment for the purpose of increasing the likelihood of eligibility is not allowed; 2. Serum total bilirubin >1.5 × the upper limit of normal (ULN). Subjects with previously documented Gilbert syndrome and bilirubin <2 X ULN are eligible; 3. ALT or AST >2.5 × ULN in subjects without hepatic metastases; ALT or AST >5 × ULN in subjects with hepatic metastases; 4. 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;

	5. Urine dipstick or urinalysis with protein ≥2+ or 24-hour urine protein ≥1.0 g/24-h. Subjects with 1+ proteinuria must undergo a 24-hour urine collection to assess urine protein level. For conversions between qualitative and quantitative results, please see Appendix 9; 6. Uncontrolled hypertension, defined as: systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg despite optimal medical management. The subject must have blood pressures below both limits. Repeated assessments are permitted; 7. International Normalized Ratio (INR) >1.5 x ULN or activated partial thromboplastin time (aPTT) >1.5 × ULN, unless the subject is currently receiving or intended to receive anticoagulants for prophylactic purposes; 8. History of, or active gastric/duodenal ulcer or ulcerative colitis, active hemorrhage of an unresected gastrointestinal tumor, history of perforation or fistulas; or any other condition that could, in the investigator's judgment, result in gastrointestinal hemorrhage or perforation; within the 6 months prior to screening; 9. History or presence of hemorrhage from any other site (eg, hemoptysis or hematemesis) within 2 months prior to screening; 10. History of a thromboembolic event, including deep vein thrombosis (DVT), pulmonary embolism (PE), or arterial embolism within 6 months prior to screening; 11. Stroke and/or transient ischemic attack within 12 months prior to screening; 12. Clinically significant cardiovascular disease, including but not limited to acute myocardial infarction or coronary artery bypass surgery within 6 months prior to enrollment, 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; 13. Corrected QT interval using the Fridericia method (QTcF) >480 msec or any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as hypokalemia, congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in a first-degree relative. 14. Concomitant medications with a known risk of causing QT prolongation and/or torsades de pointes (Source list is continuously updated online at www.crediblemeds.org); 15. Systemic anti-neoplastic therapies (except for those described in Exclusion Criterion 18) or any investigational therapy within 4 weeks prior to the first dose of study drug, including chemotherapy, radical radiotherapy, hormonotherapy, biotherapy and immunotherapy; 16. Systemic small molecule targeted therapies (eg, tyrosine kinase inhibitors) within 5 half-lives or 4 weeks (whichever is shorter) prior to the first dose of study drug; 17. Palliative radiotherapy for bone metastasis/lesion within 2 weeks prior to the initiation of study drug; 18. Brachytherapy (ie, implantation of radioactive seeds) within 60 days prior to the first dose of study drug; 19. Use of strong inducers or inhibitors of CYP3A4 within 2 weeks (or 5 half-lives, whichever is longer) before the first dose of study drug; (see Appendix 4 for a list of applicable drugs);

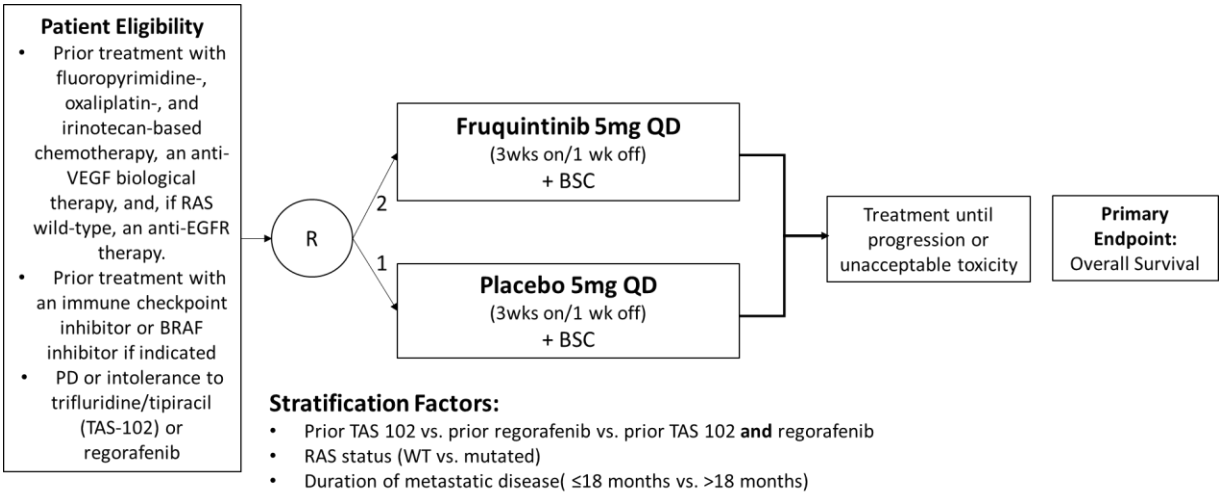
	20. Surgery or invasive procedure (ie, a procedure that includes a biopsy; central venous catheter placement is allowed) within 60 days prior to the first dose of study drug or unhealed surgical incision; 21. Any unresolved toxicities from a previous antitumor treatment greater than National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE) v5.0 grade 1 (except for alopecia or neurotoxicity grade≤2); 22. Known human immunodeficiency virus (HIV) infection; 23. Known history of active viral hepatitis. For subjects with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated. Subjects with HCV infection who are currently on treatment are eligible if they have an undetectable HCV viral load; 24. Clinically uncontrolled active infection requiring IV antibiotics; 25. Tumor invasion of a large vascular structure (eg, pulmonary artery, superior or inferior vena cava); 26. Women who are pregnant or lactating; 27. Brain metastases and/or spinal cord compression untreated with surgery and/or radiotherapy, and without clinical imaging evidence of stable disease for 14 days or longer; subjects requiring steroids within 4 weeks prior to start of study treatment are excluded; 28. Other malignancy, except for non-melanoma skin cancer, *in situ* cervical cancer or bladder cancer (Tis and T1) that have been adequately treated during the 5 years prior to screening; 29. Inability to take medication orally, dysphagia or an active gastric ulcer resulting from previous surgery (eg, gastric bypass) or a severe gastrointestinal disease, or any other condition that investigators believe may affect absorption of the investigational product; 30. Other disease, metabolic disorder, physical examination anomaly, abnormal laboratory result, or any other condition (eg, current alcohol or drug abuse) that investigators suspect may prohibit use of the investigational product, affect interpretation of study results, or put the subject at undue risk of harm based on the investigator's assessment; 31. Known hypersensitivity to fruquintinib or any of its (or placebo) inactive ingredients including the azo dyes Tartrazine - FD&C Yellow 5 and Sunset yellow FCF - FD&C Yellow 6; 32. Subjects who have received prior fruquintinib; 33. Live vaccine ≤28 days before the first dose of study drug(s). Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed.
Number of Subjects	Approximately 687 subjects will be randomized 2:1 (fruquintinib plus BSC: placebo plus BSC).
Length of Participation	Subjects may continue to receive treatment until they meet a criterion for discontinuation.
Intervention	**Investigational Drug:** Fruquintinib (HMPL-013) capsule 5 mg will be administered PO, QD, 3 weeks on, 1 week off (4-week cycles). Doses may be given either in the fasting state or after meals, around the same time each day. If dose adjustment is required, 1 mg fruquintinib capsules will be used. **Reference Drug:** Placebo capsules matching fruquintinib 5 mg will be administered PO, QD, 3 weeks on, 1 week off (4-week cycles). Doses may be

	given either in the fasting state or after meals, around the same time each day. If dose adjustment is required, 1 mg matching placebo capsules will be used.
Primary Objective	To evaluate the overall survival of fruquintinib plus BSC compared to placebo plus BSC in subjects with refractory mCRC.
Secondary Objective(s)	• To evaluate progression-free survival (PFS) of fruquintinib plus BSC compared to placebo plus BSC • To evaluate the objective response rate (ORR), disease control rate (DCR), and duration of response (DoR) • To assess the safety and tolerability of fruquintinib plus BSC compared to placebo plus BSC • To characterize the PK exposure of fruquintinib and metabolite M11 in subjects with refractory mCRC • To evaluate the effect of fruquintinib on cardiac repolarization, as detected by changes in electrocardiogram (ECG) QTc intervals, and the potential relationship with fruquintinib and M11 plasma concentrations • To evaluate the relationship between fruquintinib exposure and endpoints for efficacy and safety • To evaluate quality of life (QoL) as assessed by using QLQ-C30: cancer-specific; and EQ-5D-5L questionnaires • To assess resource utilization (for example, hospitalizations and concomitant medications)
Exploratory Objective(s)	To assess potential predictive biomarkers of response to fruquintinib
Number of Sites	This study will be conducted at approximately 160 sites globally.
Study Duration	Recruitment period is estimated to take approximately 15 months. Estimated duration for the entire study from time the study is open to enrollment until completion of data analyses is approximately 22 months.
Independent Data Safety Monitoring Committee	The IDMC will be comprised of at least 4 independent oncologists from representative geographies and at least 1 independent statistician.

1.1 Study Schematic

The study schematic is presented in Figure 1.

Figure 1 Study Design Schema



1.2 Schedule of Events

The schedules of events (SOEs) are presented in Table 1, Table 2, and Table 3.

Table 1 Schedule of Events

Protocol Activities	Screening Period		Study Treatment Period							Follow Up		
Cycle			Cycle 1		Cycle 2		Cycle 3		Cycle 4 & beyond	End of Treatment	Safety Follow Up	Survival Follow Up
Visit	Screening		C1D1	C1D21	C2D1	C2D21	C3D1	C3D21	C4D1, C5D1, etc.	7 days after last dose	30 days after EOT visit	Every 12 weeks from EOT visit
Visit Window (days)	-28 to -1	-7 to -1	N/A	N/A	±3	N/A	±3	N/A	±3	±3	±7	±14
Informed Consent [1]	X											
Medical History, Disease History and RAS status [2]	X											
Demographics [3]	X											
Prior and Concomitant Medication/ Concomitant Procedure [4]	X	X	X	X	X	X	X	X	X	X	X	
Comprehensive Physical Examination [5]		X										
Limited Physical Examination [6]				X	X	X	X	X	X	X	X	
ECOG [7, 27]		X		X	X	X	X	X	X	X	X	
Vital Signs [8, 27]		X		X	X	X	X	X	X	X	X	
Hematology [9]		X		X	X	X	X	X	X	X		
Blood Chemistry [10]		X		X	X	X	X	X	X	X		
Blood amylase and lipase [11]		X			X		X		X	X		
Coagulation [12]		X		X	X	X	X	X	X			
Thyroid Function [13]		X			X		X		X			
Urinalysis [14]		X			X		X		X			
Serum Pregnancy Test [15]		X									X	

Protocol Activities	Screening Period		Study Treatment Period							Follow Up		
Cycle			Cycle 1		Cycle 2		Cycle 3		Cycle 4 & beyond	End of Treatment	Safety Follow Up	Survival Follow Up
Visit	Screening		C1D1	C1D21	C2D1	C2D21	C3D1	C3D21	C4D1, C5D1, etc.	7 days after last dose	30 days after EOT visit	Every 12 weeks from EOT visit
Visit Window (days)	-28 to -1	-7 to -1	N/A	N/A	±3	N/A	±3	N/A	±3	±3	±7	±14
Urine pregnancy test [16]					X		X		X			
12-lead ECG [17]	X		X	X		X		X				
Echocardiogram [18]/ MUGA	X				X				X[18]			
Tumor Evaluation/Imaging [19]	Screening and every 8 weeks (±1 week) from C1D1 until progression											
Tumor Markers [20, 27]	X				X		X		X	X		
[2127]												
PK plasma sampling [21]			For PK plasma sampling schedule, see Table 2 and Table 3									
Patient Randomization [22, 27]		X										
Drug Dispense&Return [23]			X		X		X		X			
Study Treatment [24]			5 mg QD, Days 1 to 21 of each cycle									
Adverse Event [25]	Adverse Events are to be collected continuously throughout the study.											
Survival Follow Up [26]												X
QLQ-C30 Questionnaire [27]		X			X		X		X	X		
EQ-5D-5L Questionnaire [27]		X			X		X		X	X		

C1D1= cycle 1 day 1; C1D21 = cycle 1 day 21; C2D1 = cycle 2 day 1; C2D21 = cycle 2 day 21; C3D1 = cycle 3, day 1; C3D21 = cycle 3 day 21; ECG = Electrocardiogram; ECOG = Eastern Oncology Cooperative Group; EOT = End of treatment; MUGA = multiple-gated acquisition; PK = Pharmacokinetic

1.2.1 Footnotes for Schedule of Events Table 1

1. A written informed consent form should be obtained prior to any protocol-specific procedure or test. Procedural details for informed consent are available in Section 6.1.1.1.

2. Procedural details for medical history are available in Section 6.1.1.2. Tumor diagnosis, tumor treatment history, and evaluation of RAS, microsatellite instability (MSI)/mismatch repair (MMR), and BRAF status is described in Section 6.1.1.3.
3. Procedural details for patient demographics, including baseline characteristics are available in Section 6.1.1.4.
4. Procedural details for concomitant medications/treatments are available in Section 6.1.1.5.
5. Procedural details for comprehensive physical examination are available in Section 6.1.1.6.
6. Procedural details for limited physical examination are available in Section 6.1.1.7.
7. Procedural details for ECOG performance status are available in Section 6.1.1.8.
8. Procedural details for vital signs are available in Section 6.1.1.9.
9. Procedural details for hematology are available in Section 6.1.1.10.
10. Procedural details for blood chemistry are available in Section 6.1.1.11.
11. Procedural details for amylase and lipase are available in Section 6.1.1.12.
12. Coagulation tests include prothrombin time (PTT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT). Additional procedural details are available in Section 6.1.1.13.
13. Thyroid function tests include serum free triiodothyronine (fT3), serum free thyroxine (fT4) and thyroid stimulating hormone (TSH). Additional procedural details are available in Section 6.1.1.14.
14. Twenty-four-hour urine for quantitative protein should be collected from all patients with 1+ proteinuria during screening. If urine protein ≥2+ during the period of study treatment, a 24-hour urine protein should be collected within 1 week. Additional procedural details for urinalysis are available in Section 6.1.1.15.
15. All female patients of childbearing potential must complete a blood pregnancy test at screening and at the Safety Follow up Visit. Serum pregnancy test should be repeated for patients with suspected pregnancy or an equivocal urine pregnancy test. This is not applicable for postmenopausal female patients, but the date of menopause should be recorded instead. Additional procedural details are available in Section 6.1.1.16.
16. All female patients of childbearing potential must complete a urine pregnancy test at each day 1-visit starting at cycle 2.
17. See Table 2 and Table 3 for specific ECG parameters and time points. Electrocardiogram is to be performed before PK and echocardiogram assessments at each relevant visit. Other procedural details for Holter Monitor and 12-lead ECG are available in Section 6.1.1.17.

18. An echocardiogram should be done at Screening, C2D1, and on the first day, every 3 cycles thereafter. Additional procedural details for echocardiogram are available in Section 6.1.1.18. MUGA scans are acceptable if an echocardiogram cannot be performed.
19. Baseline tumor assessment should be completed within 28 days prior to enrollment. Post-baseline tumor evaluations shall be performed on C3D1, C5D1, and day 1 of every other cycle thereafter until progression of disease (PD). Each tumor assessment should document measurable lesions at the scheduled visit (every 8 weeks ± 1 week). Additional procedural details are available in Section 6.1.1.19.
20. Serum carcino-embryonic antigen (CEA) level is collected at screening and at day 1 of every cycle (±1 week) starting at cycle 2 until disease progression. Additional procedural details are available in Section 6.1.1.20.
21. 6.1.1.21See Table 2 and Table 3 for specific PK time points. Sampling for PK assessments is described in Section 6.1.2.1, and evaluation procedures are described in Section 6.1.2.2
22. Patient randomization occurs on day -2 to day 1. Additional procedural details on patient randomization are available in Section 6.1.1.22.
23. For the method of drug dispensation and return, see Section 7.2.2.
24. Study drug is taken daily on a 3 weeks on, 1 week off schedule for each 28-day cycle. On days with PK collection, treatment should be administered at the site by a delegated study staff member.
25. After informed consent, but prior to initiation of study drug, all SAEs regardless of attribution will be collected. After initiation of study drug, all SAEs and AEs regardless of attribution will be collected until 30 days after the last dose of study drug or a new treatment of anti-tumor therapy, whichever is earlier. After this period, investigators should report only SAEs that are considered related to the study drug.
26. Survival follow-up (by telephone) should be performed every 12 weeks (±2 weeks) after the end of treatment (EOT) visit. All subsequent anti-tumor therapy and information about study drug-related SAEs shall be collected. For the patients that discontinue the study without PD, all available tumor assessment results during survival follow up shall be recorded in the eCRF until confirmation of PD. The date and cause of death should be recorded, if applicable. Patients who withdraw consent are encouraged to be followed for survival. If the patient has clearly expressed his/her refusal to be followed after withdrawal of consent, he/she will terminate the study and no follow up for survival will be performed.
27. Events can be performed up to and including C1D1.

Table 2 Schedule of Events for Dense Pharmacokinetic and Electrocardiogram Evaluations for the Subset of Approximately 120 Patients with Evaluable ECGs

Study day	Time Relative to Dosing (±10 minutes)	Study Drug Intake [1]	Pharmacokinetic Samples [2]	Triplicate ECG for QTc Evaluation (Holter Monitor[4])	Safety ECG (Standard Equipment)
C1D1	Pre-dose [3]		X	X	-
	0 h	X	-	-	-
	1 h		X	X	-
	2 h		X	X	-
	3 h		X	X	-
	4 h		X	X	-
C1D21	Pre-dose [3]		X	X	-
	0 h	X	-	-	-
	1 h		X	X	-
	2 h		X	X	-
	3 h		X	X	-
	4 h		X	X	-
C2D1	Pre-dose [3]		X	-	-
	0 h	X	-	-	-
C2D21	Pre-dose [3]		X	-	-
	0 h	X	-	-	-
	2 h		X	-	X
C3D1	Pre-dose [3]		X	-	-
	0 h	X	-	-	-
C3D21	Pre-dose [3]		X	-	-
	0 h	X	-	-	-
	2 h		X	-	X
C5D1 and every other cycle thereafter	Pre-dose [3]		X	-	-
	0 h	X	-	-	-

C1D1= cycle 1, day 1; C1D21 = cycle 1, day 21; C2D1 = cycle 2, day 1; C2D21 = cycle 2, day 21; C3D1 = cycle 3, day 1; C3D21 = cycle 3, day 21; C5D1 = cycle 1, day 1 ECG = Electrocardiogram

Table 3 Schedule of Events for Sparse Pharmacokinetic and Electrocardiogram Evaluations for Patients Not Included in the Approximately 120 Evaluable Patients in the Subset in Table 2

Study day	Time Relative to Dosing (±10 minutes)	Study Drug Intake [1]	Pharmacokinetic Samples [2]	Safety ECG (Standard Equipment)
C1D1	Pre-dose [3]		X	X
	0 h	X	-	-
	2 h		X	X
C1D21	Pre-dose [3]		X	-
	0 h	X	-	-
	2 h		X	X
C2D1	Pre-dose [3]		X	-
	0 h	X	-	-
C2D21	Pre-dose [3]		X	-
	0 h	X	-	-
	2 h		X	X
C3D1	Pre-dose [3]		X	-
	0 h	X	-	-
C3D21	Pre-dose [3]		X	-
	0 h	X	-	-
	2 h		X	X
C5D1 and every other cycle thereafter	Pre-dose [3]		X	-
	0 h	X	-	-

C1D1= cycle 1, day 1; C1D21 = cycle 1, day 21; C2D1 = cycle 2, day 1; C2D21 = cycle 2, day 21; C3D1 = cycle 3, day 1; C3D21 = cycle 3, day 21; C5D1 = cycle 1, day 1; ECG = Electrocardiogram

1.2.2 Footnotes for the Schedule of Events Tables 2 and 3

1. On PK sampling day, study drug must be taken at the investigative site under the supervision of the investigator or designee and should not be taken at home on the morning of the visits. The date and time of the dose administered on the day of PK collection and one day before PK collection must be recorded in the electronic case report form (eCRF).
2. The actual date and time of the PK samples must be recorded on the eCRF. There is a window of ± 10 minutes for the PK sampling procedure.
3. Pre-dose PK and ECG should be performed within 30 minutes BEFORE study drug administration.
4. Refer to the Holter Monitor instruction manual for appropriate timing of the start of the ECG recording.

2 INTRODUCTION

During tumorigenesis, malignancies release growth factors to induce angiogenesis, which provides nutrients and oxygen for rapid tumor growth. The immature arrangement of endothelial cells on the rapidly growing blood vessels can result in exudation of tumor cells into the circulatory system, through which the tumor cells may spread to other tissues, leading to tumor metastasis. Vascular endothelial growth factor receptor (VEGFR) is one of the key factors known to induce tumor angiogenesis, and agents that target VEGF and the VEGFR are important therapies for malignant solid tumors, including colorectal cancer (Duda 2007, Jayson 2016).

Fruquintinib (HMPL-013) is a small molecule anti-tumor drug with a novel chemical structure that belongs to the quinazoline class and is a potent and highly selective tyrosine kinase inhibitor of VEGFRs. *In vitro* studies demonstrated that fruquintinib is highly selective for VEGFRs-1, -2, and -3, which are related to tumor angiogenesis, and possess weak or no measurable activity against other kinases (Sun 2014). Fruquintinib was discovered by Hutchison MediPharma Limited (hereafter referred to as the sponsor) through *in vitro* and *in vivo* biological screening of a large number of synthetic compounds.

Results from preclinical and clinical studies have provided evidence that fruquintinib has anti-cancer activity in solid tumors. The clinical development program in China has been ongoing since 2009. In the phase 3 clinical trial, FRESCO, that led to the drug's approval in China, fruquintinib improved median overall survival in patients with metastatic colorectal cancer (mCRC) in a third-line or later setting when compared to placebo from 6.6 to 9.3 months (hazard ratio for death 0.65; 95% confidence interval [CI] 0.51-0.83; $P < 0.001$)(Li 2018). The cumulative safety data from the clinical trial program has shown that fruquintinib has an acceptable level of toxicity that is consistent with other antiangiogenic drugs, particularly small molecule VEGFR inhibitors. These data provide a strong justification for the investigation of fruquintinib in patients with refractory mCRC globally.

2.1 Study Rationale

Colorectal cancer (CRC) is a major global health issue, with an estimated 1.8 million new cases and 880,000 deaths in 2018 worldwide (Bray 2018). The established initial and second-line systemic therapy for mCRC consists of fluoropyrimidine-, oxaliplatin, and irinotecan-based cytotoxic chemotherapy (eg, FOLFOX: [5-Fluorouracil, leucovorin, and oxaliplatin] and FOLFIRI [5-fluorouracil, leucovorin, and irinotecan]). In addition, a biologic anti-VEGF therapy is typically given with chemotherapy (eg, bevacizumab), and if the tumor is RAS wild type, an anti-EGFR therapy (eg, cetuximab) is administered. In the small proportion of patients that are deficient mismatch repair (dMMR)/ high levels of microsatellite instability (MSI-H) in the metastatic setting (Koopman 2009), immunotherapy with nivolumab or pembrolizumab may be used (NCCN 2019).

When there is disease progression after the first two lines of chemotherapy, the established options are either:

- Trifluridine/tipiracil (LONSURF®, TAS-102), an oral combination of trifluridine, a nucleoside metabolic inhibitor, and tipiracil, a thymidine phosphorylase inhibitor; (LONSURF® USPI) or
- Regorafenib (STIVARGA®), a multikinase inhibitor with numerous *in vitro* targets that include VEGFR (STIVARGA® USPI).

There is no standard of care for patients who have progressed on chemotherapy, relevant biologics, and TAS-102 and/or regorafenib. Accordingly, there is an unmet medical need for new medications that are safe and effective in patients with refractory mCRC who have progressed on, or had intolerable toxicity from, available standard systemic therapies, and for whom no effective therapy or standard of care exists. A recent estimation of the median overall survival (OS) for patients with mCRC, based on data from phase 3 clinical trials, observation studies, and registries, is 30 months (Grothey 2013, Mayer 2015). During this time, patients may receive several lines of therapy, with one or more "breaks." Both TAS-102 and regorafenib are approved in the third-line or greater (3+ line) of therapy after progression on chemotherapy, and there are no approved treatments following progression on these agents. In this setting, the current options for patients with good performance status are to enter a clinical trial or to be re-challenged with prior chemotherapy (eg, 5-FU). Patients with poor performance status generally enter hospice care.

Fruquintinib is currently in clinical development for a number of different cancer indications, including advanced non-small-cell lung cancer (NSCLC), gastric cancer, and mCRC. All clinical studies of fruquintinib that led to the first approval of fruquintinib (Elunate®) capsule, granted on 04 September 2018 in China for the treatment of patients with mCRC, were conducted in China in primarily Asian study populations. At the time this study was conceived, a phase 1/1b study of fruquintinib in the United States (US) was being conducted. Preliminary data indicated that the safety profile of fruquintinib from this ongoing phase 1/1b study in the US was consistent with those from the clinical studies performed in China.

This global phase 3 trial (FRESCO-2) is being conducted to confirm the results of the phase 3 FRESCO trial conducted in China in patients with refractory mCRC. This randomized, double-blind, placebo-controlled, clinical trial will compare the efficacy and safety of fruquintinib in combination with the best supportive care (BSC) versus placebo in combination with BSC in patients with refractory mCRC who have progressed on, or were intolerant to, TAS-102 and/or regorafenib.

2.2 Background

2.2.1 Justification for Dosing Strategy

The optimal fruquintinib dose and dosing regimen were determined in two Chinese phase 1 studies, 2009-013-00CH1 and 2012-013-00CH3, as well as one US phase 1/1b study, 2015-013-00US1. During dose escalation, study 2009-013-00CH1 investigated continuous daily doses of 1 mg, 2 mg, 4 mg, 5 mg, and 6 mg; in addition, 5 mg QD and 6 mg QD were studied on a regimen of 3 weeks on, 1 week off (4-week) cycles. The maximum-tolerated dose (MTD)/ recommended phase 2 dose (RP2D) was 4 mg QD (continuous) or 5 mg QD (3 weeks on, 1 week off).

In study 2012-013-00CH3, the safety and tolerability of these two dosing regimens (4 mg QD continuously versus 5 mg QD, 3 weeks on, 1 week off) were compared in patients with mCRC. The safety profile was better in the 5 mg QD (3 weeks on, 1 week off) group than the 4 mg QD (continuous) group. In addition, there was accumulation of drug over time in the 4 mg QD (continuous) group. Thus, the 5 mg PO, QD, 3 weeks on, 1 week off, dose and regimen was selected as the RP2D and the dosing regimen to be used in subsequent clinical development in China.

The RP2D and dosing regimen were tested in the phase 2 (2012-013-00CH1) and phase 3 (2013-013-00CH1 [FRESCO]) studies, which confirmed that the dose and dosing regimen were safe and

effective in patients with refractory mCRC. The 5 mg PO, QD, 3 weeks on, 1 week off, on a 28 day cycle, is the standard dose and dosing regimen in all other completed, ongoing, and planned studies in patients with advanced cancer.

In the US phase 1/1b study (2015-013-00US1), there were 2 dose cohorts in the dose escalation phase, 3 mg PO, QD (n=7) and 5 mg PO, QD (n=7). Fruquintinib was well tolerated in both dose cohorts. Therefore, 5 mg PO, QD, 3 weeks on, 1 week off, on a 28 day cycle, was confirmed as the RP2D for global studies, as well.

2.2.2 Supportive Nonclinical Data

2.2.2.1 Pharmacology

Fruquintinib is highly selective for VEGFRs -1, -2, and -3, with a 50% inhibitory concentration (IC_{50}) of 33 nM, 35 nM and 0.5 nM, respectively. Fruquintinib was found to have low activity on other kinases, with IC_{50} greater than 10 μM for cyclin-dependent kinases (CDKs 1, 2, and 5), platelet-derived growth factor receptor β (PDGFRβ), epidermal growth factor receptor (EGFR), and mesenchymal-epithelial transition factor (c-Met) in a panel of 264 kinases, which confirms the selectivity of fruquintinib.

In cellular assays, fruquintinib inhibited VEGFR family kinases and suppressed VEGFR phosphorylation with IC_{50} at low (nanomolar) levels. Consistently, in functional assays, fruquintinib blocked VEGF-dependent human umbilical vein endothelial cell (HUVEC) proliferation and tube formation and also exhibited this anti-angiogenic effect in the chorioallantoic membrane (CAM) model.

In animal models, a pharmacokinetic (PK)/pharmacodynamic study revealed that fruquintinib suppressed VEGF-induced VEGFR2 phosphorylation (p-VEGFR2) in lung tissues of nude mouse in a drug exposure-dependent manner. Fruquintinib also achieved near complete target inhibition (>80%), following a single oral dose of 2.5 mg/kg, which was maintained for >8 hours with a corresponding plasma drug concentration of 176 ng/mL at the 8-hour time point.

In multiple human tumor xenograft models in Nu/Nu mice, fruquintinib demonstrated a dose dependent anti-tumor activity accompanied by strong anti-angiogenesis effect in tumor tissues. In all tumor models tested, fruquintinib showed statistically significant tumor growth inhibition at doses as low as 2 mg/kg/day. Complete target coverage for more than 8 hours, with plasma concentration over 176 ng/mL maintained for 8 hours, was shown to significantly suppress tumor growth.

The combination of fruquintinib with cytotoxic chemotherapies (oxaliplatin or docetaxel), with molecular targeted therapies (EGFR or MET inhibitors) or with an immune checkpoint inhibitor (anti-PD-L1) demonstrated a synergistic or additive anti-tumor effect in multiple preclinical tumor models.

2.2.2.2 Metabolism and Pharmacokinetic Drug Interaction

[redacted]

In vitro, fruquintinib had no significant reversible or [redacted] on CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5 (IC_{50} >10 μM). There was also no induction of CYP1A2, [redacted] and CYP3A4 by fruquintinib at concentrations up to 10 μM.

According to the investigations on drug transporters, fruquintinib was not a substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), [redacted]

2.2.2.3 Toxicology

[redacted]

2.2.3 Supportive Clinical Data

2.2.3.1 Clinical Pharmacokinetics

Single-dose and multiple-dose PK of fruquintinib have been characterized in Chinese and US patient populations, and single-dose PK has been evaluated in healthy Chinese males.

In Chinese patients with cancer, plasma fruquintinib exposure increased proportionally over the single dose range tested from 1 mg to 6 mg. Fruquintinib was rapidly absorbed with mean T_{max} ranging from 1.5 to 4.7 hours. Mean $t_{1/2}$ ranging from 35.2 hours to 48.5 hours was observed for fruquintinib. Following continuous dosing of fruquintinib 1, 2, 4, 5, or 6 mg QD, plasma fruquintinib concentration reached steady state by 14 days after dosing with exposure accumulating 3- to 4-fold at steady state compared to day 1. Following dosing of fruquintinib at 5 mg QD and 6 mg QD at the 3 week on/1 week off schedule, plasma fruquintinib concentrations declined during the off week, as expected. Preliminary PK results from the US patient population (ongoing Study 2015-013-00US1) that received fruquintinib at 3 mg and 5 mg QD 3 weeks on/1 week off suggested that there were no meaningful differences in fruquintinib exposure between Chinese and US patients. Following fruquintinib 5 mg QD 3 weeks on/1 week off, mean fruquintinib maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve over a dosing interval (AUC_{tau}) values on day 21 were 326 ng/mL and 5969 ng*h/mL in Chinese patients (Study 2012-013-00CH3), respectively, compared with 385 ng/L and 7530 ng*h/mL in US patients, respectively.

The effect of a high fat high calorie meal on the PK of fruquintinib 4 mg (4 x 1 mg capsules) was studied in healthy Chinese males (Study 2012-013-00CH2). Food delayed T_{max} of fruquintinib by 2.6 hours. A slight decrease in fruquintinib C_{max} by 17% was seen, though there was no observed effect on the $AUC_{0-\infty}$. These results were sufficient to recommend dosing of fruquintinib without regard to food.

The results from the mass balance study conducted in healthy Chinese subjects (Study 2015-013-00CH2) indicated that 60.31% of total radioactivity was recovered in urine and 29.80% in feces. A total of 22 metabolites were identified in the plasma, urine, and feces samples. The M11 (N-demethylation product) and M9 (carboxylic acid product) were the main metabolites, where M11 accounted for 17.31% and M9 accounted for 4.46% of the plasma exposure of total radioactivity. Only a small amount of unchanged fruquintinib was detected in urine, which accounted for 0.50% of the dose administered. The amount of fruquintinib in feces accounted for 5.34% of the dose administered.

M11 is a pharmacologically active metabolite found to inhibit VEGFR2 kinase activity and VEGF-induced VEGFR2 phosphorylation, with a potency approximately 2 to 10 times lower than that of fruquintinib. After multiple doses of fruquintinib 5 mg QD to patients for 21 days (Study 2015-013-00US1, preliminary data), M11 reached T_{max} after 1 hour. The mean (standard deviation) C_{max} and area under the concentration-time curve from 0 to 24 hours after drug administration (AUC_{0-24}) values were 144 (56.2) ng/mL and 3080 (1250) h*ng/mL, respectively. M11 accumulated by 31.5-fold after multiple dosing. The mean (standard deviation) metabolite-to-parent ratio of M11 was 0.409 (0.135) at steady state. Overall, M11 is not expected to have clinically meaningful contribution to the total pharmacological activity of fruquintinib at therapeutic exposure.

2.2.3.2 Clinical Safety

As of the data cut-off date (03 Sep 2019), 7 clinical trials in patients with cancer were completed. In order to conduct a comprehensive and robust safety assessment across the fruquintinib clinical studies, a pooled dataset has been generated and analyzed, which consists of data from 739 patients in 4 completed double-blind studies (2012-013-00CH1, 2013-013-00CH1, 2014-013-00CH1, and 2015-013-00CH1) (Table 21) who received fruquintinib monotherapy. In addition, the safety data

from 2 completed early phase open-label studies (phase 1 2009-013-00CH1, phase 1b 2012-013-00CH3) and 1 completed phase 1b/2 study (2014-013-00CH3) has also been analyzed.

As of the data cut-off date, 5 clinical studies in patients with cancer were ongoing. The safety profile of fruquintinib from a US phase 1/1b open-label, multi-center study (2015-013-00US1), from a China phase 2 open-label study of fruquintinib in combination with gefitinib (2016-013-00CH1), and from a China phase 1b/2 open-label study of fruquintinib in combination with sintilimab (2018-013-00CH3) are also presented in this section. No formal analysis is available for the safety profile of fruquintinib in the other 2 ongoing studies; the China randomized phase 3 study of paclitaxel with or without fruquintinib in metastatic gastric cancer (2017-013-00CH1) remains blinded, and no patients have been enrolled into the China open label single arm study evaluating fruquintinib in elderly patients with NSCLC (2017-013-00CH2).

Adverse Events in Completed Studies:

A total of 739 patients received at least 1 dose of fruquintinib in the 4 completed double-blind, placebo-controlled, monotherapy studies, among whom 729 (98.6 %) patients reported treatment-emergent adverse events (TEAEs). The incidence of the most commonly reported TEAEs (≥10% of patients) are provided in the current investigator's brochure (IB).

In the pooled data of all-causality TEAEs reported, the most commonly reported TEAEs of grade ≥3 (≥5% of patients) included Hypertension (19.9%) and Palmar-plantar erythrodysaesthesia syndrome (10.7%).

Serious Adverse Events in Completed Studies:

A total of 1 or more serious adverse events (SAEs) have been reported by 169 (22.9%) patients out of the 739 patients who received fruquintinib. The most common SAEs (≥1.0%) by MedDRA preferred term (PT) included Infectious pneumonia in 24 (3.2%) patients, intestinal obstruction in 17 (2.3%) patients, pleural effusion in 9 (1.2%) patients, death in 10 (1.4%) patients, hepatic function abnormal in 8 (1.1%) patients, and gastrointestinal haemorrhage in 8 (1.1%) patients. The SAEs in more than 1 patient in the pooled data are summarized in the current IB.

2.2.3.3 Clinical Efficacy

Monotherapy Efficacy:

As of the data cut-off date (03 September 2019), the available fruquintinib efficacy data from the completed open-label and double-blind studies showed strong antitumor activity, including improved OS and progression-free survival (PFS), durable partial response (PR) and durable stable disease (SD), and improved overall response rate (ORR) in heavily pre-treated patients with advanced cancer.

Two proof-of-concept studies have been conducted in patients with CRC who were previously treated with two or more lines of standard chemotherapeutic regimens (2012-013-00CH1) and in patients with NSCLC who have failed 2 lines of standard chemotherapies (2014-013-00CH1). The studies both met their primary efficacy endpoint of PFS and demonstrated a significant improvement in PFS in the fruquintinib arm compared to the placebo arm.

In addition, the phase 3 pivotal trial (FRESCO) was completed in patients with CRC who were previously treated with 2 or more lines of standard chemotherapeutic regimens (2013-013-00CH1). In this study, fruquintinib significantly prolonged the OS compared to placebo with a

hazard ratio (HR) of 0.65 (95% CI: 0.51-0.83; 2-sided p <0.001). Statistically significant benefits were also seen with fruquintinib in all secondary endpoints, including as PFS, ORR, and disease control rate (DCR).

One phase 3 study of fruquintinib was completed in patients with NSCLC who had failed second-line standard chemotherapy (2015-013-00CH1): there was no significant difference between the fruquintinib group and the placebo group in the primary efficacy endpoint (OS). However, fruquintinib significantly prolonged the PFS comparing to placebo with a HR of 0.34 (95% CI: 0.279, 0.425) with p < 0.001 (stratified log-rank test). Statistically significant benefits were also shown with fruquintinib in ORR and DCR.

The efficacy data in the ongoing study of fruquintinib in patients with advanced solid tumors (2015-013-00US1) are not available as of the data cut-off date (03 September 2019).

Combination Therapy Efficacy

A phase 1b/2 study had been conducted to investigate the treatment of fruquintinib, in combination with paclitaxel, as second-line therapy in patients with gastric cancer (GC) (2014-013-00CH3). The results showed that the ORR and DCR were 27.3% (9/33) and 63.6% (21/33), respectively. The median PFS and median OS at the RP2D (fruquintinib 4 mg + paclitaxel) were 4.0 months and 8.5 months, respectively.

The efficacy data in 1 ongoing study of fruquintinib in combination with gefitinib in patients with NSCLC (2016-013-00CH1) and in 1 ongoing study of fruquintinib in combination sintilimab patients with advanced solid tumors (2018-013-00CH3) are not available as of the data cut-off date (03 September 2019).

2.2.4 Benefit/Risk Assessment

There are robust cumulative efficacy and safety data for fruquintinib from the entire clinical program in China, as well as the ongoing US phase 1/1b study. As of the data cut-off date (03 September 2019) a total of 1600 patients and 87 healthy volunteers had received at least one dose of fruquintinib or placebo through development programs. Among them, 955 patients and 87 healthy volunteers had received at least one dose of fruquintinib, 284 patients had received at least one dose of blinded treatment (fruquintinib versus placebo), and 361 patients had received at least one dose of placebo.

2.2.4.1 Risk Assessment

A total of 739 patients received at least 1 dose of fruquintinib in the 4 completed double-blind studies, among whom 739 (98.6 %) patients reported TEAEs.

In the pooled data of all-causality TEAEs reported in the 3 completed double-blind, monotherapy studies, the most commonly reported TEAEs of grade ≥3 (≥5% of patients) included hypertension (19.9 %) and palmar-plantar erythrodysaesthesia syndrome (10.7 %).

The incidence of the most commonly reported TEAEs (≥10% of patients) is provided in the current IB.

The safety analysis that resulted in the identified risks was performed on the pooled data set from 4 completed double-blind studies (N= 739 fruquintinib; N= 361 placebo), in which the incidence of adverse events (AEs) in fruquintinib-treated patients was compared with those in the placebo-

treated control patients. The identified risks presented by Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) are presented in Table 54 of the current IB.

2.2.4.2 Benefit Assessment

The efficacy data in the phase 1 study conducted in China (2009-013-00CH1) showed encouraging clinical activity for fruquintinib. A response was observed in the majority of heavily pre-treated patients with advanced cancers (see the current IB). The results of two phase 2 proof-of-concept (POC) studies provided evidence of clinical efficacy in patients with metastatic CRC (2012-013-00CH1, third or later lines therapy) and NSCLC (2014-013-00CH1, third-line therapy) as compared with placebo. The PFS results established POC in both studies by meeting their respective primary efficacy endpoints. Clinical efficacy was also provided by the phase 3, double-blind, placebo-controlled trial, 2013-013-00CH1 (FRESCO).

2.2.4.3 Overall Benefit/Risk Conclusion

The safety profile of fruquintinib is consistent with those of other anti-angiogenic therapies, particularly the small molecule tyrosine kinase inhibitors (ie, sorafenib, regorafenib, axitinib, and sunitinib), as demonstrated by the identified risks for fruquintinib (Section 2.2.4.1). In addition, safety data from the completed and ongoing studies showed that fruquintinib was well tolerated, with most of the AEs reported as grade 1 to 2 (see current IB). There have been no new or unexpected safety findings from the ongoing clinical trials to date.

3 OBJECTIVES AND ENDPOINTS

3.1 Primary Objective

To evaluate the overall survival (OS) of fruquintinib plus BSC compared to placebo plus BSC in subjects with refractory mCRC

3.2 Secondary Objectives

- To evaluate PFS of fruquintinib plus BSC compared to placebo plus BSC
- To evaluate the objective response rate (ORR), disease control rate (DCR), and duration of response (DoR)
- To assess the safety and tolerability of fruquintinib plus BSC compared to placebo plus BSC
- To characterize the PK exposure of fruquintinib and metabolite M11 in subjects with refractory mCRC
- To evaluate the effect of fruquintinib on cardiac repolarization, as detected by changes in electrocardiogram (ECG) QTc intervals, and the potential relationship with fruquintinib and M11 plasma concentrations
- To explore the relationship between fruquintinib exposure and endpoints for efficacy and safety
- To evaluate quality of life (QoL) as assessed by using QLQ-C30: cancer-specific; and EQ-5D-5L questionnaires
- To assess resource utilization (for example, hospitalizations and concomitant medications)

3.3 Exploratory Objectives

- To assess potential predictive biomarkers of response to fruquintinib

The objectives and corresponding endpoints are summarized in Table 4.

Table 4 Objectives and Corresponding Endpoints

Tier	Objectives	Endpoints
Primary	To evaluate the overall survival (OS) of fruquintinib plus BSC compared to placebo plus BSC in subjects with refractory mCRC	OS
Secondary	To evaluate progression-free survival (PFS) of fruquintinib plus BSC compared to placebo plus BSC	PFS
	To evaluate the objective response rate (ORR), disease control rate (DCR), and duration of response (DoR)	• ORR • DCR • DoR

Table 4 Objectives and Corresponding Endpoints

Tier	Objectives	Endpoints
	To assess the safety and tolerability of fruquintinib plus BSC compared to placebo plus BSC	Safety including TEAEs, SAEs, deaths, ECG's, and clinical laboratory abnormalities
	To characterize the pharmacokinetic (PK) profile of fruquintinib in subjects 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 electrocardiogram (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 quality of life (QoL) as assessed by 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 (for example, hospitalizations and concomitant medications)	Resource utilization including all concomitant medications, days in hospital
Exploratory	To assess potential predictive biomarkers of response to fruquintinib	• Change from baseline in ctDNA • Change from baseline in tumor markers (CEA) • Pharmacogenomics

4 STUDY PLAN

Detailed information on the fruquintinib clinical trial program in China and in the US can be found in Appendix 5 and in the fruquintinib IB.

4.1 Study Design

This is a global, randomized, double-blind, placebo-controlled, multicenter phase 3 clinical trial to compare the efficacy and safety of fruquintinib in combination with BSC versus placebo in combination with BSC in advanced colorectal cancer patients who have progressed on or were intolerant to chemotherapy, biologics and TAS-102 or regorafenib.

Metastatic colorectal cancer cannot be cured by surgery. Therefore, treatment principals are primarily aimed at controlling disease progression and prolonging survival. Standard first- and second-line therapy includes cytotoxic drugs such as 5-fluorouracil, oxaliplatin, and irinotecan; anti-VEGF therapy; and, if RAS wild type, anti-EGFR therapy. After the first two lines of chemotherapy, standard third-line treatment is either TAS-102 or regorafenib. 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. Consequently, there is an unmet medical need for additional safe and effective treatment.

4.1.1 Enrollment in Study

After checking the eligibility criteria, subjects will be randomized into either fruquintinib in combination with BSC group (fruquintinib group) or placebo in combination with BSC group (placebo group) in a 2:1 ratio (Figure 1).

- 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.

A 2:1 randomization ratio is used in this study as it is expected that fruquintinib will produce better efficacy results and robust safety data compared to the placebo arm. This is supported by robust efficacy and safety data from the fruquintinib clinical program, including from the pivotal phase 3 FRESCO trial.

A treatment cycle is 4 weeks. Subjects' safety assessment and drug accountability will be performed at each treatment cycle. Continuous drug safety monitoring and assessment will be performed through the whole study period (including a 30-day observation period after the end of treatment).

As described in Section 2.2.3.3, in the phase 3 FRESCO trial that led to the drug's approval in China, fruquintinib improved the median OS in patients with mCRC in a third line or later setting when compared to placebo (median OS 9.3 versus 6.6 months); HR for death was 0.65 (95% CI, 0.51-0.83; $P < 0.001$) (Li 2018). The results of the FRESCO study indicate that fruquintinib is a candidate therapy for patients with refractory mCRC globally, and provides the strongest rationale for the current clinical trial.

Since the current standard of care for patients with mCRC in the US, EU, and Japan is different than it was in China during the conduct of the FRESCO trial, the current study is necessary to

evaluate fruquintinib in a patient population that is representative of global treatment practices. In FRESCO, prior therapy included the standard first two lines of cytotoxic chemotherapy (fluoropyrimidine-, oxaliplatin- and irinotecan-based), but only about 30% of patients had received prior therapy with a VEGF inhibitor (bevacizumab), and patients with prior exposure to VEGFR inhibitors such as regorafenib were excluded.

4.1.2 Electrocardiogram Collection and Pharmacokinetic Sampling

4.1.2.1 Rationale for Electrocardiogram Collection and Pharmacokinetic Sampling Schedule

In accordance with International Conference on Harmonization (ICH) E14 guideline, QT evaluation is expected to be routine in oncology drug development, and a thorough QT (TQT) study should be conducted, if possible. In the case of fruquintinib, in view of nonclinical (hERG and CV safety study) and clinical data suggesting no apparent relationship between fruquintinib and QT prolongation, an alternative design to the TQT study has been chosen.

In this study, changes in QTc interval following drug administration will be evaluated relative to the baseline measurement. Electrocardiogram time points have been selected to match the expected PK profile of fruquintinib and metabolite M11. The ECG time points have also been selected to explore a potential relationship between exposure and effect on QTc.

4.1.2.2 Electrocardiogram Collection and Pharmacokinetic Sampling Schedule

In order to assess the QTc interval prior to exposure to fruquintinib, baseline triplicate ECG assessments will be performed prior to first study drug administration on cycle 1 day 1 (within 30 minutes before dosing). A baseline PK sample will also be collected at pre-dose, immediately after the ECGs have been collected and prior to the first dose of fruquintinib or placebo. Subsequently, the purpose of all other ECGs is to assess for potential prolongation of the QTc interval and other ECG changes as a result of fruquintinib administration, with ECG collection coinciding with PK measurements to establish correlations between ECG changes and drug exposure. Triplicate ECGs, followed by blood samples for PK assessment, will be collected at multiple time points post-dose around T_{max} of fruquintinib and metabolite M11 after the first dose and at steady-state as described in Table 2.

4.1.2.3 Temporary and Permanent Changes in Pharmacokinetic Sampling, Holter Monitor QTc Evaluations, and Circulating Tumor DNA Sample Collection

During the conduct of this 2019-013-GLOB1 study, the COVID-19 pandemic caused significant delays in laboratory kit production and delivery from the central vendor. In order to mitigate the delays and allow study sites to screen and treat patients, temporary and permanent measures have been implemented as needed to permit changes in the collection of PK and ctDNA sampling and Holter monitor QTc evaluations until the supply issues that affected the laboratory kits have been resolved. These temporary measures have been implemented in region-specific addenda to this 2019-013-GLOB1 protocol. The temporary pauses on blood sample collection and Holter monitoring were terminated once the issues that affected the laboratory kits had been resolved. The details of the country-level changes are detailed in separate country-level addenda.

Due to a continued shortage of tubes for ct

DNA collection, an adequate supply to ensure continued collection of all samples for all patients cannot be maintained and ctDNA collections will be permanently discontinued in Protocol Amendment 4.

Subjects who do not have PK and ctDNA sample collection and Holter monitor QTc evaluations and post-dose safety ECG evaluations performed during the time that an addendum for the region is effective are to have "Not Done" entered in the corresponding eCRFs. Queries are to be issued for these pages, and site responses are to include "COVID-19 – supply chain" as the reason for missed assessment.

Pharmacokinetic and ctDNA sample collection and Holter monitor QTc evaluations do not affect patient safety and are not required for subject-level treatment decisions on this study. Additionally, with the resumption of PK and ctDNA sample collection and Holter monitor QTc evaluations, the integrity of trial data will be preserved and the eventual evaluation of the respective secondary objectives will not be compromised.

5 POPULATION

5.1 Recruitment

To randomize 687 patients, approximately 160 sites will be opened globally for patient recruitment.

5.2 Definitions

Subjects officially enter the Screening Period after providing informed consent, either directly or via a legally authorized representative, where permissible.

Subjects who withdraw from the study after signing the ICF and before the randomization will be considered screen failures. Subjects who failed the original screening may be screened again using their original subject number as assigned by interactive web response system (IWRS). A subject may only be re-screened once. Randomization will occur centrally using IWRS. Subjects will be assigned randomly in a 2:1 ratio to receive fruquintinib + BSC or placebo + BSC using centrally randomized blocks stratified according to stratification factors.

A randomized subject is one who has been deemed eligible and has been assigned to a treatment group by Interactive Response Technology /IWRS.

5.3 Inclusion Criteria

Subjects may be enrolled in this study only if they satisfy all the following criteria:

1. Provide written informed consent;
2. Age ≥18 years;
3. Histologically and/or cytologically documented metastatic colorectal adenocarcinoma. RAS, BRAF, and microsatellite instability (MSI)/mismatch repair (MMR) status for each subject must be documented, according to country level guidelines;
4. Subjects must have progressed on or been intolerant to treatment with either trifluridine/tipiracil (TAS-102) or regorafenib. 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 (eg, bevacizumab, aflibercept, ramucirumab). [*Please note that regorafenib is NOT an anti-VEGF biologic*], **and**,
    - if RAS wild-type, an anti-EGFR therapy (eg, cetuximab, panitumumab);
    -
5. Subjects with microsatellite-high (MSI-H) or mismatch repair deficient (dMMR) tumors must have been treated with immune checkpoint inhibitors if approved and available in the subject's country unless the subject is ineligible for treatment with a checkpoint inhibitor;

6. Subjects who received oxaliplatin in the adjuvant setting and developed metastatic disease during or within 6 months of completing adjuvant therapy are considered eligible without receiving oxaliplatin in the metastatic setting. Subjects who developed metastatic disease more than 6 months after completion of oxaliplatin-containing adjuvant treatment must be treated with oxaliplatin-based therapy in the metastatic setting to be eligible;
7. Body weight ≥40kg;
8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1;
9. Have measurable disease according to RECIST Version1.1 (RECIST v1.1), assessed locally. Tumors that were treated with radiotherapy are not measurable per RECIST v1.1, unless there has been documented progression of those lesions;
10. Expected survival >12 weeks;
11. For female subjects of childbearing potential and male subjects with partners of childbearing potential, agreement to use a highly effective form(s) of contraception, that results in a low failure rate (<1% per year) when used consistently and correctly, starting during the screening period, continuing throughout the entire study period, and for 90 days after taking the last dose of study drug. Such methods include: oral hormonal contraception (combined estrogen/ progestogen, or progestogen-only) associated with inhibition of ovulation, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal ligation, vasectomized partner, or true sexual abstinence in line with the preferred and usual lifestyle of the subject. Highly effective contraception should always be combined with an additional barrier method (eg, diaphragm, with a spermicide). The same criteria are applicable to male subjects involved in this clinical trial if they have a partner of childbirth potential, and male subjects must always use a condom;
12. Subjects with BRAF-mutant tumors must have been treated with a BRAF inhibitor if approved and available in the subject's country unless the subject is ineligible for treatment with a BRAF inhibitor.

5.4 Exclusion Criteria

Subjects are not eligible for enrollment into this study if they have any of the following criteria:

1. Absolute neutrophil count (ANC) $<1.5\times10^9$/L, platelet count $<100 \times 10^9$/L, or hemoglobin <9.0 g/dL. Blood transfusion within 1 week prior to enrollment for the purpose of increasing the likelihood of eligibility is not allowed;
2. Serum total bilirubin >1.5 × the upper limit of normal (ULN). Subjects with previously documented Gilbert syndrome and bilirubin <2 X ULNare eligible;
3. ALT or AST >2.5 × ULN in subjects without hepatic metastases; ALT or AST >5 × ULN in subjects with hepatic metastases;
4. 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;

5. Urine dipstick or urinalysis with protein ≥2+ or 24-hour urine protein ≥1.0 g/24-h. Subjects with 1+ proteinuria must undergo a 24-hour urine collection to assess urine protein level. For conversions between quantitative and qualitative results, please see Appendix 9;
6. Uncontrolled hypertension, defined as: systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mm Hg despite optimal medical management. The subject must have blood pressures below both limits. Repeated assessments are permitted;
7. International Normalized Ratio (INR) >1.5 x ULN or activated partial thromboplastin time (aPTT) >1.5 × ULN, unless the subject is currently receiving or intended to receive anticoagulants for prophylactic purposes;
8. History of, or active gastric/duodenal ulcer or ulcerative colitis, active hemorrhage of an unresected gastrointestinal tumor, history of perforation or fistulas; or any other condition that could, in the investigator's judgment, result in gastrointestinal hemorrhage or perforation; within the 6 months prior to screening;
9. History or presence of hemorrhage from any other site (eg, hemoptysis or hematemesis) within 2 months prior to screening;
10. History of a thromboembolic event, including deep vein thrombosis (DVT), pulmonary embolism (PE), or arterial embolism within 6 months prior to screening;
11. Stroke and/or transient ischemic attack within 12 months prior to screening;
12. Clinically significant cardiovascular disease, including but not limited to acute myocardial infarction or coronary artery bypass surgery within 6 months prior to enrollment, 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;
13. Corrected QT interval using the Fridericia method (QTcF) >480 msec or any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as hypokalemia, congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in a first-degree relative;
14. Concomitant medications with a known risk of causing QT prolongation and/or torsades de pointes (Source list is continuously updated online at www.crediblemeds.org);
15. Systemic anti-neoplastic therapies (except for those described in Exclusion Criterion 18) or any investigational therapy within 4 weeks prior to the first dose of study drug, including chemotherapy, radical radiotherapy, hormonotherapy, biotherapy and immunotherapy;
16. Systemic small molecule targeted therapies (eg, tyrosine kinase inhibitors) within 5 half-lives or 4 weeks (whichever is shorter) prior to the first dose of study drug;
17. Palliative radiotherapy for bone metastasis/lesion within 2 weeks prior to the initiation of study drug;
18. Brachytherapy (ie, implantation of radioactive seeds) within 60 days prior to the first dose of study drug;

19. Use of strong inducers or inhibitors of CYP3A4 within 2 weeks (or 5 half-lives, whichever is longer) before the first dose of study drug (see Appendix 4 for a list of applicable drugs);
20. Surgery or invasive procedure (ie, a procedure that includes a biopsy; central venous catheter placement is allowed) within 60 days prior to the first dose of study drug or unhealed surgical incision;
21. Any unresolved toxicities from a previous antitumor treatment greater than National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE) v5.0 grade 1 (except for alopecia or neurotoxicity grade≤2);
22. Known human immunodeficiency virus (HIV) infection;
23. Known history of active viral hepatitis. For subjects with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated. Subjects with HCV infection who are currently on treatment are eligible if they have an undetectable HCV viral load;
24. Clinically uncontrolled active infection requiring IV antibiotics;
25. Tumor invasion of a large vascular structure (eg, pulmonary artery, superior or inferior vena cava);
26. Women who are pregnant or lactating;
27. Brain metastases and/or spinal cord compression untreated with surgery and/or radiotherapy, and without clinical imaging evidence of stable disease for 14 days or longer; subjects requiring steroids within 4 weeks prior to start of study treatment are excluded;
28. Other malignancy, except for non-melanoma skin cancer, in situ cervical ca or bladder ca (Tis and T1) that have been adequately treated during the 5 years prior to screening;
29. Inability to take medication orally, dysphagia or an active gastric ulcer resulting from previous surgery (eg, gastric bypass) or a severe gastrointestinal disease, or any other condition that investigators believe may affect absorption of the investigational product;
30. Other disease, metabolic disorder, physical examination anomaly, abnormal laboratory result, or any other condition (eg, current alcohol or drug abuse) that investigators suspect may prohibit use of the investigational product, affect interpretation of study results, or put the subject at undue risk of harm based on the investigator's assessment;
31. Known hypersensitivity to fruquintinib or any of its (or placebo) inactive ingredients including the azo dyes Tartrazine - FD&C Yellow 5 and Sunset yellow FCF - FD&C Yellow 6;
32. Subjects who have received prior fruquintinib;
33. Live vaccine ≤28 days before the first dose of study drug(s).
    Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed.

6 STUDY CONDUCT

6.1 Study Procedures

6.1.1 Study Assessments

The following procedures will be performed according to the schedule in Table 1. All assessments must occur within ± 3 days (±1 day during cycle 1) from the scheduled date, unless otherwise noted.

6.1.1.1 Informed Consent

All subjects must sign the informed consent form (ICF) prior to any study-related examinations or protocol procedures. Tumor assessments completed as standard of care prior to signing the informed consent, but within 28 days of first dose of study treatment, may be used as baseline scans.

All subjects who sign ICF are to be entered into the IWRS system. The system will generate a subject identification number, which will be assigned to the subject.

6.1.1.2 Medical History

A complete medical history, including the subject's medical history, disease history and prior therapies for disease prior to signing of the ICF, should be recorded at screening. Comorbidities that began prior to signing the ICF should be recorded and followed as medical history.

6.1.1.3 Tumor Diagnosis and Treatment History

Tumor diagnosis should include the date of primary diagnosis of CRC and its type, disease stage, the date of first metastasis, type of previous treatment, start and end date/s, best overall response, date of PD, adverse reaction with severity ≥ grade 3. Prior use (yes/no) of trifluridine/tipiracil (Lonsurf®, TAS-102), regorafenib (Stivarga®), or both of these drugs, prior use of fluoropyrimidine-, oxaliplatin, and irinotecan-based chemotherapy must be documented. Prior use of a biological anti-VEGF therapy (yes versus no), prior RAS gene status (mutant versus wild type) and prior use of a biologic anti-EGFR therapy (yes versus no) must also be documented.

RAS, BRAF, and MSI)/MMR status for each subject must be documented, if available. If the RAS gene test was not performed previously, it should be performed during screening. Unless medically contraindicated or not available in the subject's country of residence, the following therapies should have been received based on tumor types in order to be considered eligible:

- Subjects with a RAS wild type tumor must have received an anti-EGFR therapy.
- Subjects with a BRAF-mutant tumor must have received a BRAF inhibitor.
- Subjects with a MSI/MMR deficient tumor must have received an immune checkpoint inhibitor.

The subject's history of radiation therapy, including the start and end date/s and the site of radiation must be recorded. Surgical history, including operations and less-invasive diagnostic or therapeutic procedures (such as GI endoscopy, biopsy, etc.), the start and end date/s, name of each procedure and operation site must also be recorded at screening and in the appropriate eCRF.

6.1.1.4 Demographics

Demographic characteristics, including year of birth, sex, ethnic group/race, and any relevant lifestyle habits should be recorded at screening and in the applicable eCRF (as permitted by local regulations).

6.1.1.5 Concomitant Medication and Procedures

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a subject. All concomitant medications within 28 days before randomization must be recorded in the eCRF, including the generic name of the drug and daily dose, the reason/s for using the medication, as well as the start and stop date/s of the medication. Concomitant medications should be reviewed during the study according to the schedule in Table 1.

6.1.1.6 Comprehensive Physical Examination

A comprehensive physical examination includes subject height, weight and general condition, as well as an examination of the head, heart, chest (including the lungs), abdomen, extremities, skin, lymph nodes, nervous system and additional areas/systems as clinically indicated.

6.1.1.7 Limited Physical Examination

Limited physical examination includes vital signs and any change from baseline, any new abnormalities, examination of the thorax, abdomen, and additional areas/systems as clinically indicated. In order to assess changes from baseline and to evaluate for new abnormalities, the limited physical examination should assess for new or changed skin lesions, enlarged lymph nodes, palpable masses, and appropriate examination to address any subject-reported symptoms.

6.1.1.8 Eastern Cooperative Oncology Group (ECOG) Performance Status

Subject performance status will be graded according to the ECOG PS scale at study visits as detailed in Table 1. It is recommended that ECOG PS scores be evaluated by the same investigator throughout the study. Details on the ECOG assessment and grading scale are available in Appendix 2.

6.1.1.9 Vital Signs

Vital signs include blood pressure, heart rate, respiration rate, temperature, and weight. For subjects with a baseline history of hypertension or hypertension that develops on study, blood pressure should be monitored per institutional standard practice.

6.1.1.10 Hematology

Hematology assessments include red blood cell count, hemoglobin, hematocrit, platelet count, white blood count with differential (absolute counts).

Note: If neutrophil count $\leq 1.0\times10^9$/L or platelet count$\leq 25\times10^9$/L, hematology assessments should be conducted per institutional standard practice.

6.1.1.11 Blood Chemistry

The blood chemistry panel includes sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, magnesium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase (ALP), lactate dehydrogenase, non-fasting total cholesterol, triglycerides, uric acid, total protein, and albumin.

Blood chemistry tests for subjects with ALT or AST increase by >3x ULN, or increase by >2x baseline value should performed per institutional standard practice.

Creatinine clearance (CrCl) rate (units, mL/min) should be calculated using the baseline serum creatinine (Scr) value according to the Cockroft-Gault formula (Appendix 10).

6.1.1.12 Blood Amylase and Lipase

Tests for blood amylase and lipase will be performed during the study according to the schedule of events in Table 1.

6.1.1.13 Coagulation

Coagulation tests include prothrombin time (PTT), international normalized ratio (INR), and activated partial thromboplastin time (APTT).

6.1.1.14 Thyroid Function

Thyroid function tests include serum free triiodothyronine (fT3), serum free thyroxine (fT4) and thyroid stimulating hormone (TSH).

6.1.1.15 Urinalysis

Urinalysis parameters include urine pH, protein, glucose, and blood; microscopic for white blood cell and red blood cell count. A 24-hour urine for quantitative protein must be collected from all subjects with 1+ proteinuria during screening. If urine protein ≥2+ during the period of study treatment, a 24-hour urine protein should be collected within 1 week. For conversions between quantitative and qualitative results, please see Appendix 9.

6.1.1.16 Pregnancy Test

All female subjects of childbearing potential must complete a blood pregnancy test at screening and within 30 days at the Safety Follow Up Visit, and a urine pregnancy test on day 1 of every cycle starting at cycle 2. Serum pregnancy test should be repeated for women with suspected pregnancy or an equivocal urine pregnancy test. This is not applicable for postmenopausal female subjects (ie, no menses for 12 months without an alternative medical cause), and the date of menopause should be recorded instead. Pregnancy testing and contraception are not required for women with documented permanent sterilization (eg, hysterectomy, bilateral salpingectomy and bilateral oophorectomy, or tubal ligation).

6.1.1.17 Electrocardiograms Monitoring

Single 12-lead ECG will be collected in all subjects using standardized equipment, as described in Table 1 and Table 3 during cycles 1 to 3. Any ECGs from standard equipment will be evaluated

for safety by the principal investigator. All ECGs for the purposes of screening will be performed using standard, local equipment.

In addition, continuous 12-lead Holter monitor will be used for QTc evaluation during cycle 1 in a subset of subjects and will be sent for central reading (see below in Continuous 12-Lead Holter Monitor for QTc Evaluation for details). From cycle 4 onward, ECG will only be performed as clinically indicated. Vital signs will be measured, a symptom-directed physical exam will be conducted, and safety related blood samples will be collected as per the time points in Table 1. These assessments should be completed before the start of any ECG recordings.

Continuous 12-Lead Holter Monitor for QTc Evaluation

As described in Section 4.1.2.3, continuous ECG recordings using 12-lead Holter monitoring was planned to be collected from the first approximately 120 subjects (80 fruquintinib, 40 placebo) enrolled in the study to evaluate the effects of fruquintinib on ventricular repolarization. However, the COVID-19 pandemic caused significant delays in laboratory kit production and delivery from the central vendor starting in October 2020. In order to allow sites to screen and treat subjects without delay, a US and Europe Addendum to 2019-013-GLOB1, version 1, was issued on 13 November 2020 to pause collection of blood for PK sampling and ctDNA and Holter monitoring for QTc evaluations. Due to continued supply chain issues in January 2021, version 2 of the addendum was issued on 22 January 2021 to extend the hold on blood sample collection and Holter monitoring to 01 April 2021. Blood sample collection for PK sampling and ctDNA and Holter monitor collection was resumed in 2019-013-GLOB1 Amendment 3. Continuous ECG recordings using 12-lead Holter monitoring will be collected from approximately 120 evaluable subjects (80 fruquintinib, 40 placebo) enrolled in the study to evaluate the effects of fruquintinib on ventricular repolarization. The assessments will be conducted at pre-dose and post-dose on cycle 1 day 1 and cycle 1 day 21 at specific time points summarized in Table 2.

Any subject with a pacemaker will not be a candidate for Holter monitor evaluation according to Table 2. If a subject has a pacemaker, please contact the Sponsor for consideration of ECG and PK assessments according to the schedule in Table 3.

Subjects should reside in a quiet setting without distractions (eg, television, cell phones, and staff talking) at each scheduled time point for ECG measurements. Subjects should rest in a supine position for at least 10 minutes before and 5 minutes after the scheduled time point and should refrain from talking or moving arms or legs. Skin preparation should be optimal to obtain high quality ECGs; if deemed appropriate, the chest should be shaved and prepared with light abrasion.

Continuous digital 12-lead Holter ECGs will be recorded as described in the ECG/Holter manual. Good quality 12-lead ECG selection and extraction will occur during a 10-minute timeframe starting 5 minutes before and ending 5 minutes after the scheduled ECG time point. All Holter recorder devices (as supplied by the central ECG laboratory) will be of the same brand and model with the same software, and would have been recently serviced and calibrated. Documentation describing the brand, type, software, and service/calibration history of Holter recorders will be provided by the central ECG laboratory and archived at the site as well as in the sponsor's study file. Transfer of the Holter recordings and extraction of the ECG tracings will be performed as described in the ECG/Holter manual.

Ten-second digital ECG tracings will be extracted from the Holter device in triplicate by the central ECG laboratory according to the following principles:

- The actual time of dosing will be communicated to the central ECG laboratory on the Holter acquisition form completed by the site.
- Using visual inspection or automated tools as appropriate, the central ECG laboratory will identify a period of stable heart rate on the continuous Holter tracing within ±5 minutes of the nominal ECG time point (determined relative to the actual dosing time for an individual subject). Three 10-second ECGs will be extracted in close succession from this identified segment.
- The scheduled time points for triplicate ECG extraction are summarized in Table 2.

Unless warranted by a specific safety endpoint of the study, the Holter tracings will not be routinely analyzed for rhythm and conduction abnormalities. These analyses will only be performed on individual subject's Holter if warranted by TEAEs (eg, syncope).

6.1.1.18 Echocardiogram

An echocardiogram should be done at Screening, cycle 2 day 1, and on day 1, every 3 cycles thereafter. Assessment parameters include left ventricular ejection fraction and general assessment of cardiac function. MUGAs are permitted if echocardiograms cannot be performed.

Echocardiograms completed as standard of care prior to signing the informed consent, but within 28 days of first dose of study treatment, may be used as baseline assessment.

6.1.1.19 Tumor Evaluation/Imaging

Tumor assessments (local) will be performed at study visits specified in Table 1.

All measurable and evaluable lesions should be assessed and documented using image-based evaluation. All subjects are to be evaluated utilizing contrast-enhanced computed tomography (CT) scan of the chest, abdomen, and pelvis, or other acceptable cross-sectional imaging per RECIST v1.1. Evaluations should include other areas of the body, as clinically indicated. Disease status will be assessed by the investigator or designated site staff using RECIST v1.1. The same imaging procedure used to define measurable lesions at baseline must be used throughout the study for each subject, unless medically contra-indicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

Tumor assessments completed as standard of care prior to signing the informed consent, but within 28 days of first dose of study treatment, may be used as baseline scans.

Imaging for all subjects will also be collected for central storage. Please refer to the study-specific central imaging manual for collection and shipping instructions.

6.1.1.20 Tumor Markers

Assessment of serum carcino-embryonic antigen (CEA) levels will be performed according to the schedule in Table 1. The dates of blood sampling must be recorded in the eCRF.

6.1.1.21 Circulating Tumor DNA

Blood samples for circulating Tumor DNA will no longer be collected as of Protocol Amendment 4 due to continued shortage of collection tubes. All previously collected samples will be analyzed according to the statistical analysis plan (SAP).

6.1.1.22 Subject Randomization

On day -2 to day 1, after verifying the subject's eligibility, the site will log into the IWRS and the subject will be randomized by the system. The system will generate a serial number matching a bottle of investigational product in the site's inventory. The site will take investigational product with the serial number assigned by IWRS from inventory and dispense it to the subject. The first dose should be administered on cycle 1 day 1.

6.1.1.23 Quality of Life Assessment

A quality of life assessment, using QLQ-C30: cancer-specific; and EQ-5D-5L: general, must be performed during the screening visit as well as day 1 of each cycle until treatment is discontinued.

6.1.2 Pharmacokinetics Evaluations

6.1.2.1 Sample Collection and Handling

Samples for PK analysis will be collected in all subjects according to the schedule in Table 2 and Table 3. The actual dates and times of PK sampling should be recorded in appropriate eCRF. In addition, the dates and times of the dose administered on the day of PK collection and one day before PK collection must be recorded in the eCRF.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided to the sites. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

6.1.2.2 Analytical Procedures

Plasma samples will be analyzed to determine concentrations of fruquintinib and its active metabolite M11 using a validated, specific, and sensitive Liquid Chromatography-Tandem Mass Spectrometry (LC MS/MS) method.

If required, then plasma samples may be analyzed to document the presence of circulating metabolites using a qualified research method.

6.1.3 End of Treatment Visit

Subjects who have completed the study or have discontinued study treatment will be asked to return to the investigational site to receive safety examinations and assessments within 7 (±3) days after the last dose of study drug.

6.1.4 Safety Follow-Up Visit

All subjects who have completed an End of Treatment Visit will have a Safety Follow-Up Visit. The Safety Follow-Up Visit will be conducted at 30 (±7) days from the EOT Visit.

6.1.5 Efficacy Follow-Up

Any subject who discontinues study treatment for any reason other than disease progression should be followed until progression is documented or until a new anti-cancer treatment is initiated for PFS assessment and until death for OS assessment.

6.1.6 Survival Follow-Up

Every 12 weeks (±2 weeks) after the End of Treatment Visit the investigator or their designee should call the subject to collect information related to survival status and their use of other anti-cancer treatments, including drug name, dosage, treatment start and end dates, and efficacy. Information related to radiotherapy received after disease progression is also needed, including radiotherapy location, radiation dose, start date, and end date.

6.1.7 Long-term Extension

Subjects who are still on study treatment at the time of study completion may continue to receive study treatment if they are experiencing clinical benefit and no undue risks.

Continued access will apply to this study only if at least 1subject is still on study treatment when study completion occurs. The sponsor will notify investigators when the continued access period begins.

6.2 Discontinuation or Withdrawal

6.2.1 Permanent Discontinuation of Treatment

The investigator has the right to discontinue a subject from the study for any medical condition that the investigator determines is in the best interest of the subject, reasons of non-compliance (eg, missed doses, visits), or pregnancy.

Any subject who discontinues treatment should be encouraged to return to the study site for an End of Treatment Visit and continue with the remaining study visits outlined in Table 1. The primary reason for discontinuation must be recorded on the appropriate eCRF.

Subjects could be discontinued from treatment for any of the following reasons:

1. Disease progression (according to RECIST v1.1). If the subject is experiencing a treatment benefit, in the opinion of the investigator, the subject may continue study treatment beyond radiographic progression until clinical progression. Determination of clinical progression is at the discretion of the investigator and may include both objective and subjective data. The continuation decision should be made by the investigator in consultation with the sponsor;
2. Withdrawal of consent;
3. Intolerable toxicity or AEs that warrant withdrawal of study treatment as determined by the principal investigator;
4. Poor subject compliance;
5. Use of other antitumor treatment during the study;
6. Pregnancy;
7. Subject is lost to follow-up;
8. The investigator or sponsor determines it is in the best interest of the subject;
9. Study is terminated by the sponsor;
10. Death;
11. End of this study.

6.2.2 Withdrawal from Study

All study participants have the right to withdraw from the study at any time. During the treatment period and follow-up period, a subject who withdraws consent to continue participation in the study will not be followed for any reason after consent has been withdrawn. Every effort should be made to obtain information on subjects who discontinue study treatment but who do not withdraw consent to continue participation in the study. If a participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

6.2.3 Replacement of Subjects

Subjects will not be replaced in this study.

6.2.4 Subjects Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

Should the participant continue to be unreachable, he/she will be considered to be withdrawn from the study.

6.3 Study Termination

The sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

6.4 End of Study

The end of the study defined as the last visit of the last subject in the study.

7 STUDY DRUGS

7.1 Study Drug Administration

Fruquintinib (at a dose of 5 mg) or matching placebo will be administered PO, QD, on a 3 weeks on, 1 week off schedule. One treatment cycle is 4 weeks. The administration time should be recorded accurately. Study drug may be given either in the fasting state or after meals, around the same time each day. If dose adjustment is required, 1 mg fruquintinib or matching placebo capsules will be used.

On days with PK collection, treatment should be administered at the site by a delegated study staff member.

If vomiting occurs after dosing, study drug doses should not be replaced. If a dose is missed, the missed dose can be taken within a 12-hour window of time the subject typically takes the dose. A double dose should not be administered to make up for missed individual doses.

7.2 Description of Products

Fruquintinib will be provided as 1 mg or 5 mg capsules for oral administration. Matching placebo capsules for each strength will also be provided.

7.2.1 Formulation, Storage, Preparation and Handling

The investigational drugs are formulated as capsules, which are packaged in labeled bottles. The drug information is provided in Table 5. Additional information is available in the pharmacy manual.

Table 5 Information on Investigational Products

Name	Dosage Form	Specification	Administration Method
Fruquintinib	Capsule	5 mg	Oral
Fruquintinib	Capsule	1 mg	Oral
Matching placebo*	Capsule	5 mg	Oral
Matching placebo *	Capsule	1 mg	Oral

* The appearance of the matching placebo is identical to that of the study drug.

All the investigational drugs should be sealed and stored in a secure, limited access area under appropriate conditions. The storage temperature should be between 10℃ to 30℃. Investigational drugs should not be used beyond expiration date provided by the manufacturer.

The temperature-monitoring log should be recorded and filed in the study binder.

7.2.2 Drug Accountability

7.2.2.1 Assignment/Disposal (Study Site)

All study drug required for this study will be provided by Hutchison MediPharma Limited. The recipient will acknowledge receipt of the drug by returning the appropriate documentation form indicating shipment content and condition. Damaged supplies will be replaced.

Accurate records of all study drug received at, dispensed from, returned to and disposed of by the study site should be recorded by using the Drug Inventory Log.

Study drug will be disposed of at the study site according to the study site's institutional standard operating procedure or returned to Hutchison MediPharma Limited or a Hutchison identified entity with appropriate documentation, as determined by the study site. If the study site chooses to destroy study drug, the method of destruction must be documented.

7.2.2.2 Drug Return (Subject)

On day -2 to day 1, only subject randomization and drug assignment will be performed. Subjects will be provided with a pill diary at randomization and be instructed on how to account for each day's dose appropriately. Subjects should return all unused study drug and containers from the previous cycle on day 1 (date of scheduled visits) of each subsequent cycle, and new study drug will be dispensed on the same day. Site study staff should review subjects pill diary and provide a new diary if necessary at the day 1 visit of each cycle.

If a dose adjustment is required (eg, decrease from 5 mg QD to 4 mg QD), the subject must return to the investigational site and return all unused study drug. The site must log into the IWRS, adjust the dose, reassign the drug serial number, and dispense new study drug dose (in 1 mg capsules) to the subject. If the dose is adjusted a second time, ie, from 4 mg QD to 3 mg QD, the site must log into the IWRS and record the second dose adjustment. On this occasion, it is not necessary to reassign a new drug serial number. If tumor evaluation shows PD during the previous cycle and new drug has been dispensed, the subject must return all unused study drug on the 30-day safety visit after EOT.

7.3 Treatment Assignment and Bias Minimization

7.3.1 Treatment Allocation

Treatment will be allocated using IWRS randomization strategy and procedure (refer to the IWRS manual). After screening, subjects who meet the eligibility criteria will be randomized into the fruquintinib or placebo group in a 2:1 ratio. Randomization will be stratified by:

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

7.3.2 Extent and Maintenance of Blinding

The study subject, investigators, and study site personnel will remain blinded to all randomization assignments throughout the study except for the specific circumstances described in Section 7.3.3. The sponsor's study director, study monitor, and any other sponsor and contract research organization (CRO) personnel who are in regular contact with the study site will remain blinded to all subject randomization assignments, except sponsor pharmacovigilance personnel for the purpose of IND safety reports.

7.3.3 Unblinding Procedures

7.3.3.1 Emergency Unblinding

Unblinding of the study treatment can occur in emergency cases and should not occur unless it is needed to manage a subject's medical condition.

- In an emergency, when specific knowledge of the subject's treatment assignment is needed to manage a subject's medical condition, the Investigator can unblind the subject using the IWRS to obtain the subject's treatment assignment. It is recommended that the Investigator then inform the Sponsor's Medical Monitor of the case.
- In a non-emergent situation, the Investigator is encouraged to contact the Sponsor's Medical Monitor to discuss the case prior to unblinding.

Once unblinded, the subject should discontinue the treatment but will continue to be followed for safety and efficacy. The investigator should record the event in the source document.

7.4 Assessment and Verification of Compliance

The investigator is responsible for ensuring the subject's treatment compliance. The sponsor will provide supervision through on-site monitoring visits made by its representatives. The investigators should maintain complete and accurate records of drug use. The dosing regimen and subject's actual dosing should be recorded in the original treatment records as well as the eCRF. At each treatment visit, the investigators or study staff should comprehensively assess the subject's treatment compliance according to the drug dispensing and return status at each visit and the actual dosing conditions, such as missed doses and overdosing reported by the subject. The subjects must return all drug bottles and remaining capsules at the end of the study. The investigational sites must return all remaining supplies and drugs to the sponsor or provide evidence of destruction at the conclusion of the study.

7.5 Prior and Concomitant Therapies

7.5.1 Prohibited Therapies

Any therapy intended for the treatment of cancer (with the exceptions as noted in Section 7.5.2), whether currently marketed or experimental, is prohibited. This includes, but is not limited to, the following: chemotherapy, hormonal therapy, biologic therapy, radiotherapy, or herbal therapy.

Concomitant use of medications that have a known risk of causing QT prolongation and/or torsades de pointes (see "combined" list at http://www.crediblemeds.org, with attention to those drugs listed as KR ("known risk") are prohibited.

Live vaccines are prohibited during the study and for 3 months after the last dose of study drug(s). Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed.

7.5.2 Permitted Therapies

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a subject. All concomitant therapy within 28 days prior to randomization and to the Safety Follow Up visitshould be reported to the investigator and recorded on the appropriate eCRF.

Subjects who use oral contraceptives, hormone-replacement therapy, or other allowed maintenance therapy may continue their use if indicated.

Prophylactic use of anticoagulation for the maintenance of patency of permanent indwelling central venous access devices or for subjects at high risk of venous thromboembolism is permitted during study treatment. If subjects are receiving anti-coagulation, they should be very closely monitored for potential hemorrhage.

Please see Appendix 7 for additional information on the clinical management of severe or serious hemorrhagic AEs.

Subjects that develop arterial thromboembolic events should discontinue the study drug. If a subject suffers a venous thromboembolic event while still receiving study drug, it may still be possible for him or her to remain on study treatment under close monitoring and dose modification of study drug.

Prophylactic antiemetic, granulocyte colony stimulating factors, granulocyte macrophage colony-stimulating factors, platelet simulating factors or erythropoietin are permitted as clinically indicated.

Palliative radiation for symptom control is allowed provided it does not compromise tumor assessments of target lesions. However, study treatment should be suspended during the radiation period and not resumed until at least 7 days after radiation only after meeting the following criteria:

- Radiation related toxicities resolves to grade ≤2;
- No disease progression observed.

All supportive measures consistent with optimal subject care will be given throughout the study.

7.5.3 Drug-Drug Interactions (Therapies to Avoid or Use with Special Caution)

In vitro metabolism data indicate that CYP3A plays an important role in the metabolism of fruquintinib. The potential effects of medications that can affect the PK of fruquintinib via the CYP3A pathway have not been tested in the clinic. Therefore, medications that are strong inhibitor or strong inducer of CYP3A should not be administered concomitantly with fruquintinib. Examples of these medications to avoid are listed in Appendix 4.

In vitro, fruquintinib is shown to have the potential to inhibit P-gp and BCRP (see Section 2.2.2.2). Avoid concomitant use with medications that are sensitive substrates of P-gp or BCRP where possible. If used together, monitor subjects more frequently for adverse reactions, and consider dose reduction of the P-gp or BCRP substrate medication. Examples of the medications that are sensitive substrates of P-gp and BCRP are listed in Appendix 4.

7.5.4 Rescue Therapies

Not applicable.

7.5.5 General Dose Adjustment Note

The severity of AEs will be graded according to the NCI CTCAE v5.0. Reasons for dose modifications or delays, the supportive measures taken, and the outcome should be documented in the subject's chart and recorded in the eCRF.

- For any concomitant conditions already apparent at baseline, the dose modifications will apply according to the corresponding shift in toxicity grade, if the investigator feels it is appropriate. For example, if a subject has grade 1 asthenia at baseline that increases to grade 2 during treatment, this will be considered a shift of one grade and treated as grade 1 toxicity for dose-modification purposes.
- For toxicities that are considered by the investigator to be unlikely to develop into serious or life-threatening events, treatment can be continued at the same dose.
- To recover from acute toxicity, unless otherwise indicated, the treatment can be delayed for up to 14 days. If a treatment delay longer than 14 days is required, treatment should be discontinued. Continuation/resumption of fruquintinib treatment after an interruption of more than 14 days must be discussed with the medical monitor or his or her designee.
- Where several toxicities with different grades or severity occur at the same time, the dose modifications should be according to the highest grade observed.

7.5.6 Dose Modification Guidance

7.5.6.1 Dose Modification Sequence by Starting Dose and for General Hematologic and Non-Hematologic Toxicity

The dose reduction sequence by starting dose is shown in Table 6. Subjects are allowed to have no more than 2 dose reductions: one reduction from 5 mg QD to 4 mg QD, and if not tolerated, then a second reduction from 4 mg QD to 3 mg QD (see Table 6). Once a dose has been reduced, it cannot be re-escalated.

Table 6 Dose Modification Sequence by Starting Dose

Dose Level 0* (Original dose)	5 mg QD 3 weeks on, 1 week off	Fruquintinib of 5 mg, 1 capsule, or 1 capsule of the matching placebo
Dose Level -1* (the 1st dose reduction)	4 mg QD 3 weeks on, 1 week off	Fruquintinib of 1 mg, 4 capsules, or 4 capsules of the matching placebo
Dose Level -2* (the 2nd dose reduction)	3 mg QD 3 weeks on, 1 week off	Fruquintinib of 1 mg, 3 capsules, or 3 capsules of the matching placebo

* Doses are daily, on days 1-21 each 28-day cycle (3 weeks on, 1 week off)
QD = once daily

Dose reduction guidelines for hematologic and non-hematologic toxicities, other than Palmar-plantar erythrodysesthesia (PPE), Proteinuria, Hypertension, Decreased platelet count, Hemorrhage, and liver function impairment, are shown in are shown in Table 7. Treatment should be held until AE/toxicity resolves or improves to ≤ grade 1. If a subject has a grade 3 toxicity that is expected to be manageable and reversible with a dose reduction, treatment should be held until toxicity resolves to ≤grade 1. Subjects with grade 3 non-hematologic toxicity not described below that does not resolve to ≤grade 1 within 14 days should permanently discontinue the study drug unless approval to continue is obtained in writing from the sponsor.

Table 7 Dose Modifications for Hematologic and Non-Hematologic Toxicity

NCI CTCAE v5.0 Toxicity Grading	Action
Grade 1 or 2[a]	None
Grade 3[b]	Interrupt the dose until the toxicity resolved to ≤grade 1 or baseline level within 14 days, then reduce the dose to a lower dose level
Grade 4	Discontinue treatment permanently

a. If amylase and/or lipase are elevated, and if clinically indicated, further evaluation for pancreatitis should be performed.
b. Including grade 3 diarrhea and stomatitis, etc. that are ineffectively treated by drug therapies, but excluding grade 3 menstrual cycle extension.

7.5.6.2 Dose Modifications for Important Identified Risks and Potential Risks

This section provides details of the recommended dose modifications for the currently identified and potential risks that have been determined in both clinical and nonclinical studies. The dose modification and treatment suggestions for both potential risks and specific important identified risks are provided in Table 8 (potential risks) Table 9(dermatological toxicity), Table 10 (proteinuria), Table 11 (hypertension), Table 12 (decreased platelet count), Table 13 (hemorrhage at any site), and Table 14 (abnormal liver function).

Table 8 Dose Modification for Potential Risks

AE	Dose Adjustment
Gastrointestinal perforation	Study drug should be discontinued.
Arterial Thrombosis[a]	Study drug should be discontinued.
Reversible Posterior Leukoencephalopathy Syndrome (RPLS)[b]	If suspected as RPLS, the study drug should be discontinued.
Delayed Wound Healing	The general guidance for dose interruptions/reductions/discontinuations in response to AEs should be followed.

RPLS = Reversible Posterior Leukoencephalopathy Syndrome.

a. The event term of arterial thrombosis encompasses the preferred terms (PT) of Aortic thrombosis, Cerebrovascular insufficiency, Embolism arterial, Peripheral embolism, Retinal artery occlusion, Subclavian artery thrombosis, and Transient ischemic attack.
b. The signs and symptoms of RPLS include seizure, headache, altered mental status, visual impairment or cortical blindness with or without hypertension. The diagnosis of RPLS must be verified using brain magnetic resonance imaging (MRI).

Table 9 Dose Modifications for Dermatological Toxicity

AE Grading Standard	Dose Adjustment	Treatment Suggestions
Grade 1	None.	Active supportive treatment can be adopted to relieve the symptoms; for example, moisturizing skin cream, lotion, or hydrophilic urea ointment can be used.
Grade 2	• Hold treatment. • If the AE recovers to grade 1 or baseline level within 14 days, resume treatment at the same dose level.	Active supportive treatment can be adopted to relieve the symptoms; for example, moisturizing skin cream, lotion, or hydrophilic urea ointment can be used.
Grade 3	• Hold treatment. • If the AE recovers to grade 1 or baseline level within 14 days, resume treatment with a dose reduction to the next lower dose level.	Active supportive treatment can be adopted to relieve the symptoms; Should the same AE occur for 3 times or still occurs after 2 times of dose reduction, the drug should be terminated.
Grade 4	• Permanently discontinue study treatment.	Emergent medical treatment.

AE = adverse event

Table 10 Dose Modifications for Proteinuria[a]

AE Grading Standard	Dose Adjustment	Treatment Suggestions
Grade 1: Proteinuria 1+ by urinalysis; 24-hour urine protein quantitation <1.0 g	None	Follow up at scheduled study visits.
Grade 2: Proteinuria 2+ by urinalysis; 24-hour urine protein quantitation is between 1.0 to <2.0 g	None	Provide supportive treatment and increase the frequency of urine monitor to once a week; consult nephrologist if necessary.
Grade 2: Proteinuria 2+ or above by urinalysis; 24-hour urine protein quantitation is between 2.0 to <3.5 g (excluding 3.5 g)	• Hold treatment. • If the AE recovers to grade 1 or baseline level within 14 days, resume treatment with a dose reduction to the next lower dose level.	Provide supportive treatment and increase the frequency of urine monitor to once a week; consult nephrologist if necessary.
Grade 3: 24-hour urine protein quantitation ≥3.5 g	• Hold treatment. • If the AE recovers to grade 1 or baseline level within 14 days, resume treatment with a dose	Provide supportive treatment and increase the frequency of urine monitor to once or twice a week; consult nephrologist if necessary. Should the same AE occur for 3 times or still occurs after 2 times of dose reduction, the drug should be terminated.

Table 10 Dose Modifications for Proteinuria[a]

AE Grading Standard	Dose Adjustment	Treatment Suggestions
	reduction to the next lower dose level.	

AE = adverse event.

a: If protein ≥ 2+ on urinalysis during the study, a 24-hour urine test should be conducted within 1 week, and dose modification will be done by the result of 24-hour urine protein quantitation.

Table 11 Dose Modifications for Hypertension

AE Grading	Dose adjustment	Treatment Suggestions
Grade 1	None.	Follow up as planned schedule
Grade 2:	None.	Treatment objective: lower the blood pressure to <140/90 mm Hg (or <130/80 mm Hg in subjects with chronic renal disease and/or diabetes). Refer to Appendix 8.
Grade 3:	• If BP >160/100mmHg lasts for >7 days after initiation of anti-hypertensive treatment or modification of current anti-hypertensive treatment, treatment should be held. • If hypertension resolves to grade 1 or baseline level within 14 days, resume treatment with a dose reduction to the next lower dose level.	Treatment objective: lower the blood pressure to <140/90 mmHg (or <130/80 mm Hg in subject with chronic renal disease and/or diabetes). Refer to Appendix 8.
Grade 4:	Permanently discontinue study treatment.	Emergent medical treatment.

BP = Blood pressure

Table 12 Dose Modifications for Decreased Platelet Count

AE Grading	Dose Adjustment	Treatment Suggestions
Grade 1:	None.	Perform follow up visit as scheduled.
Grade 2:	• Hold treatment. • If the AE recovers to grade 1 or baseline level within 7 days, resume treatment at the same dose level.	Hematology test should be monitored every 2-3 days; active treatment for platelet elevation is recommended.
	• Hold treatment. • If the AE recovers to grade 1 or baseline level within 14 days, resume treatment with a dose	Hematology test should be monitored every 2-3 days; active treatment for platelet elevation is recommended.

Table 12 Dose Modifications for Decreased Platelet Count

AE Grading	Dose Adjustment	Treatment Suggestions
	reduction to the next lower dose level.	
Grade 3:	• Hold treatment. • If the AE recovers to grade 1 or baseline level within 14 days, resume treatment with a dose reduction to the next lower dose level.	Hematology test should be monitored every 2-3 days; active treatment (platelet transfusion) to elevate the platelet count is recommended. Hematology examination should be performed once every week in the follow up visit.
Grade 4:	Permanently discontinue study treatment.	Hematology test should be performed once daily until the AE recovers to grade 2 or a lower grade; platelet transfusion or other active treatment should be provided

AE = Adverse event

Table 13 Dose Modifications for Hemorrhage at Any Site

AE Grading	Dose Adjustment	Treatment Suggestions
Grade 1	None	Perform follow up visit as scheduled.
Grade 2	• Hold treatment. • If the AE recovers to grade 1 or baseline level within 14 days, resume treatment with a dose reduction to the next lower dose level.	Provide active treatment
Grade 3 or above [a]	Permanently discontinue study treatment.	Emergent medical intervention

AE = Adverse event
a Refer to Appendix 7 for clinical management of severe or serious hemorrhage.

Table 14 Dose Modifications for Abnormal Liver Function

AE Grading[a]	Dose Adjustment	Treatment Suggestions
Grade 1	None.	Follow up per planned schedule.
Grade 2 or 3 (Liver function is abnormal but the biochemical criteria for Hy's Law[b] are not met)	• Hold treatment. • If the AE recovers to grade 1 or baseline level within 14 days, resume treatment with a dose reduction to the next lower dose level.	Provide supportive care and increase the frequency of liver function monitoring to 1-2 times a week.
Grade 2 or 3 (Liver function is abnormal and the biochemical criteria for Hy's Law[b] are met)	The study drug should be terminated immediately.	Provide supportive care and increase the frequency of liver function monitoring to 2-3 times a week. Urgent medical intervention indicated.

Table 14 Dose Modifications for Abnormal Liver Function

AE Grading[a]	Dose Adjustment	Treatment Suggestions
Grade 4	The study drug should be terminated.	Urgent medical intervention indicated.

AE = adverse event.

a Including increasing of ALT, AST, and total bilirubin, whether or not the biochemical criteria for Hy's Law have been met.

b Hy's Law is an increase in serum AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN, and no other reason can be found to explain the biochemical changes, for example, new or worsening hepatobiliary metastases, elevated serum alkaline phosphatase indicating cholestasis, viral hepatitis, another suspect drug, or any other specific cause of severe hepatocellular injury. The elevation in transaminases must precede or be coincident with (ie, on the same day as) the elevation in total bilirubin, but there is no specified timeframe within which the elevations in transaminases and total bilirubin must occur. See Section 8.2.2 for special reporting requirements and Appendix 6 for additional information regarding Hy's Law.

8 SAFETY MONITORING

8.1 Definitions

8.1.1 Adverse Event

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product or other protocol-imposed intervention, whether or not considered related to the medicinal product. Adverse events will be assessed according to the NCI CTCAE v5.0.

8.1.2 Serious Adverse Event

An AE is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE. An event is considered "life-threatening" if, in the view of the investigator, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction (AR) that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject or patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.2 Adverse Event Reporting

8.2.1 Adverse Event Reporting Period

After informed consent, but prior to initiation of study drug, all serious adverse events (SAEs) regardless of attribution will be collected. After initiation of study drug, all SAEs and AEs regardless of attribution will be collected until 30 days after the last dose of study drug or a new treatment of anti-tumor therapy, whichever is earlier. After this period, investigators should report only SAEs that are considered to be related to the study drug.

8.2.2 Expedited Reporting

Certain events require immediate reporting to allow the sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events (both initial and follow-up) to the sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that

the investigator must report to the sponsor within 24 hours after first learning of the event, regardless of relationship to study drug:

- SAEs (from informed consent to 30 days following the last dose of study drug or a new treatment of anti-tumor therapy),
- Abnormal hepatic function is defined as serum AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN, regardless of seriousness.
    - For management for hepatic function abnormal event, refer to Table 14 (Dose Adjustment for Abnormal Liver Function). Hy's Law is an increase in serum AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN, and no other reason can be found to explain the biochemical changes, for example, new or worsening hepatobiliary metastases, elevated serum ALP indicating cholestasis, viral hepatitis, another suspect drug, or any other specific cause of severe hepatocellular injury. The elevation in transaminases must precede or be coincident with (ie, on the same day as) the elevation in total bilirubin, but there is no specified timeframe within which the elevations in transaminases and total bilirubin must occur. See Appendix 6 (Clinical Evaluation of Possible Drug-Induced Liver Injury [DILI]) for additional information regarding Hy's Law.
- CTCAE grade ≥3 hemorrhagic event,
    - When there is a grade ≥3 hemorrhagic event per NCI CTCAE (Version 5.0). The management of severe or serious hemorrhagic events will be conducted according to Appendix 7 (Clinical Management of Severe or Serious Hemorrhagic Events).
- Pregnancy,

8.3 Eliciting Adverse Events

A consistent methodology of non-directive questioning for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinic visit?"
- "Have you had any new or changed health problems since you were last here?"

8.4 Assessment of Severity

Investigators will seek information on AEs and SAEs at each subject contact. All AEs and SAEs, whether reported by the subject or noted by authorized study personnel, will be recorded in the subject's medical record and on the appropriate AE/SAE form.

For each AE and SAE recorded on the applicable eCRF, the investigator will make an assessment of severity through clinical description by referring to the five-grade determination standard in the NCI CTCAE v5.0. Please use the guideline below for the assessment of severity when the observed or reported AE is not listed in the NCI CTCAE v5.0:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
- Grade 3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

Note:
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

8.5 Causality assessment

Investigators should use their knowledge of the subject, the circumstances surrounding the AE, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the study drug. To ensure consistency of causality assessments, investigators should apply the general guidelines in provided as below:

- **Related:** There is a reasonable possibility that the event may have been caused by the product under investigation. Factors that point toward this assessment include but are not limited to: a positive re-challenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation or dose reduction, a biologically plausible relationship between the drug and the AE, or a lack of an alternative explanation for the AE.

- **Not Related:** There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

8.6 Documenting Adverse Events

When an AE or SAE is recorded, the preferred medical terminology or concept should be used. Abbreviations and colloquialisms (eg, jargon or slang) should be avoided.

All AEs (including SAEs) should be recorded on the AE eCRF, and the check box for "Serious" should be ticked for entries that fit the criteria for SAEs. The investigator should also complete an SAE report and submit this to the sponsor or its designee within 24 hours of knowledge of the event.

Only one medical concept should be recorded in the event field on the eCRF.

8.6.1 Diagnosis versus Symptoms and Signs

If known, a diagnosis should be recorded on the eCRF rather than individual signs and symptoms (eg, hepatic failure should be recorded instead of jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the eCRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

8.6.2 Adverse Event Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (eg, cascade events or clinical sequelae) should be identified by their primary cause with the exception of severe or serious secondary events. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the eCRF if the dehydration is mild.

However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the eCRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the eCRF.

8.6.3 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution between subject evaluation time points. Such events should only be recorded once in the eCRF unless the severity changes. If a persistent AE becomes more or less severe, it should be recorded again in a new eCRF entry. Please refer to the eCRF Completion Guidelines for information on completing each eCRF.

A recurrent AE is one that occurs and resolves between subject evaluation time points and subsequently recurs. All recurrent AEs should be recorded on the eCRF respectively.

8.6.4 Abnormal Laboratory Values or Abnormal Vital Signs

Not every laboratory abnormality/abnormal vital sign qualifies as an AE. A laboratory test result/abnormal vital sign must be reported as an AE if it is a change from baseline and meets any of the following criteria:

- Accompanied by clinical symptoms,
- Results in a change in study treatment (eg, dosage modification, treatment interruption, or treatment discontinuation),
- Results in a medical intervention (eg, potassium supplementation for hypokalemia) or a change in concomitant therapy,
- Clinically significant in the investigator's judgment.

Investigators are responsible for reviewing all laboratory findings and abnormal vital signs and determining whether or not each abnormality should be reported as an AE.

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (eg, ALP and bilirubin 5 × ULN associated with cholecystitis), only the diagnosis (eg, cholecystitis) needs to be recorded on the eCRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the eCRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7.0 mmol/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the eCRF, unless their severity, seriousness, or etiology changes.

8.6.5 Preexisting Medical Condition

A preexisting medical condition is one that is present at screening. Such conditions should be recorded on the eCRF as medical history. A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study (excluding deterioration of the study disease conditions). When such events are recorded on the eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (eg, "more frequent headaches").

8.6.6 Pregnancy

A female subject must be instructed to stop taking the study drug and immediately inform the investigator if she becomes pregnant during the study. The investigator should report all pregnancies within 24 hours of awareness to the sponsor (the reporting period for pregnancy continues up to 30 days after completion of the study drug). The investigator should counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the subject should continue until outcome of the pregnancy. Pregnancies occurring up to 30 days after the completion of the study drug must also be reported to the investigator.

Male subjects must also be instructed to inform the investigator immediately if their partner becomes pregnant during the study or within 90 days after the last dose of study drug. If such an event occurs, it should be reported as described above.

Pregnancy loss of any kind should always be classified as serious AE (as the sponsor considers these medically significant), recorded on the eCRF, and expeditiously reported to sponsor.

Any congenital anomaly/birth defect in a child born to a female subject or female partner of a male subject exposed to the investigational product should be recorded and reported as an SAE.

8.6.7 Worsening of Solid Tumor

Worsening and/or progression of the subject's solid tumor should not be recorded as an AE or SAE. These data will be captured as efficacy assessment data only. If there is any uncertainty about an AE being related only to the disease under study, it should be reported as an AE or SAE.

8.6.8 Death

All deaths that occur during the protocol-specified AE reporting period must have the underlying cause reported to the sponsor as an SAE with death listed as the outcome. Deaths due to the progression of disease must also be reported to the sponsor as an SAE. Death events that occur after 30 days following last dose of study drug must be reported to the sponsor as an SAE only if it is confirmed as related to study drug. If the primary cause of death is unknown and cannot be ascertained at the time of reporting, please record "Unknown cause death" on the eCRF, and the "unexplained/unknown death" should be reported expeditiously as an SAE. The SAE should be reported before the specific cause of death has been determined.

8.7 Duration of Follow-up for Adverse Events

The investigator will follow all unresolved AEs and SAEs until the events are resolved or stabilized, the subject is lost to follow-up, subject death, or end of study. Resolution of AEs and SAEs (with dates) should be documented on the appropriate eCRF and in the subject's medical record to facilitate source data verification (SDV). For SAEs, if, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded in the additional case details section of the eCRF.

For some SAEs, additional case details deemed necessary to appropriately evaluate the SAE report (eg, hospital discharge summary, consultant report, or autopsy report) may be followed-up by telephone, fax, email, and/or a monitoring visit.

All pregnancies that occur during the study should be followed until pregnancy outcome.

9 STATISTICAL ANALYSIS

9.1 Statistics and Analysis Method

A separate statistical analysis plan (SAP) will provide specific details on analytical methods.

9.1.1 Statistical Hypothesis

This study is 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 is 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).

9.1.2 Sample Size Rationale

The total sample size and number of OS events required for efficacy assessment in the ITT population is calculated based on the following assumptions:

- A one-sided significance level of 0.025;
- Assuming an OS HR (fruquintinib arm/placebo arm) of 0.73, this sample size yields approximately 90% statistical power to detect superiority of the fruquintinib arm over placebo arm. 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);
- An enrollment rate of 30 subjects per month during the first 3 months and 50 subjects per month thereafter;
- Yearly dropout rate of 10%;
- Randomization ratio = 2:1 (fruquintinib arm vs placebo arm).
- Data maturity = 70%;
- One interim futility analysis when 1/3 of the total number of OS events (ie, 160 OS events) have occurred, the Lan-DeMets spending function is used in the calculation.

Under the premise of these assumptions, approximately 687 subjects will be randomized to this study over approximately 15 months in this study. OS will be analyzed when 480 OS events are observed, which is expected to occur in approximately 7 months after the end of enrollment. East® version 6.5 software (www.cytel.com) was utilized for the calculation. In clinical practice, TAS-102 is used more commonly than regorafenib. To ensure that the subject population is representative of clinical practice, post-regorafenib subjects will be capped at 344 subjects if there is an unanticipated enrichment of that population. This will ensure that at least 50% of the subjects will be post-TAS. Subjects are considered in post-TAS-102 or post-regorafenib populations if they have received at least one dose of either agent, respectively, prior to entering the study. Based on the similar mechanisms of action between regorafenib and fruquintinib, it will be of clinical interest to evaluate the magnitude of benefit in each of the populations when compared to the ITT population.

9.1.3 Analysis Sets

Intent-to-Treat (ITT) Population

All randomized subjects will be included in the ITT population. Subjects will be analyzed by treatment arm as randomized. The ITT population will be the primary population for evaluating all efficacy endpoints and patient characteristics.

Safety Analysis Population

All randomized subjects who received at least one dose of study treatment will be included in the safety analysis population. Subjects in this population will be analyzed according to the treatment they actually received. This population will be used for all safety analyses.

9.2 Primary and Secondary Endpoints

9.2.1 Primary Endpoint

The primary endpoint of the study is OS, defined as the time (months) from date of randomization to death from any cause. Subjects without report of death at the time of analysis will be censored at the date last known alive. Subjects lacking data beyond the date of randomization will have their survival time censored at the date of randomization. OS will not be censored if a subject receives subsequent anticancer treatments after discontinuation of the study drugs.

9.2.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include PFS, ORR, DCR, and DoR.

9.2.2.1 Key Secondary Endpoint: Progression-free Survival

PFS is defined as the time (months) from randomization until the first radiographic documentation of objective progression as assessed by investigator using RECIST v1.1, or death from any cause, whichever comes first. More specifically, PFS will be determined using all data until the last evaluable visit prior to or on the date of: (i) radiographic disease progression per RECIST v1.1; (ii) withdrawal of consent to obtain additional scans on study; or (iii) initiation of subsequent anticancer therapy other than the study drugs, whichever is earlier. Censoring rules for subjects who do not experience PD or death will be described in the study SAP. Additional sensitivity analyses may be conducted and will be specified in the SAP.

9.2.2.2 Objective Response Rate

Objective response rate is defined as the proportion of subjects achieving a best overall response of confirmed complete response (CR) or partial response (PR), per RECIST v1.1, as determined by the investigator.

9.2.2.3 Disease Control Rate

Disease control rate is defined as proportion of subjects achieving a best overall response of confirmed CR, PR, or SD, per RECIST v1.1, as determined by the investigator. To be qualified for SD, the duration of SD should last for at least 7 weeks.

9.2.2.4 Duration of Response

Duration of response is defined as the time (months) from the first occurrence of PR or CR, whichever comes first, until the date of radiographic PD or death. The duration of response will be determined for subjects with best overall response of confirmed CR or PR.

9.2.3 Secondary Safety Endpoints

Safety endpoints include AE, laboratory tests, vital signs and weight, ECG, echocardiogram/MUGA (especially LVEF) and ECOG PS.

All AEs, whether related to the drug or not, will be recorded in the eCRF including the start/end date, measures taken, treatment affected (yes versus no) and the outcome. For all the events, the causality with the treatment and the severity will be determined by the investigator.

9.2.4 Other Endpoints

9.2.4.1 Patient Reported Outcomes

Quality of life will be assessed using European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and EQ-5D-5L questionnaires. Quality of life score, change from baseline, subjects achieving minimally important difference (MID) cut-off, and time to deterioration (TTD) will be assessed.

9.2.4.2 Assessment of Resource Utilization

Health care resource utilization assessments such as physician visits, emergency room visits, hospital care (eg, inpatient and outpatient), drug prescriptions etc. will be assessed.

9.2.5 Statistical Methods

9.2.5.1 Analysis of Efficacy Endpoints

Efficacy analyses will be based on ITT population. All secondary endpoints based on radiological assessments of tumor burden will be derived from investigator assessment using RECIST v1.1. Additional sensitivity analyses may be performed and will be outlined in the SAP.

9.2.5.1.1 Primary Endpoint - Overall Survival

A 1-sided stratified log-rank test will be used for the comparison of OS of the fruquintinib with placebo group at a significance level of 0.025. The same stratification factors used for randomization (Section 7.3.1) will be used for analysis. Kaplan-Meier methodology will be used to estimate the median OS and its 2-sided 95% Confidence Interval (CI) for each treatment arm. Plots will be produced by treatment arm. The HR between the 2 treatment groups (fruquintinib vs placebo), together with its 95% CI, will be calculated from a stratified Cox proportional hazard model stratified by the randomization stratification factors.

9.2.5.1.2 Secondary Efficacy Endpoints (PFS, ORR, DCR, DoR)

First secondary endpoint is to evaluate PFS in subjects with refractory mCRC treated with fruquintinib plus BSC versus placebo plus BSC. Kaplan-Meier methodology will be used to estimate the median PFS and its 2-sided 95% CI for each treatment arm. Plots will be produced by treatment arm.

The hazard ratio (HR) between the 2 treatment groups (fruquintinib vs placebo), together with its 95% CI, will be calculated from a stratified Cox proportional hazard model stratified by the randomization stratification factors.

The estimates of DCR and ORR in each treatment group and their 2-sided 95% CIs will be presented. Comparison of DCR and ORR between treatment groups will be performed using stratified Cochran-Mantel-Haenszel test. The CI of difference in DCR and ORR between treatment groups will be calculated using the approximate normal distribution method of binomial distribution.

Duration of response (DoR) will only be determined for subjects who responded (confirmed best overall response of CR or PR). Statistical test will not be conducted, as subjects with response are not randomized. Descriptive analysis will be adopted for DoR. For each treatment group, results will be presented by Kaplan-Meier estimates and distribution curve.

9.2.5.1.3 Multiplicity Adjustment for the Primary Endpoint OS and Key Secondary Endpoint PFS

To ensure strong control of family-wise Type I error rate among the analyses for the primary endpoint OS and the key secondary endpoint PFS at a 2-sided $\alpha = 0.05$ level, a fixed-sequence procedure will be applied. In this testing procedure, the analyses of OS will be conducted first and once the statistical significance is established for OS at a 2-sided 0.05 level, the analysis of PFS can then be performed at a 2-sided 0.05 level.

9.2.5.1.4 Subgroup Analyses

Subset analyses may be conducted, for example, by age, performance status, prior lines of therapy, prior use of TAS-102, prior use of regorafenib, region, and others as deemed appropriate.

9.2.5.2 Analysis of Safety Endpoints

All safety parameters will be summarized and listed by using the safety population.

TEAEs will be summarized by MedDRA system organ class (SOC) and PT. The incidence and percentage of subjects with at least 1 occurrence of a preferred term will be included according to the most severe NCI-CTCAE version 5.0. Relationship to study therapy (causality) will be summarized separately. If more than one AE was recorded for a subject within a PT, the subject will be counted once in the most severe grade.

Laboratory data will be summarized by visit. All TEAEs and abnormal laboratory variables shall be evaluated by the NCI CTC AE Version 5.0 Classification System. Other safety data including vital signs, ECG, ECOG PS will be summarized using descriptive statistics.

9.2.5.3 Analysis of Other Endpoints

9.2.5.3.1 Subject Reported Outcomes

Subject reported outcomes will be assessed using EORTC QLQ-C30 and EQ-5D-5L questionnaires. The number and percentage of subjects who completed the questionnaires will be summarized for each treatment arm by visit. Reasons for non-completion will be presented. Quality of life scores and change from baseline scores will be compared between treatment arms using mixed model repeated measures approach adjusting for covariates. For each scale, appropriate minimally important difference (MID) cut-off will be determined and number and percent of subjects achieving the MID will be presented. In addition, time to deterioration (TTD) will be summarized using Kaplan-Meier methodology.

9.2.5.3.2 Resource Utilization

Health care resource utilization data including number and percent of subjects hospitalized, reasons for hospitalizations, emergency room visits, drug prescriptions will be summarized.

9.3 Pharmacokinetic and Pharmacodynamic Analyses

9.3.1 Population PK and Exposure-Response Analyses

Descriptive statistics (including but not limited to arithmetic mean, standard deviation, coefficient of variation, median, minimum, maximum and geometric mean) will be provided for the observed concentrations for fruquintinib and metabolite M11.

Population PK analysis of plasma concentration-time data of fruquintinib and metabolite M11 will be performed using nonlinear mixed-effects modeling. The population PK modeling will include all subjects with sufficient and interpretable PK assessments. The data from the population PK samples may be combined together with the data from other studies for the population PK analysis. If relevant and sufficient data are available, the relationship of exposure to fruquintinib and M11 to measures of efficacy and AEs may also be analyzed. Details of the population PK and/or exposure-response analysis will be given in a population PK/pharmacodynamic analysis plan. The results of the population PK/pharmacodynamic analysis will be presented in a separate report.

9.3.2 Pharmacodynamic (ECG) Analysis

Subjects who 1) receive at least 1 dose of study drug, and 2) have baseline and at least 1 post-dose ECG measurement will be evaluable for pharmacodynamic (ECG) evaluation. Subjects who had reduced dosage, prolonged dose interruption of >2 days in cycle 1, or who had any dose interruption within 7 days before cycle 1 day 21, or were discontinued from the study prior to the completion of ECG data collection (cycle 1 day 21) will be excluded. For each of the ECG parameters, the average values from the 3 readings of a triplicate ECG set will be used in the analysis.

For all ECG parameters, the baseline will be defined as the mean values of the triplicate ECG measurements taken at pre-dose on cycle 1 day 1.

9.3.2.1 QTc Intervals

The terminology QTc is used in this section as a general notation for corrected QT intervals using any of the specified methods.

The QT interval data will be corrected for heart rate using 2 correction methods (Fridericia – QTcF and Bazett – QTcB). For each QTc correction method, the relationship between QTc and RR at baseline will be evaluated graphically by plotting the logarithm of baseline QTc values against the logarithm of corresponding RR intervals. Fridericia will be used as the primary correction method for statistical analysis. If the correlation between QTc and RR intervals remains significant using the Fridericia correction method, an alternative correction method may be considered for statistical analysis in addition to QTcF.

For the statistical analysis based on the primary correction method (QTcF), the mean changes from baseline (ΔQTc) at each time point will be summarized (mean, standard deviation, median and range, 2-sided 90% confidence interval). The difference in ΔQTc between fruquintinib and placebo (ΔΔQTc) for each individual will also be calculated at each time point (individual ΔQTc for fruquintinib – mean ΔQTc for placebo at the same time point). Mean values for the difference and 2-sided 90% CI for mean difference will be calculated at each time point.

The primary analysis will focus on the maximum mean change from baseline in QTc (ΔQTc) on cycle 1 day 21, which will be estimated by the mean QTc change at around T_{max}, the time when the maximum plasma concentration is reached (ie, steady state). The same analysis will be performed for ΔQT data using other correction methods if data warrant. The mean change from baseline in QTc (±standard deviation) over time will be plotted.

In addition, QTc will be categorized based on ICH E14 guidelines. Tables will present the number and percentage of subjects meeting or exceeding the following categories:

- QTc interval prolongation:
  - Absolute values > 450 to ≤ 480 msec
  - Absolute values > 480 to ≤ 500 msec
  - Absolute values > 500 msec
- QTc interval change from baseline:
  - Increase from baseline > 30 to ≤ 60 msec
  - Increase from baseline > 60 msec

9.3.2.2 Heart Rate, QRS, and PR intervals

For each treatment and time point of measurement, heart rate , QRS interval and PR interval, as well as the change from baseline in heart rate, QRS and PR (ΔHR, ΔQRS, ΔPR), will be summarized using descriptive statistics (mean, standard deviation, median, range, and 90% CI). The number and percentage of subjects with heart rate >100 bpm will be tabulated for each time point. The number and percentage of subjects with QRS >110 msec will be tabulated for each time point. The number and percentage of subjects with PR >200 msec will be tabulated for each time point.

9.3.2.3 T-wave and U-wave Morphology

The number and percentage of subjects having T-wave morphology changes from baseline and/or the occurrence of abnormal U-waves that represent the appearance or worsening of the morphological abnormality will be summarized. Subjects with abnormal ECG findings will be listed. Additional analyses will be performed if deemed necessary.

9.3.3 QTc-PK Analysis

The potential relationship between QTc and PK will be evaluated using data from all evaluable subjects who have data from baseline and at least 1 post-dose ECG measurement following the first dose. QTc change from baseline before and after correction for placebo (ΔQTc and ΔΔQTc) using the primary correction method (see Section 9.3.2.1) at each time point of measurement will be plotted against the corresponding plasma concentrations of fruquintinib and M11 separately. Additional plots will be produced, if deemed necessary.

A linear mixed effects model will be fitted to the ΔQTc and ΔΔQTc data from cycle 1 day 1 and cycle 1 day 21 with either parent or metabolite concentration as a predictor and subject as a random effect; if the intercept term is not significant, the model will be re-fitted with a zero intercept term. Based upon these relationships, the predicted population average ΔQTc and ΔΔQTc as well as their corresponding upper 90% 2-sided confidence interval bound will be computed at the mean maximum plasma concentrations (ie, C_{max}) of fruquintinib and M11, or other concentrations of interest.

9.4 Interim Analysis

An independent data monitoring committee (IDMC) will be convened to review accumulating safety data. During the study, safety interim analyses will be performed approximately every 6 months. The frequency of safety interim analysis may be modified upon IDMC recommendation.

One interim non-binding futility analysis will be performed when approximately 1/3 of the total number of OS events (ie, 160 OS events) has occurred. The IDMC will be instructed to recommend stopping the study for futility if the 1-sided p-value from a stratified log-rank test is at least 0.772 (corresponding to an observed HR of at least 1.133). Otherwise, the study will continue with full enrollment. There is a 22.8% chance of terminating the study for futility at the interim analysis if the true median OS in fruquintinib arm is 5 months, ie, fruquintinib is ineffective. There is a 0.4% chance of stopping for futility, declaring fruquintinib ineffective at the interim if the true median OS in fruquintinib arm is 6.8 months, ie, fruquintinib is effective in our study population.

Although there are 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 1 error, a fraction of alpha (0.0001) will be spent at the interim analysis based on an O'Brien-Fleming stopping boundary.

10 ETHICAL CONSIDERATIONS

10.1 Good Clinical Practice

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct, consensus and the ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, Applicable ICH GCP Guidelines that have their origin in the Declaration of Helsinki, and applicable regulations and guidelines governing clinical study conduct.

10.2 Ethics Review

The Independent Ethics Committee (IEC)/Institutional Review Board (IRB) must review the protocol and amendments, investigator's brochure, informed consent form, study-relevant materials (such as advertisements for subject recruitment) and any other essential documents. IEC/IRB approval is to be obtained prior to the study.

All amendments are to be reviewed and approved by the IEC/IRB and applicable regulatory authorities (as required) and documented. All unexpected SAEs should be reported to the sponsor, IEC/IRB and applicable regulatory authorities as required. During the study, protocol deviations that may increase a subject's risk should be reported to the IEC/IRB in a timely manner.

Protocols and any substantial amendments to the protocol will require health authority approval (as required) prior to initiation, except for changes necessary to eliminate an immediate hazard to study subjects.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European Regulation 536/2014 for Clinical Studies (if applicable), European Medical Device Regulation 2017/745 for Clinical Device Research (if applicable), and all other applicable local regulations.

10.3 Informed Consent

The following will be followed for informed consent:

- Investigators or designees, if locally permissible, must obtain the signed ICF from subjects prior to conducting any study-related procedures.
- The Investigator or his/her representative will explain the nature of the study to the subject or to their legally authorized representative, if locally permissible, and answer all questions regarding the study.

- Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative, if locally permissible, will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- Subjects must be informed that they may withdraw consent to participate in the study without any limitations. If the subject cannot sign the ICF, a legally acceptable representative of the subject must sign the ICF if locally permissible.
- If the subject and the legally acceptable representative are not able to read and write, an impartial witness should be present throughout the whole process of providing informed consent. Once the subject and the legally acceptable representative, if locally permissible, give their oral consent, the ICF should be signed by the impartial witness to confirm that the subject and the legally acceptable representative fully understand the study and their right to withdraw informed consent without any limitations.
- Informed consent should be recorded in the eCRF.
- If the risk/benefit assessment changes after the safety analysis, the ICF must be reviewed and updated, and all updated information should be provided to subjects (including subjects who have already received the study drug).

10.4 Data Privacy

All information about fruquintinib (such as patent application, formulation, manufacturing process and basic study information) is considered confidential as long as it is unpublished.

All information obtained in the study is considered confidential. Hutchison MediPharma Limited will open the information to investigational personnel, the National Medical Products Administration, and any other regulatory authority when necessary. To ensure the completeness of the study analysis data, investigational personnel are accountable for providing all results and data to the sponsor.

Investigators must guarantee the privacy of subjects by not disclosing subject-related information to third parties without authorization. eCRFs and other documents submitted to the sponsor should not contain the subject's name.

- Subjects will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information that would make the subject identifiable will not be transferred.
- Subjects are identified only by the unique identifier. Investigators may retain the identification forms, which include subject numbers, names, and addresses. ICFs and other documents should be documented properly, and should not be given to the Sponsor.
- Subjects must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent.

- Subjects must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.5 Disclosure

Final study results will be published on a public clinical trial website according to applicable local guidelines and regulations.

10.6 Biological Specimens and Data

For subjects who provide informed consent agreeing to participate in future biomedical research, any unused samples for study-related research, as well as unused PK samples, may be stored for no longer than 15 years, or other period as per local requirements, after the final date of the database lock. After this storage period, any residual samples will be destroyed. The Sponsor will store the samples in a secure storage space with adequate measures to protect confidentiality.

The results of these future biomedical research analyses will not be shared with subjects and will not be presented in the CSR.

If there are specific site or country requirements involving the pharmacogenomic analyses that the sponsor is unable to comply with, samples will not be collected at those sites.

All samples will be single/double coded as defined by ICH guideline E15.

10.7 Data Quality Assurance

- To ensure the safety of subjects in the study, and to ensure accurate, complete, and reliable data, the Investigator will keep records of laboratory tests, clinical notes, and subject medical records in the subject files as original source documents for the study.
- All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the CRF Completion Guidelines.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study, including quality review of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, CROs).

11 OVERSIGHT

11.1 Independent Monitoring

11.1.1 Independent Data Monitoring Committee

An IDMC will be established in this study. The IDMC will consist of at least 4 independent clinical oncology physicians and 1 independent statistician with no conflicts of interest with the sponsor. The IDMC will evaluate the safety data regularly, and the subjects' safety will be determined by the evaluation of the risk/benefit at a regular review meeting. The responsibilities of the IDMC will include:

- Regular (approximately every 6 months) unblinded review of the study data to provide suggestions such as "continue as planned, suspend, protocol amendment, terminate study" so as to prevent subjects from being exposed to unsafe dose and treatment regimes.
- Review of interim analysis data to provide suggestions such as "continue as planned, suspend, protocol amendment, terminate study."

Upon completion of the data review, the IDMC will provide suggestions on whether or not to continue the study, if modification of the protocol is recommended or if study termination is required. The final decision shall be made by Hutchison MediPharma Limited. The IDMC membership and governance is outlined in a separate IDMC charter.

11.2 Quality Control and Assurance

The clinical study will be executed and reported following GCPs, all applicable regulatory requirements, and applicable standard operating procedures, including quality control of documents.

The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site. The sponsor and investigator ensure that any individual or party who performs trial-related duties or functions on behalf of the sponsor/investigator is qualified to perform the trial-related duties or functions.

The overall procedures for quality assurance of clinical study data are described in the sponsor or designee's standard operational procedures. The planned quality assurance and quality control procedures for the study are described in the following sections.

11.2.1 Monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, the Sponsor's personnel (or designated CRO) will review the protocol and eCRFs with the Investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of subject records, the accuracy of entries on the eCRFs, the adherence to the protocol to GCP, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel, including the Investigator, must be available to assist the field monitor during these visits.

The Investigator must give the field monitor access to all relevant source documents to confirm their consistency with the eCRF entries. The Sponsor's monitoring standards require full verification of the informed consent, adherence to the inclusion/exclusion criteria, and

documentation of SAEs. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

11.2.2 Audits

Authorized representatives of the sponsor, a regulatory/competent authority, and/or an IRB/IEC representative may visit the site to perform audits or inspections, including source data verification. Should this occur, the Investigator is responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received and authorizing the Sponsor's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the Sponsor immediately
- Taking all appropriate measures requested by the Sponsor to resolve the problems found during the audit or inspection
- Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB/EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the Sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the Investigator's institution.

In all instances, the confidentiality of the data must be respected.

11.2.3 Records

11.2.3.1 Data Capture and Management

The term case report form (CRF) or eCRF should be understood to refer to electronic data capture (EDC) system. The EDC system is the database where pertinent study data are collected. For all subjects, including screen failures, data will be collected on source documents first. The Principal Investigator is responsible for assuring that the data entered into eCRFs is complete, accurate, and that entry and updates are performed in a timely manner. Blood and tumor samples for PK and biomarkers assessments will be collected by study sites and sent to the designated central laboratory for processing. Data from ECG assessments will be collected at the study sites, and the data will be transmitted to a designated CRO for centralized analysis, as well as for further processing and data reconciliation. Imaging data will be collected at the study sites, and a designated CRO will perform further processing, data reconciliation, and holding.

At all times, the Principal Investigator has final responsibility for the accuracy and authenticity of all clinical and laboratory data entered in the EDC. Subject source documents are the Investigator's/physician's subject records maintained at the study site. In cases where the source documents are the hospital or the physician's chart, the information collected in the EDC must match those charts. All final data recorded in EDC system will be copied onto CDs and kept by

the Sponsor. A copy of these CDs will also be kept at the clinical site. All data recorded on source documents will be kept at the clinical site.

The completed pages of the EDC system are the sole property of the Sponsor and should not be made available in any form to third parties without written permission from the Sponsor, except for authorized representatives of the Sponsor or appropriate regulatory authorities.

11.2.3.2 Source Documentation

- The Investigator/institution should maintain adequate and accurate source documents and study records for all subjects that support the information entered in the CRF.
- Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable and not obscure the original entry.
- All information recorded on eCRFs must be traceable to source documents in the subject's file. Any changes should be explained if necessary (eg, via an audit trail).

11.2.3.3 Records Retention

Records and documents, including signed ICFs, source documents, study drug documents, monitoring visit records, regulatory documents, and all other correspondence and documents pertaining to the conduct of this study must be retained by the Investigator for at least 5 years after study completion, unless local regulations or institutional policies require a longer retention period.

If the documents cannot be stored properly at the investigational site, the documents can be transferred by the Investigator and Sponsor to an approved storage facility. The documents must be sealed for storage and easily found for review in the case of a regulatory authority audit. No records may be transferred to another location or party without written notification to the Sponsor.

No records may be destroyed during the retention period following study completion or discontinuation without the written approval of the Sponsor. Records must be destroyed in a manner that ensures confidentiality.

11.3 Study Termination or Study Site Closure

The Sponsor and the Investigator have the right to close out a site prematurely.

Investigator's Decision

The Investigator must notify the Sponsor of a desire to close out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the Sponsor. Both parties will arrange the close out procedures after review and consultation

Sponsor's Decision

The Sponsor will notify the Investigator(s) of a decision to close out a study site in writing. Reasons may include the following, among others:

- The Investigator has received all items and information necessary to perform the study, but has not enrolled any subject within a reasonable period of time
- The Investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines

- The total number of subjects required for the study are enrolled earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CROs used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

12 PUBLICATION POLICY

The study results may be published in scientific journals. The names of investigators who make an important contribution to the study implementation and management, and personnel who make an important contribution to the study design, analysis, and interpretation (such as staff or consultants) will be listed in the publication. The Sponsor agrees to provide the article to investigators for review prior to publishing any study results. Investigators must obtain approval from the Sponsor before contributing to any related articles or abstracts.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

13 FINANCING AND INSURANCE

Financing and insurance information will be addressed in a separate agreement.

14 REFERENCES

American Cancer Society, Key Statistics for Colorectal Cancer, 2019. URL: www.cancer.org/ cancer/ colon-rectal-cancer/about/key-statistics.html; accessed February 12, 2019.

Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018 Nov;68(6):394-424

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.

Duda DG, Batchelor TT, Willett CG, Jain RK. VEGF-targeted cancer therapy strategies: current progress, hurdles and future prospects. *Trends Mol Med*. 2007 Jun;13(6):223-30.

Grothey A, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, Humblet Y, Bouché O, Mineur L, Barone C, Adenis A, Tabernero J, Yoshino T, Lenz HJ, GoldbergRM, Sargent DJ, Cihon F, Cupit L, Wagner A, Laurent D; CORRECT Study Group. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013 Jan 26;381(9863):303-12.

Izzedine H, Ederhy S, Goldwasser F, Soria JC, Milano G, Cohen A, Khayat D, Spano JP. Management of hypertension in angiogenesis inhibitor-treated patients. *Ann Oncol*. 2009 May;20(5):807-15.

Jayson GC, Kerbel R, Ellis LM, Harris AL. Antiangiogenic therapy in oncology: current status and future directions. *Lancet*. 2016 Jul 30;388 (10043):518-29.

Koopman M, Kortman GA, Mekenkamp L, Ligtenberg MJ, Hoogerbrugge N, Antonini NF, Punt CJ, van Krieken JH. Deficient mismatch repair system in patients with sporadic advanced colorectal cancer. *Br J Cancer*. 2009 Jan 27;100(2):266-73.

Li J, Qin S, Xu R, et al. Effect of fruquintinib vs placebo on overall survival in patients with previously treated metastatic colorectal cancer. *JAMA*. 2018;319(24):2486-96.

LONSURF® (trifluridine and tipiracil) Prescribing Information. Taiho Pharmaceutical Co, Taiho Oncology, Inc. Princeton NJ, USA. Revised Feb 2019

Mayer R, Van Cutsem E, Falcone A, et al. Randomized Trial of TAS-102 for Refractory Metastatic Colorectal Cancer (RECOURSE). *N Engl J Med* 2015; 372: 1909-19.

National Comprehensive Cancer Network (NCCN), Version 2019.

STIVARGA® (regorafenib) Prescribing Information. Bayer HealthCare Pharmaceuticals, Inc, Whippany NJ, USA. Revised Apr 2017.

Sun Q, Zhou J, Zhang Z, Guo M et al., Discovery of fruquintinib, a potent and highly selective small molecule inhibitor of VEGFR 1, 2, 3 tyrosine kinases for cancer therapy. *Cancer Biol Ther*. 2014;15 (12):1635-45.

15 APPENDICES

APPENDIX 1 COVID-19 RISK ASSESSMENT

Hutchison MediPharma acknowledges that the subjects to be enrolled in this study are patients with refractory cancer, and therefore, may be at higher risk for complications if they contract COVID-19. Available data indicate that the elderly and people with underlying health conditions such as chronic respiratory, cardiovascular, or kidney disease; diabetes; active cancer; and more generally severe chronic diseases are more vulnerable to experience complications. However, there is an unmet medical need for new medications that are safe and effective in patients with refractory cancer who have limited treatment options.

During the COVID-19 pandemic, patients may be at additional risk as a result of going to a healthcare facility and interacting with healthcare staff and providers. Patients may be screened and enrolled if the site has procedures in place to test and appropriately follow new patients on trial and to ensure patient safety and data integrity. Potential patients with a known or suspected COVID-19 infection are ineligible. Patients with a known COVID-19 infection may be considered for participation following 2 subsequent negative tests per guidelines. It is at the principal investigator's discretion to balance the risk/benefit to determine when enrollment is appropriate, and patient safety should always be considered.

The risk management and mitigation steps being taken by Hutchison MediPharma Limited and its designee are as follows. These steps were developed to align with COVID-19 guidance on clinical trials issued by the US Food and Drug Administration and European Medicines Agency.

1. Subject safety
    a. Patient education on COVID-19-related risks will be provided by the principal investigator (ie, using cancer patient guidelines at European Society for Medical Oncology web site).
    - Patient time in clinic should be minimized when possible. Blood sampling/visits may be performed at another location if this can be done within local restrictions on social distancing to reduce site burden and risk for infection (eg, utilizing a local laboratory, a home nurse, or a satellite site). The laboratory results must be reviewed by the principal investigator, and laboratory normal ranges must be collected and documented.
    - Study visits may be conducted with patients using telemedicine, where the principal investigator and site personnel can videoconference with the patient. In this setting, the principal investigators should perform as many assessments as possible, including any adverse events (AEs), concomitant medications, and Eastern Cooperative Oncology Group performance status.

    b. Reduce the risk for COVID-19 infection associated with traveling to and from the clinic by providing a safer option to avoid public transportation (eg, car/taxi service) if necessary and permitted by local process.
    c. If a patient enrolled into the study subsequently tests positive for COVID-19, the data will be entered into the eCRF as an AE, with proper source documentation.
2. Investigational Medicinal Product handling

Investigational Product may be delivered to the patient's house if permitted under the site's Standard Operating Procedures and patient chain of custody and patient privacy is protected.

3. Management of protocol deviations due to the COVID-19 pandemic

   Hutchison MediPharma and its designee will adhere to all applicable health authority guidelines for documenting and reporting any protocol deviations due to the COVID-19 pandemic. The deviations will be reported to the authorities or institutional review boards/independent ethics committees as instructed.

4. Remote monitoring

   Hutchison MediPharma and its designee agree to perform remote monitoring where feasible and permitted. For remote source data verification, country legislation will be followed and performed only where allowed with written agreement of the principal investigator. The planned site-level procedures will be described in detail and approvals sought as required. If a site cannot support remote monitoring with Electronic Medical Record access, the site will not be permitted to consent new patients. Remote visits will also be conducted to facilitate site selection, initiation and training.

5. External factors related to COVID-19

   Central supply chains may be affected, and tubes used for ctDNA may not reach the study sites in adequate time for the enrollment of subjects. In these cases, tests should be performed, if possible, using investigator site-supplied equipment. If this is not possible, deviations should be appropriately documented as in number 3 above. If other tests are problematic due to local conditions related to COVID-19, please check with the sponsor.

The benefit-risk balance for patients to enroll into this study according to the inclusion and exclusion criteria defined in the protocol and according to the defined COVID-19 risk mitigation measures in this document remains favorable.

Hutchison MediPharma and its designee will continue to evaluate the impact of COVID-19 on the ability of each site to initiate and execute the trial. Site-specific positions will be evaluated prior to the site initiation visit, with the outcomes and any resultant actions documented and filed in the Trial Master File.

As the COVID-19 situation may be temporary, regulatory guidance will be continuously reevaluated and any changes will be communicated when necessary.

APPENDIX 2 ECOG PERFORMANCE STATUS

Grade	Activity Level
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled, cannot carry on any self-care, totally confined to bed or chair
5	Death

APPENDIX 3 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST V1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1, are presented below.

1 Measurability of Tumor at Baseline

1.1 Definitions

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below.

1.1.1 Measurable Tumor Lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by CT or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray
- Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and follow-up, only the short axis will be measured and followed.

1.1.2 Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 but < 15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

1.1.3 Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

1.2 Specifications by Methods of Measurements

1.2.1 Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

1.2.2 Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested.

Chest X-Ray. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the

study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

2 Tumor Response Evaluation

2.1 Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

2.2 Baseline Documentation of Target and Non-Target Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is >10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should

be considered non-target lesions. Nodes that have a short axis of <10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then, as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as a reference to characterize further any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression."

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (eCRF) (eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

2.3 Response Criteria

2.3.1 Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

- Complete response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.
- Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

2.3.2 Special Notes on the Assessment of Target Lesions

Lymph Nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to < 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Target Lesions That Become Too Small to Measure. During the study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist

may not feel comfortable assigning an exact measure and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the eCRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and BML (below measurable limit) should be ticked. (BML is equivalent to a "less than" sign.) (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm, and in that case BML should not be ticked.

Lesions That Split or Coalesce on Treatment. When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

2.3.3 Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- Complete response (CR): Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- Progressive disease (PD): Unequivocal progression of existing non-target lesions. The appearance of one or more new lesions is also considered progression.

2.3.4 Special Notes on Assessment of Progression of Non-Target Disease

When the Patient Also Has Measurable Disease. In this setting, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Patient Has Only Non-Measurable Disease. This circumstance arises in some phase 3 trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large" or an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in therapy." If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

2.3.5 New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

(18) F-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET)

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly, possible "new" disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

A negative FDG-PET scan at baseline with a positive FDG-PET scan during the study is a sign of PD based on a new lesion.

In the case of no FDG-PET scan at baseline and a positive FDG-PET scan during the study:

- If the positive FDG-PET scan during the study corresponds to a new site of disease confirmed by CT, this will be considered PD.
- If the positive FDG-PET scan during the study is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine whether there is truly

progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

- If the positive FDG-PET scan during the study corresponds to a preexisting site of disease on CT that is not progressing on the basis of the anatomic images, this will not be considered PD.

2.4 Evaluation of Response

2.4.1 Time Point Response (Overall Response)

It is assumed that at each protocol-specified time point, a response assessment occurs. Table 15 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 16 is to be used.

Table 15 Time Point Response: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table 16 Time Point Response: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

2.4.2 Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with 3 measured lesions and, during the study, only 2 lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be "unable to assess" since the patient is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be "unable to assess" except where there is clear progression. Overall response would be "unable to assess" if either the target response or the non-target response is "unable to assess" except where this is clear evidence of progression, as this equates with the case being not evaluable at that time point.

2.4.3 Best Overall Response: All Time Points

The best overall response is determined once all the data for the patient is known. Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a

subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 17.

Table 17 Best Overall Response When Confirmation of Complete Response and Partial Response is Required

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD =progressive disease, and NE = inevaluable.

a: If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 0 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the eCRF.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients

is to be determined by evaluation of target and non-target disease as shown in Table 15 and Table 16.

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

In studies for which patients with advanced disease are eligible (ie, primary disease still or partially present), the primary tumor should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of complete response if the primary tumor is still present but not evaluated as a target or non-target lesion.

2.5 Frequency of Tumor Re-evaluation

Frequency of tumor re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of phase 2 studies where the beneficial effect of therapy is not known, follow-up every 6–8 weeks (timed to coincide with the end of a cycle) is reasonable. Smaller or greater time intervals than these could be justified in specific regimens or circumstances. The protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumor type under study) and how often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

After the end of the treatment, the need for repetitive tumor evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death). If 'time to an event' (eg, time to progression, disease-free survival, progression-free survival) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomized comparative trials in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6–8 weeks on treatment or every 3–4 months after treatment) and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

2.6 Confirmatory measurement/duration of response

2.6.1 Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials (see the paper by Bogaerts et al. in this Special Issue10). However, in all other circumstances, for example in randomized trials (phase 2 or 3) or in studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies that are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

2.6.2 Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

2.6.3 Duration of stable disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

APPENDIX 4 PROHIBITED MEDICATION

A series of strong inducers and strong inhibitors of CYP3A are listed in Table 18 and Table 19 below. Examples of sensitive substrates of P-gp and BCRP are listed in Table 20.

Patients who received a CYP3A strong inducer or strong inhibitor within 2 weeks (3 weeks for hyperforin perforatum/St. John's Wort treatment) prior to the first dose of the study drug will not be allowed to participate in the study. During the study, co-administration of strong inducers and inhibitors of CYP3A with fruquintinib should be avoided unless investigators consider it necessary. In this case, fruquintinib efficacy reduction or toxicity increases resulting from the interaction should be closely monitored.

Not all the medications are listed in the following tables. Other drugs known possibly to affect CYP3A activity and to be substrates of P-gp and BCRP should be used with caution. When combining fruquintinib with other drugs the prescription information of all concomitant medications should be reviewed.

Table 18 Typical Strong Inhibitors of CYP3A4

Strong Inhibitors of CYP3A4
Boceprevir
Clarithromycin
Conivaptan
Elvitegravir/Ritonavir
Fluconazole
Grapefruit juice[a,b]
Indinavir
Itraconazole
Ketoconazole
Lopinavir/Ritonavir
Mibefradil
Nelfinavir
Posaconazole
Ritonavir
Saquinavir
Telaprevir
Telithromycin
Tipranavir/Ritonavir
Troleandomycin
Voriconazole

a Super-concentrated grapefruit juice

b During the study, patients should not consume large amounts of grapefruit or lime (or products that include these fruits, such as grapefruit juice, Seville oranges, and orange jam). No more than one cup (120 mL) of grapefruit juice, half a grapefruit or a spoon full (15 g) of orange jam should be consumed each day.

Table 19 Typical Strong Inducers of CYP3A4

Strong Inducers of CYP3A4
Apalutamide
Avasimibe
Carbamazepine
Enzalutamide
Mitotane
Phenobarbital
Phenytoin
Rifabutin
Rifampin (or rifampicin)
St. John's wort

Table 20 Sensitive Substrates of P-gp or BCRP

Substrates of P-gp	Substrates of BCRP
Aliskiren	Methotrexate
Ambrisentan	Mitoxantrone
Colchicine	Imatinib
Dabigatran etexilate	Irrinotecan
Digoxin	Lapatinib
Everolimus	Rosuvastatin
Fexofenadine	Sulfasalazine
Imatinib	Topotecan
Lapatinib	
Maraviroc	
Nilotinib	
Posaconazole	
Ranolazine	
Saxagliptin	
Sirolimus	
Sitagliptin	
Talinolol	
Tolvaptan	
Topotecan	

APPENDIX 5 STUDY PLAN

Table 21 Summary of Clinical Trial Program of Fruquintinib in China and the US*

Study Number NCT# (Name) Indication	Study Title	Study Objectives and Phase	Study Subjects	Study Design
Studies in Cancer Patients				
2013-013-00CH1 NCT01645215 (FRESCO) 3rd+ line mCRC	A Phase III clinical trial of Fruquintinib or placebo in treatment of advanced colorectal cancer patients who have progressed after second-line chemotherapy	Confirmatory safety/efficacy. Phase 3	Fruquintinib: N=278; Placebo: N=138 (Total: 416)	Randomized, double-blind, placebo-controlled, multicenter Phase III clinical trial
2015-013-00US1 NCT03251378 Advanced solid tumors; Refractory mCRC	A Multi-Center, Open-Label, Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Anticancer Activity of Fruquintinib in Patients with Advanced Solid Tumors of any Type, and in Patients with Refractory Metastatic Colorectal Cancer	Safety, Tolerability, PK Phase 1/1b	N=130 (planned)	Two-phase, open-label multi-center study. Phase 1/1b: dose escalation phase Phase 2: expansion phase
2009-013-00CH1 NCT01645215 Advanced solid tumors	A single center, open label, and dose escalation study to determine the maximal tolerated dose (MTD) and safety of fruquintinib in patients with advanced malignant solid tumors	Dose escalation: safety, tolerability, and PK Dose expansion: safety, tolerability, PK and preliminary efficacy; Phase 1	N=40	Two stages: Open-label, single center study Stage 1: dose escalation Stage 2: selected dose regimen expansion
2012-013-00CH3 NCT01975077 3rd or above line mCRC	A Phase Ib, Randomized, Open-Label Study for Comparing Two Different Dosing Regimens of Fruquintinib as Third-Line or up Therapy for Advanced Colorectal Cancer in Patients Who Had Failed with Standard Therapy	Compare two dosing regimens of fruquintinib. (Safety, tolerability, PK, preliminary efficacy) Phase 1b	N=62	Randomized, two-stage, open-label, multicenter study. Stage 1: two arms, two dose regimens, randomized Stage 2: selected dose regimen expansion

Table 21 Summary of Clinical Trial Program of Fruquintinib in China and the US*

Study Number NCT# (Name) Indication	Study Title	Study Objectives and Phase	Study Subjects	Study Design
2012-013-00CH1 NCT02691299 3rd line mCRC	A Randomized, Double-blind, Placebo-controlled, Multi-center Phase II Clinical Trial to Evaluate the Efficacy and Safety of Fruquintinib Plus Best Supportive Care in advanced colorectal cancer patients who have progressed after second-line chemotherapy	PFS (Fruquintinib versus PBO), OS, ORR, safety Phase 2	Fruquintinib: N=47; Placebo: N=24 Total N=71	Randomized, double-blind, placebo-controlled, multicenter study
2014-013-00CH1 NCT02590965 3rd line NSCLC	A Randomized, Double-blind, Placebo-controlled, Multi-center Phase II Clinical Trial to Evaluate the Efficacy and Safety of Fruquintinib Plus Best Supportive Care in Patients With Advanced Non-squamous Non-small Cell Lung Cancer	(Fruquintinib versus PBO), OS, ORR, safety Phase 2	Fruquintinib N=61. Placebo: N=30 Total N=91	Randomized, double-blind, placebo-controlled, multicenter study
2015-013-00CH1 NCT02691299 (FALUCA) 3rd line NSCLC	A Randomized, Double-blind, Placebo-controlled, Multi-center Phase III Clinical Trial in Patients With Advanced Non-squamous Non-small Cell Lung Cancer Treated With Fruquintinib	Confirmatory efficacy and safety NSCLC. Phase 3	Fruquintinib N=352 Placebo N= 171 Total N=523	Randomized, double-blind, placebo-controlled, multicenter study
2017-013-00CH1 NCT03223376 2nd line gastric cancer	A Phase III Study to Evaluate the Efficacy and Safety of Fruquintinib in Combination With Paclitaxel Versus Paclitaxel Alone in Second Line Gastric Cancer	Phase 3	N=544 (planned)	Randomized, double-blind, placebo-controlled, multicenter study
2014-013-00CH3 NCT02415023 2nd line gastric cancer	A Phase Ib/2 Clinical Study to Evaluate the Safety, Pharmacokinetic Characteristics and Preliminary Efficacy of Fruquintinib Combined With Paclitaxel in Patients With Advanced Gastric Cancer	(Fruquintinib + paclitaxel combo), safety, tolerability, PK, preliminary efficacy Phase 1b/2	N=34	Two-stage, open-label, multicenter study. Stage 1: dose escalation. Stage 2: selected dose regimen expansion (combination + paclitaxel)

Table 21 Summary of Clinical Trial Program of Fruquintinib in China and the US*

Study Number NCT# (Name) Indication	Study Title	Study Objectives and Phase	Study Subjects	Study Design
2016-013-00CH1 NCT02976116 1st line NSCLC, EGFR+ sensitive EGFR+ (combo with gefitinib)	Fruquintinib in Combination With Gefitinib as First-line Therapy in Patients With Advanced Non-squamous Non-small-cell Lung Cancer Harboring Activating EGFR Mutations : a Single-arm, Multicenter, Phase II Study	Phase 2	N=40 (planned)	Randomized, double-blind, placebo-controlled, multicenter study
2017-013-00CH2 NCT03684967	Study of Fruquintinib (HMPL-013) in High Risk Patients With Advanced NSCLC	Phase 2	Cohort 1: N=25 Cohort 2: N=75 (planned)	Open-label, single arm, 2 cohorts, multi-center Cohort 1: patients of ≥75 years of age and ECOG PS of 0 to 2; Cohort 2: patients of 18 to 75 years of age and ECOG PS of 0 to 2
Studies in Healthy Volunteers				
2012-013-00CH2 NCT01955304	A Single-Center, Randomized, Open-Label, Single-Dose, Two-Cycle, and Cross-over Clinical Trial to Investigate the Effect of Food on Pharmacokinetics of Fruquintinib Capsule in Healthy Subjects	Primary: to determine the effect of food on the PK Secondary: to assess the safety and tolerability; to verify the major metabolites; and to explore the excretion of fruquintinib Phase 1	Healthy males N=29	Randomized, open-label, two-period crossover, two-stage, single center, food effect study Stage 1: dose escalation. Stage 2: selected dose regimen expansion
2013-013-00CH2	A Single Center, Open-label, Randomized, Two-period Crossover Study to Evaluate the Pharmacokinetics and Bioequivalence in Healthy Male Chinese Volunteers Following Single Doses of Fruquintinib Capsules Produced by Two Different Manufacturers	Primary: to determine the bioequivalence of fruquintinib produced at two manufacturing sites. Secondary: to assess the safety and tolerability Phase 1	Healthy males N=28	Randomized, open-label, two-period crossover, two-stage, single center study. Stage 1: Exploring preliminary study. Stage 2: Bioequivalence study

Table 21 Summary of Clinical Trial Program of Fruquintinib in China and the US*

Study Number NCT# **(Name)** **Indication**	**Study Title**	**Study Objectives and Phase**	**Study Subjects**	**Study Design**
2014-013-00CH5	A Single Center, Open-label, Randomized, Two-period Crossover Study to Evaluate the Pharmacokinetics and Bioequivalence in Healthy Male Chinese Volunteers Following Single Doses of Fruquintinib Capsules Produced by Two Different Manufacturers	Primary: to assess the bioequivalence of fruquintinib produced at two manufacturers; Secondary: safety, explore metabolism and excretion Phase 1	Healthy Males N=24	Randomized, open-label, two-period crossover, two-stage, single center study.
2015-013-00CH2 NCT02689752	Absorption, Metabolism and Excretion of [^{14}C] Fruquintinib in Healthy Male Volunteers after a Single Oral Administration of 5mg/100 μCi/Subject of [^{14}C] Fruquintinib	Evaluate mass balance in healthy male volunteers following a single oral administration of 5 mg/100 μCi/Subject of [^{14}C] fruquintinib Phase 1	Healthy Males N=6	To investigate the absorption, drug biotransformation and mass balance and to evaluated the PK and safety of fruquintinib. To identify the compound's major metabolites

Source: Fruquintinib Investigator's Brochure

*See the Fruquintinib Investigator's Brochure for up-to-date information.

APPENDIX 6 CLINICAL EVALUATION OF POSSIBLE DRUG-INDUCED LIVER INJURY (DILI)

If ALT or AST is elevated to higher than 3 x ULN **and** bilirubin is elevated to higher than 2 X ULN, treatment should be discontinued immediately, and supportive treatment should be given. This combination of lab abnormalities meets the biochemical criteria for Hy's law, which is associated with a markedly increased possibility of severe drug-induced liver injury (DILI), and may progress to liver transplantation or death (FDA Guidance for Industry - Drug-Induced Liver Injury: Premarketing Clinical Evaluation. FDA, 2009).

If the biochemical criteria for Hy's law are met, fruquintinib should be immediately discontinued, and patients need to be very closely monitored (bilirubin, ALP, AST, and ALT measured 2-3 times weekly until the results return to baseline or normal), and other causes of liver injury evaluated (eg, new or worsening hepatobiliary metastases; non-malignant biliary obstruction; viral hepatitis A, B, or C; alcoholic or autoimmune hepatitis; preexisting or acute liver disease; ischemic liver injury; right-sided congestive heart failure; new or worsening liver metastases; or concomitant medication that could cause the observed injury). Consultation with a gastroenterologist or hepatologist should be considered.

If the biochemical criteria for Hy's Law have been met, expedited reporting is required (see Section 8.1), before waiting for the evaluation of other causes to be completed.

Recommended Data Collection for Suspected DILI

The investigator is recommended to obtain the following information, so as to further evaluate and follow up and complete the clinical data. Data should be recorded on eCRFs where possible, and supplemented by investigator reporting as text in the clinical database:

- Medical history of the patient
    - Detailed history of current symptoms, diagnosis of complications and medical history
    - Previous medical history (viral hepatitis, alcoholic hepatitis, autoimmune disease, biliary tract disease and cardiovascular disease, etc.)
    - History of concomitant medication (including OTC and prescription drugs, herbal medicine and dietary supplements), alcohol consumption, recreational drugs and special diet
    - History of exposure to potentially hepatotoxic chemicals
- Complete the following laboratory tests:
    - Hematology
    - Clinical biochemistry: ALT, AST, bilirubin (including total bilirubin and direct bilirubin), ALP, albumin, PTT or INR, amylase, lipase, fasting blood glucose, cholesterol and triglycerides
    - Other Serum Tests: Hepatitis A (Anti-IgM and Anti-IgG), hepatitis B (HbsAg, Anti-HBs and HBV DNA), hepatitis C (Anti-HCV, and HCV RNA test is required for any patient with positive test result), hepatitis D (Anti-IgM and Anti -IgG), hepatitis E (Anti-HEV and Anti-HEV IgM).
- Complete appropriate auxiliary examination:

- Patients with confirmed elevation of ALT/AST combined with TBili are required to receive abdominal ultrasonography or other clinically applicable imaging examination within 48 hours (to exclude biliary tract, pancreatic, or intrahepatic causes, such as new or worsening hepatobiliary metastases or biliary calculi) and obtain the liver imaging result as soon as possible. If an alternative cause (such as biliary tract, pancreatic, or intrahepatic causes) of abnormal hepatic results cannot be confirmed by imaging, consultation with a gastroenterologist or hepatologist should be considered ;
- If suspected cardiovascular causes exist, cardiac ultrasonography is recommended to exclude cardiovascular dysfunction (ie, right heart failure);

Long-term follow-up: Perform close monitoring on the patient through repetitive tests of ALT, AST and bilirubin (including total bilirubin and direct bilirubin) two to three times weekly until the laboratory ALT and/or AST abnormality becomes stable or recovers, and then proceed according to the protocol.

APPENDIX 7 CLINICAL MANAGEMENT OF SEVERE OR SERIOUS HEMORRHAGIC EVENTS

If hemorrhagic events are evaluated as severe (CTCAE grade ≥3) or SAEs, study treatment should be discontinued or interrupted immediately, and appropriate treatment measures initiated to control bleeding (eg transfusion, radiologic, endoscopic, or elective operative intervention as indicated). When the patient is not well enough to tolerate an invasive procedure or operation, best supportive care is given (see Section 7.5.6.2). Patients need to be very closely monitored, both clinically (continuously), and by relevant laboratory testing (INR, aPTT, platelet count, hemoglobin) every 2-3 days until the results return to baseline or normal). During the initial assessment, a focused history and physical examination, with collection of vital signs and laboratory evaluation and imaging evaluation should be obtained, aimed at determining the time of onset, location, severity of bleeding, and whether bleeding is ongoing. Clinicians should be mindful of comorbidities and concomitant treatments (eg. anti-platelet therapy and/or thrombocytopenia, or liver disease) that could also contribute to bleeding and manage them as appropriate. Consultation with other department clinicians should be considered when necessary.

If a hemorrhagic event is evaluated as a severe (CTCAE grade ≥3) or SAE after taking fruquintinib, the investigator is required to report the event in an expedited fashion (within 24 hours of first awareness) to sponsor (see Section 8.2.2).

See Figure 2 below for guidance on the management of severe or serious hemorrhage at any site.

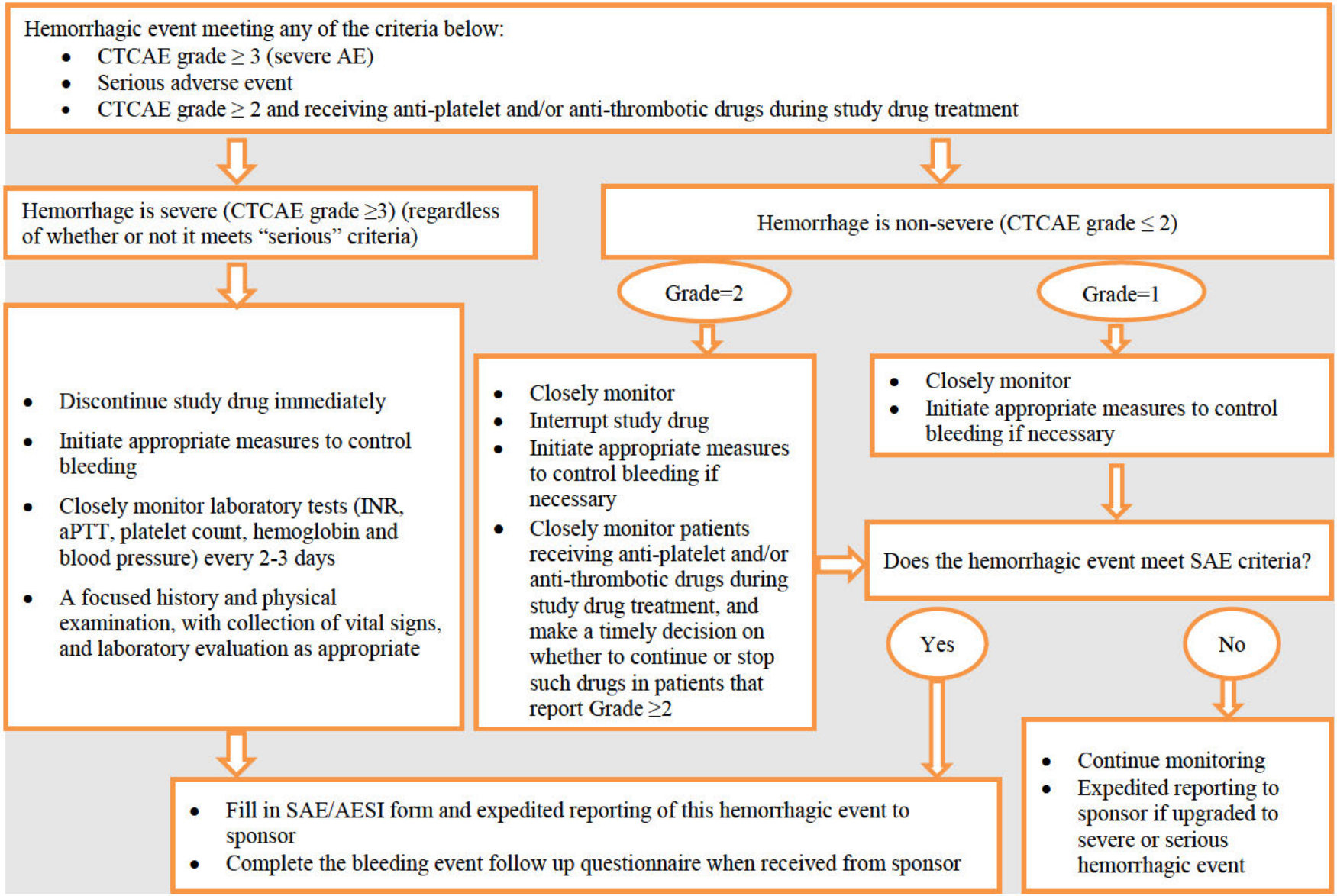
Recommended Data Collection for Severe or Serious Hemorrhagic Events:

The investigator is recommended to obtain the following information, so as to further evaluate and follow up and complete the clinical data. Data should be recorded on SAE/AESI report form where possible, and supplemented by Bleeding Event Follow-Up Questionnaire:

- Medical history of the patient
  - Detailed history of current symptoms, diagnosis of complications and medical history
  - Previous medical history
  - History of concomitant medication (
    - Vitamin K antagonists (eg warfarin)
    - NSAIDs (eg aspirin)
    - Anti-platelet drugs (eg, clopidogrel/glycoprotein GPIIb/IIIa inhibitors/dipyridamole)
    - Other anticoagulants (eg heparin/thrombolytics/SSRIs)
    - Food and herbal supplements with anticoagulant property
    - Immunosuppressants
    - Alcohol consumption
    - Recreational drugs and special diet
  - Family history of bleeding events
- Complete the following laboratory tests:
  - Hematology: hemoglobin, platelet, hematocrit, reticulocyte count
  - Clinical biochemistry: bleeding time, PTT, aPTT, INR
- Complete appropriate auxiliary examination:
  - Patients with confirmed bleeding are required to receive upper or lower GI endoscopy, bronchoscopy or other clinically applicable procedure or radiologic imaging within 48 hours, to confirm the site of bleeding.

- If suspected cardiovascular causes exist, cardiac ultrasonography is recommended to exclude cardiovascular dysfunction (ie, right heart failure).

Figure 2 Severe or Serious Hemorrhagic Events Management Flow Chart



APPENDIX 8 MANAGEMENT OF HYPERTENSION IN PATIENTS RECEIVING FRUQUINTINIB

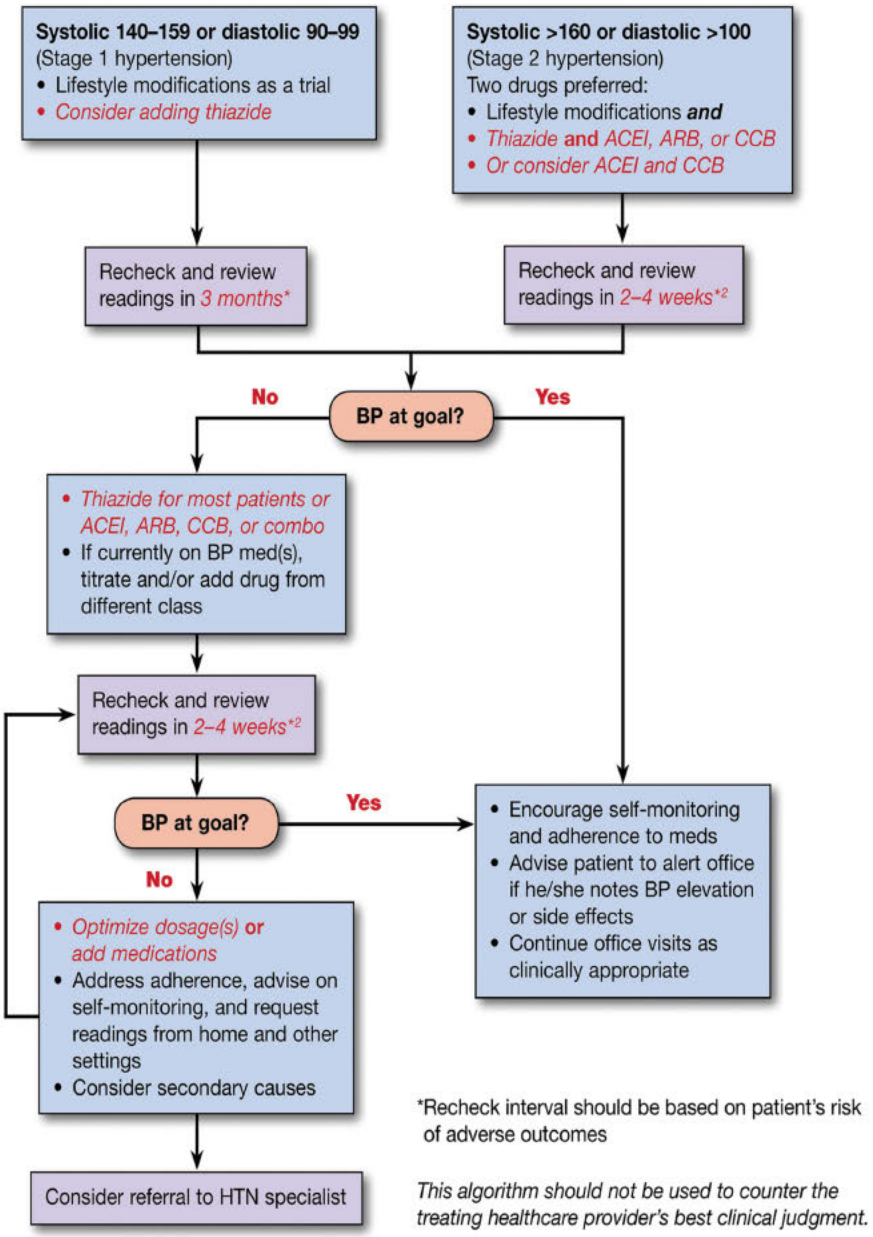
Hypertension is a common AE that has been reported in patients taking angiogenesis inhibitors (Izzedine 2009), including fruquintinib. Grade 3 AEs have been reported in 16% of patients treated with fruquintinib; no Grade 4 events have been reported to date. It appears that hypertension is a class-effect of VEGFR inhibitors (either antibodies or small molecules).

There is no standard therapy for angiogenesis inhibitor-induced hypertension because there have not been any published controlled clinical trials with specific agents. Therefore, one can take an approach based on the clinical characteristics of particular patients. Calcium channel blockers and angiotensin converting enzyme inhibitors (ACEI) are a reasonable first choice in most cases. For patients with proteinuria, chronic renal disease or metabolic disease, an ACE inhibitor or angiotensin II receptor blockers (ARB) may be preferred; for elderly patients, dihydropyridine calcium channel blockers may be preferred. In this appendix is a summary of the most recent American Heart Association (AHA)/American College of Cardiology (ACC) hypertension treatment guidelines. A cardiologist may be consulted if appropriate.

The objective of antihypertensive therapy in general is to control the blood pressure to a target level <140/90 mmHg. For high-risk populations, such as patients with chronic renal disease and/or diabetes, it may be appropriate to aim for a target blood pressure < 130/80 mmHg. On the following two pages (Figure 3), please see a summary of the most recent AHA/ACC hypertension treatment guidelines.

Figure 3 Schema from American Heart Association/ American College of Cardiology for Controlling Hypertension in Adults

Controlling Hypertension in Adults[1]



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Controlling Hypertension in Adults

The blood pressure (BP) goal for an individual is set by utilizing a combination of factors including scientific evidence, clinical judgment, and patient tolerance. For most people, the goal is <140 and <90;[3] however, lower targets may be appropriate for some populations such as African-Americans, the elderly, or patients with LV hypertrophy, systolic or diastolic LV dysfunction, diabetes mellitus or chronic kidney disease. Lifestyle modifications (LM) should be initiated in all patients with hypertension (HTN) and they should be assessed for target organ damage and existing cardiovascular disease. Self-monitoring[4] is encouraged for most patients throughout their care, and requesting and reviewing readings from home and community settings can help the provider assist the patient in achieving and maintaining good control. For patients with hypertension in combination with certain clinical conditions, specific medications should be considered first-line treatments.

Suggested Medications for Treatment of Hypertension in Presence of Certain Medical Conditions

- Coronary artery disease/Post MI: *BB, ACEI*
- Systolic heart failure: *ACEI or ARB, BB, ALDO ANTAG, thiazide*
- Diastolic heart failure: *ACEI or ARB, BB, thiazide*
- Diabetes: *ACEI or ARB, thiazide, BB, CCB*
- Kidney disease: *ACEI or ARB*
- Stroke or TIA: *thiazide, ACEI*

Lifestyle Modifications[3] (LM)

Modification	Recommendation	Approximate SBP Reduction (Range)**
Reduce weight	Maintain normal body weight (body mass index 18.5–24.9 kg/m^2)	5–20 mm Hg/10 kg
Adopt DASH*[5] eating plan	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat	8–14 mm Hg
Lower sodium intake[6]	a. Consume no more than 2,400 mg of sodium/day; b. Further reduction of sodium intake to 1,500 mg/day is desirable since it is associated with even greater reduction in BP; and c. Reduce intake by at least 1,000 mg/day since that will lower BP, even if the desired daily sodium intake is not achieved	2–8 mm Hg
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 min per day, most days of the week)	4–9 mm Hg
Moderation of alcohol consumption	Limit consumption to no more than 2 drinks (e.g., 24 oz beer, 10 oz wine, or 3 oz 80-proof whiskey) per day in most men, and to no more than 1 drink per day in women and lighter weight persons	2–4 mm Hg

*DASH, dietary approaches to stop hypertension
**The effects of implementing these modifications are dose and time dependent, and could be greater for some individuals

Abbreviations

ACEI, angiotensin-converting-enzyme inhibitor; ALDO ANTAG, aldosterone antagonist; ARB, angiotensin II receptor blocker; BB, β-blocker; BP, blood pressure; CCB, calcium channel blocker; HTN, hypertension; MI, myocardial infarction; SBP, systolic blood pressure; TIA, transient ischemic attack

References

1. Go AS, Bauman M, Coleman King SM, Fonarow GC, Lawrence W, Williams K, Sanchez E. An effective approach to high blood pressure control: a science advisory from the American Heart Association, the American College of Cardiology, and the Centers for Disease Control and Prevention. *Hypertension.* 2013: published online before print November 15, 2013, 10.1161/HYP.0000000000000003.
2. Jaffe MG, Lee GA, Young JD, Sidney S, Go AS. Improved Blood Pressure Control Associated with a Large-Scale Hypertension Program. *JAMA.* 2013;310(7):699-705.
3. National Heart, Lung, and Blood Institute, National Institutes of Health. *The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure — Complete Report.* National Heart, Lung, and Blood Institute, National Institutes of Health. NIH Publication No. 04-5230, 2004.
4. Centers for Disease Control and Prevention. *Self-Measured Blood Pressure Monitoring: Action Steps for Public Health Practitioners.* Atlanta, GA: Centers for Disease Control and Prevention, US Dept of Health and Human Services; 2013.
5. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med.* 2001;344:3-10.
6. Eckel RH, Jakicic JM, Ard JD, Hubbard VS, de Jesus JM, Lee I-M, Lichtenstein AH, Loria CM, Millen BE, Houston Miller N, Nonas CA, Sacks FM, Smith SC Jr, Svetkey LP, Wadden TW, Yanovski SZ. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013: published online before print November 12, 2013, 10.1161/01.cir.0000437740.48606.d1.

Hypertension Guidelines From: Go A, Bauman M, Coleman King S, et al. An Effective Approach to High Blood Pressure Control. A Science Advisory from the American Heart Association, the American College of Cardiology, and the Centers for Disease Control and Prevention. *J Am Coll Cardiol* 2014; 63:1230-8.

APPENDIX 9 CONVERSION TABLES FOR URINALYSIS RESULTS

Blood			**Leucocytes**		
Negative	0	0 cells/μL	Negative	0	<10 mg/dL
Trace	1+	1-24 cells/μL	Trace	1+	11-99 mg/dL
Small	2+	25-79 cells/μL	Small	2+	99-299 mg/dL
Medium	3+	80-199 cells/μL	Medium	3+	300-999 mg/dL
Large	4+	≥ 200 cells/μL	large	4+	>1000 mg/dL

Proteinuria		
NCI-CTCAE Grade	Protein by urinalysis	24-hour protein quantitation
1	1+	<1.0g
2	2+	<2.0g
2	≥2+	<3.5 g (excluding 3.5 g)
3	N/A	≥3.5 g

APPENDIX 10 COCKGROFT GAULT FORMULA

The Cockcroft-Gault formulas are as follows:

- CrCl (male) = ([140-age] × weight in kg)/(serum creatinine × 72)
- CrCl (female) = CrCl (male) × 0.85

Source: Cockcroft 1976

APPENDIX 11 AMENDMENT HISTORY

Amendment 3.1 (25 March 2021)

This 2019-013-GLOB1 Protocol Amendment 3.1 was an administrative amendment to correct a formatting numbering error in the Inclusion Criteria (Section 5.3) and to add a clarification in Table 14 in the 2019-013-GLOB1 Protocol Amendment 3.

Amendment 3 (16 March 2021)

Section	Summary of Change	Rationale for Change
Section 4.1.2.3 - Temporary Change of Pharmacokinetic Sampling, Holter Monitor QTc Evaluations, and Circulating Tumor DNA Sample Collection	Addition of notes regarding temporary change of PK sampling, electrocardiogram (ECG) collection, and ctDNA sample collection	Delays in laboratory kit production and delivery resulting from COVID-19-related disruptions
Section 6.1.1.17 - Electrocardiograms Monitoring	Addition of notes regarding temporary change of PK sampling, ECG collection, and ctDNA sample collection	Delays in laboratory kit production and delivery resulting from COVID-19-related disruptions
Table 2 Schedule of Events for Dense Pharmacokinetic and Electrocardiogram Evaluations for the Subset of Approximately 120 Patients (revised title) Table 3 Schedule of Events for Sparse Pharmacokinetic and Electrocardiogram Evaluations for Patients Not Included in the Approximately 120 Patients in the Subset in Table 2 (revised title)	Revised table titles to reflect that first 120 patients did not have dense PK sampling	Due to COVID-related supply chain issues, dense PK sampling and concurrent Holter ECG monitoring were not performed on first 120 patients in the study but will be sampled in approximately 120 patients
Section 1 - Synopsis, Exclusion Criteria #5 Section 5.4 - Exclusion Criteria #5	Added urinalysis along with urine dipstick for initial evaluation for protein in urine during screening	To align with current clinical practice as dipsticks are not used universally
Section 9.2.5.1.1 - Primary Endpoint - Overall Survival	Specified that the hazard ratio between the fruquintinib and placebo groups will be calculated from a stratified Cox proportional hazard model stratified by the randomization stratification factors	Clarification
Section 1 - Synopsis, Exclusion Criteria #14 Section 5.4 - Exclusion Criteria #14	Deleted the reference to Appendix 4 for concomitant medications with a known risk of causing QT prolongation and/or torsades de pointes as these details are not located in the appendix	Clarification of the location from a reference to Appendix 4 to appropriate web site

Section	Summary of Change	Rationale for Change
Table 1 Schedule of Events	Added the option of conducting some assessments up to and including Cycle 1, Day 1	Providing the sites with flexibility for timing of assessments
Section 7.1 - Study Drug Administration	Specified that study drug should be administered around the same time each day and that a missed dose can be administered within 12 hours of usual administration time	Clarification
Section 7.3.3.1 - Emergency Unblinding	Language changed to encourage, but not require, consultation with the sponsor prior to emergency unblinding of a patient's study treatment allocation	Request by the UK Medicines and Healthcare Products Regulatory Agency (MHRA)
Section 7.5.1 - Prohibited Therapies	Added specification to prohibit live vaccines during the study and for 3 months after the last dose of study drug(s)	Request by the UK MHRA
Section 9.2.5.1.2 - Secondary Efficacy Endpoints (PFS, ORR, DCR, DoR)	Clarified statistical methods	Request by the US Food and Drug Administration (FDA)
Section 2.1 - Study Rationale (formerly Section 2.2) Section 2.2 - Background (formerly Section 2.1)	Moved Study Rationale to the beginning of the Introduction, revised and removed text that was redundant with Background	To align with sponsor-approved template text across all clinical study protocols
Section 10.1 - Good Clinical Practice (revised section header) Section 10.2 - Ethics Review Section 10.3 - Informed Consent Section 10.4 - Data Privacy Section 10.7 - Data Quality Assurance (formerly Section 10.6)	Revised and updated text in Ethical Considerations section.	To align with sponsor-approved template text across all clinical study protocols
Section 10.3 – Ethical Conduct of the Study (deleted section) Section 11.2.3 – Protocol Deviation (deleted section) Section 11.2.4.2 – Study Files (deleted section)	Deleted sections	To remove text that was redundant with other sections in other section of Section 10 and align with sponsor-approved template text across all clinical study protocols
Section 10.6 - Biological Specimens and Data	Added section	To align with sponsor-approved template text across all clinical study protocols

Section	Summary of Change	Rationale for Change
Section 11.2 - Quality Control and Assurance Section 11.2.1 - Monitoring Section 11.2.2 - Audits Section 11.2.3.2 - Source Documentation Section 11.2.3.3 - Records Retention	Revised subsections under Oversight	To align with sponsor-approved template text across all clinical study protocols
Section 2.1.1 – Administration Regimen (deleted section)	Deleted section	To remove text that was redundant with information in Section 7.1 and align with sponsor-approved template text across all clinical study protocols

Amendment 2 (30 October 2020)

Section	Summary of Change	Rationale for Change
Section 1 - Synopsis - Study Design Section 5.1 - Recruitment Section 9.1.2 - Sample Size Rationale	Changed estimated number of subjects to 687.	Change made to increase the statistical power of the study from 80% to 90%.
Section 1 - Synopsis – Inclusion Criteria #3 Section 5.3 - Inclusion Criteria #3	Provided country level flexibility for molecular characterization of MSI/MMR status.	MSI/MMR status not available for determination in every country.
Section 1 - Synopsis – Inclusion Criteria #6 Section 5.3 - Inclusion Criteria #6	Added clarifying language for the inclusion of subjects post receipt of oxaliplatin in the adjuvant setting.	Clarified language.
Section 1 - Synopsis – Inclusion Criteria #11 Section 5.3 - Inclusion Criteria #11	Clarified contraception language.	Change made per Belgian Health Authority (HA) request.
Section1 - Synopsis - Inclusion Criteria #12 Section 5.3 - Inclusion Criteria #12	Added new inclusion criterion to address previous treatment with BRAF inhibitor.	Per German HA request. BRAF inhibitors are not approved and available in every country.
Section1 - Synopsis - Exclusion Criteria #5 Section 5.4 - Exclusion Criteria #5	Added clarifying language.	To correct inconsistency
Section 1 - Synopsis - Exclusion Criteria #19 Section 5.4 - Exclusion Criteria #19	Added “(or 5 half-lives)” to the “within 2 weeks” amount of time from use of CYP3A4 inhibitors prior to first dose of study drug.	Belgian HA request
Section 1 - Synopsis - Exclusion Criteria #31 Section 5.4 - Exclusion Criteria #31	Added “including the azo dyes Tartrazine - FD&C Yellow 5 and Sunset yellow FCF - FD&C Yellow 6” to the Exclusion Criteria.	Belgian and German HA request

Section	Summary of Change	Rationale for Change
Section 1 - Synopsis - Exclusion Criteria #32 Section 5.4 - Exclusion Criteria #32	Added in Exclusion Criteria for previous treatment with fruquintinib.	Clarification
Section 1 - Synopsis - Exclusion Criteria #33 Section 5.4 - Exclusion Criteria #33	Added in an exclusion criterion for vaccine use prior to enrollment.	Additional detail
Section 1 - Synopsis - Number of Sites	Increased planned number of sites from 100 sites to 140 sites.	Change to reflect the planned increase in number of patients in study.
Section 1 - Synopsis - Study Duration	Increased study duration.	Change to reflect the planned increase in number of subjects.
Section 1.1 - Study Schematic	Updated Figure 1 by adding "Prior treatment with an immune checkpoint inhibitor of BRAF inhibitor, if indicated".	Clarified language for alignment.
Table 1 Schedule of Events and Footnote 2 Section 6.1.1.3 - Tumor Diagnosis and Treatment History	Added in characterization of MSI/MMR and BRAF mutation in the Tumor Diagnosis and Treatment History assessment.	Clarified language for alignment.
Table 1 Schedule of Events and Footnote 11 (footnote added) Section 6.1.1.12 - Blood Amylase and Lipase (section added)	Added assessments for amylase and lipase.	Per German HA request.
Table 1 Schedule of Events Section 6.1.1.16 - Pregnancy Test	Added "or an equivocal urine pregnancy test" in pregnancy testing requirements.	To ensure an equivocal urine test is followed-up by a more sensitive serum pregnancy test.
Table 2 Schedule of Events for Dense Pharmacokinetic and Electrocardiogram Evaluations for the Subset of Approximately 120 Patients Table 3 Schedule of Events for Sparse Pharmacokinetic and Electrocardiogram Evaluations for Patients Not Included in the Approximately 120 Patients in the Subset in Table 2	Added in a ±10-minute time window for acquisition of PK samples.	Provide more flexibility for sites and less chance of deviations.
Section 4.1.1 - Enrollment in Study	Added additional rationale for 2:1 randomization.	Belgian HA request
Section 5.2 - Definitions	Additional details of randomization.	Belgian HA request
Section 6.1.1.17 - Electrocardiograms Monitoring	Added "All ECGs for the purposes of screening will be performed using standard, local equipment."	Clarified language
Section 6.1.1.3 - Tumor Diagnosis and Treatment History	Clarified requirements for RAS, BRAF, MSI/MMR status.	Italian HA request, to align with IC #3.

Section	Summary of Change	Rationale for Change
Section 6.2.1 - Permanent Discontinuation of Treatment reason #3	Added discontinuation details to intolerable toxicity	German HA request
Section 7.1 - Study Drug Administration	Added instructions for study drug if subject vomits	Added for clarity
Section 7.3.3.1 - Emergency Unblinding	Added language to request sponsor medical monitor notification if possible before emergency unblinding	German HA request
Section 7.5.2 - Permitted Therapies – Permitted Therapies Table 13 Dose Adjustment for Hemorrhage at Any Site Appendix 6 Clinical Evaluation of Possible Drug-Induced Liver Injury (DILI)	Removed paragraph and footnote about monitoring subjects receiving anti-platelet and/or anti-thrombotic drugs.	Belgian HA request
Section 7.5.6.2 - Dose Modification for Important Identified Risks and Potential Risks	Changed title of section to "Dose Modification for Important Identified Risks and Potential Risks	Belgian HA request
Section 7.5.6.2 - Dose Modification for Important Identified Risks and Potential Risks Table 9 Dose Modification for Dermatological Toxicity (revised table heading)	Changed Palmar Plantar Erythrodysesthesia and abbreviation of PPE to more broad term of Dermatological Toxicity.	Belgian HA request
Section 9.1.2 - Sample Size Rationale Section 9.2.1 - Primary Endpoint Section 9.2.2.1 - Key Secondary Endpoint: Progression-free Survival Section 9.2.5.1.1 - Primary Endpoint - Overall Survival Section 9.2.5.1.2 - Secondary Efficacy Endpoints (PFS, ORR, DCR, DoR) Section 9.2.5.1.3 - Multiplicity Adjustment for the Primary Endpoint OS and Key Secondary Endpoint PFS Section 9.4 - Interim Analysis	Additional details added	Clarification of statistical methods
Section 11.3.2 – Protocol Deviations	Edited language	Clarification of responsibilities
Table 1 Schedule of Events	Removed the visit window for cycle 1 day 21	Reflect need for PK sampling 1 day before and 1 day after cycle 1 day 21 visit

Amendment 1 (08 April 2020)

Section	Summary of Change	Rationale for Change
Section 1 Synopsis - Inclusion Criteria, #3 Section 5.3 Inclusion Criteria, #3	Provided additional detail for molecular characterization of RAS, BRAF, and MSI/MMR status	Requested by CHMP
Section 6.2.1 Permanent Discontinuation of Treatment	Added statement that patients may continue to receive treatment following progressive disease by RECIST	Provide clarity as requested by FDA
Section 1 Synopsis - Inclusion Criteria, #4 Section 5.3 Inclusion Criteria, #4	Modified requirement for prior treatment with TAS-102 or regorafenib	Provide additional clarity as requested by FDA
Section 7.5.6.2 Dose Modification for Important Identified Risks Table 9 Dose Modification for Dermatological Toxicity Table 10 Dose Modification for Proteinuria Table 11 Dose Modification for Hypertension Table 12 Dose Adjustment for Decreased Platelet Count Table 13 Dose Adjustment for Hemorrhage at Any Site	Edited "Dose Adjustment" requirements in Table 8, Table 9, Table 10, Table 11, and Table 12 to provide clear guidance	Provide clarity for dose modification requirements for specific adverse events as requested by FDA
Section 1 Synopsis - Exclusion Criteria, #4 Section 5.4 Exclusion Criteria, #4 (deleted)	Removed exclusion criterion #4	Revised in response to FDA comment. Exclusion criterion #4 was redundant with criterion #22 (currently #21), which provides appropriate guidance for resolution of toxicity from prior therapy
Section 1 Synopsis - Inclusion Criteria, #5 Section 5.3 Inclusion Criteria, #5	Added additional detail regarding prior treatment with immune checkpoint inhibitors	Provide additional clarity
Section 8.6.3 Persistent or Recurrent Adverse Events	Removed section	Avoid potential confusion. Details on data entry will be addressed in CRF Completion Guidelines.

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Approval	[redacted]MO 01-Jul-2021 21:21:57 GMT+0000

Approval	[redacted]CSO 02-Jul-2021 14:47:22 GMT+0000

Signature Page for VV-CLIN-000381 v1.0

Statistical Analysis Plan Summary of Changes

Amendment 4

Section	Summary of Change
Section 7.5.3 - Drug-Drug Interactions (Therapies to Avoid or Use with Special Caution)	Removed instruction that subjects should avoid proton pump inhibitor drugs and H2 blockers
Section 1 - Synopsis Section 5.1 - Recruitment	Revised the planned estimated number of study sites from 140 to 160
Section 1 - Synopsis, Inclusion Criterion #4 Section 5.3 - Inclusion Criteria, #4	For the inclusion criterion requiring patients must have received treatment with prior therapy, including anti-VEGF or anti-EGFR, examples of these treatments were added
Section 1 - Synopsis, Exclusion Criterion #5 Section 5.4 - Exclusion Criteria, #5	Changed the protein level for which a 24-hour urine assessment is required.
Section 1 - Synopsis, Exclusion Criterion #6 Section 5.4 - Exclusion Criteria, #6	Added in details for blood pressure assessment process.
Section 1.2 – Schedule of Events Table 1 Schedule of Events	Removed visit window day 21 of cycle 2 and cycle 3
Table 2 Schedule of Events for Dense Pharmacokinetic and Electrocardiogram Evaluations for the Subset of Approximately 120 Patients with Evaluable ECGs	Revised title
Table 3 Schedule of Events for Sparse Pharmacokinetic and Electrocardiogram Evaluations for Patients Not Included in the Approximately 120 Evaluable Patients in the Subset in Table 2	Revised title
Table 1 Schedule of Events Section 1.2.1 - Footnotes for Schedule of Events Table 1, #21 (footnote removed) Section 6.1.1.21 - Circulating Tumor DNA	Removed requirement for the collection of blood to evaluate ctDNA. Further noted that analysis of ctDNA samples collected would be performed according to the statistical analysis plan
Section 6.1.1.17 - Electrocardiograms Monitoring	Added that any subject with a pacemaker should undergo PK and safety ECG evaluations according to the schedule outlined in Table 3
Section 6.1.1.18 - Echocardiogram	Added that echocardiograms completed as standard of care prior to signing the informed consent, but within 28 days of first dose of study treatment, may be used as baseline assessment.
Section 1.2.2 - Footnotes for the Schedule of Events Tables 2 and 3, #4 (footnote added)	Added instruction to refer to the Holter Monitor instruction manual for appropriate timing of the start of the ECG recording.
Appendix 9 Conversion Tables for Urinalysis Results	Added table to aid in conversion of proteins measured by urinalysis for assessment of proteinuria

Amendment 3.1 (25 March 2021)

This 2019-013-GLOB1 Protocol Amendment 3.1 was an administrative amendment to correct a formatting numbering error in the Inclusion Criteria (Section 5.3) and to add a clarification in Table 14 in the 2019-013-GLOB1 Protocol Amendment 3.

Amendment 3 (16 March 2021)

Section	Summary of Change
Section 4.1.2.3 - Temporary Change of Pharmacokinetic Sampling, Holter Monitor QTc Evaluations, and Circulating Tumor DNA Sample Collection	Addition of notes regarding temporary change of PK sampling, electrocardiogram (ECG) collection, and ctDNA sample collection
Section 6.1.1.17 - Electrocardiograms Monitoring	Addition of notes regarding temporary change of PK sampling, ECG collection, and ctDNA sample collection
Table 2 Schedule of Events for Dense Pharmacokinetic and Electrocardiogram Evaluations for the Subset of Approximately 120 Patients (revised title) Table 3 Schedule of Events for Sparse Pharmacokinetic and Electrocardiogram Evaluations for Patients Not Included in the Approximately 120 Patients in the Subset in Table 2 (revised title)	Revised table titles to reflect that first 120 patients did not have dense PK sampling
Section 1 - Synopsis, Exclusion Criteria #5 Section 5.4 - Exclusion Criteria #5	Added urinalysis along with urine dipstick for initial evaluation for protein in urine during screening
Section 9.2.5.1.1 - Primary Endpoint - Overall Survival	Specified that the hazard ratio between the fruquintinib and placebo groups will be calculated from a stratified Cox proportional hazard model stratified by the randomization stratification factors
Section 1 - Synopsis, Exclusion Criteria #14 Section 5.4 - Exclusion Criteria #14	Deleted the reference to Appendix 4 for concomitant medications with a known risk of causing QT prolongation and/or torsades de pointes as these details are not located in the appendix
Table 1 Schedule of Events	Added the option of conducting some assessments up to and including Cycle 1, Day 1
Section 7.1 - Study Drug Administration	Specified that study drug should be administered around the same time each day and that a missed dose can be administered within 12 hours of usual administration time
Section 7.3.3.1 - Emergency Unblinding	Language changed to encourage, but not require, consultation with the sponsor prior to emergency unblinding of a patient's study treatment allocation
Section 7.5.1 - Prohibited Therapies	Added specification to prohibit live vaccines during the study and for 3 months after the last dose of study drug(s)
Section 9.2.5.1.2 - Secondary Efficacy Endpoints (PFS, ORR, DCR, DoR)	Clarified statistical methods
Section 2.1 - Study Rationale (formerly Section 2.2) Section 2.2 - Background (formerly Section 2.1)	Moved Study Rationale to the beginning of the Introduction, revised and removed text that was redundant with Background
Section 10.1 - Good Clinical Practice (revised section header) Section 10.2 - Ethics Review Section 10.3 - Informed Consent Section 10.4 - Data Privacy	Revised and updated text in Ethical Considerations section.

Section 10.7 - Data Quality Assurance (formerly Section 10.6)	
Section 10.3 – Ethical Conduct of the Study (deleted section) Section 11.2.3 – Protocol Deviation (deleted section) Section 11.2.4.2 – Study Files (deleted section)	Deleted sections
Section 10.6 - Biological Specimens and Data	Added section
Section 11.2 - Quality Control and Assurance Section 11.2.1 - Monitoring Section 11.2.2 - Audits Section 11.2.3.2 - Source Documentation Section 11.2.3.3 - Records Retention	Revised subsections under Oversight
Section 2.1.1 – Administration Regimen (deleted section)	Deleted section

Amendment 2 (30 October 2020)

Section	**Summary of Change**
Section 1 - Synopsis - Study Design Section 5.1 - Recruitment Section 9.1.2 - Sample Size Rationale	Changed estimated number of subjects to 687.
Section 1 - Synopsis – Inclusion Criteria #3 Section 5.3 - Inclusion Criteria #3	Provided country level flexibility for molecular characterization of MSI/MMR status.
Section 1 - Synopsis – Inclusion Criteria #6 Section 5.3 - Inclusion Criteria #6	Added clarifying language for the inclusion of subjects post receipt of oxaliplatin in the adjuvant setting.
Section 1 - Synopsis – Inclusion Criteria #11 Section 5.3 - Inclusion Criteria #11	Clarified contraception language.
Section1 - Synopsis - Inclusion Criteria #12 Section 5.3 - Inclusion Criteria #12	Added new inclusion criterion to address previous treatment with BRAF inhibitor.
Section1 - Synopsis - Exclusion Criteria #5 Section 5.4 - Exclusion Criteria #5	Added clarifying language.
Section 1 - Synopsis - Exclusion Criteria #19 Section 5.4 - Exclusion Criteria #19	Added “(or 5 half-lives)” to the “within 2 weeks” amount of time from use of CYP3A4 inhibitors prior to first dose of study drug.
Section 1 - Synopsis - Exclusion Criteria #31 Section 5.4 - Exclusion Criteria #31	Added “including the azo dyes Tartrazine - FD&C Yellow 5 and Sunset yellow FCF - FD&C Yellow 6” to the Exclusion Criteria.
Section 1 - Synopsis - Exclusion Criteria #32 Section 5.4 - Exclusion Criteria #32	Added in Exclusion Criteria for previous treatment with fruquintinib.
Section 1 - Synopsis - Exclusion Criteria #33 Section 5.4 - Exclusion Criteria #33	Added in an exclusion criterion for vaccine use prior to enrollment.
Section 1 - Synopsis - Number of Sites	Increased planned number of sites from 100 sites to 140 sites.
Section 1 - Synopsis - Study Duration	Increased study duration.
Section 1.1 - Study Schematic	Updated Figure 1 by adding “Prior treatment with an immune checkpoint inhibitor of BRAF inhibitor, if indicated”.

Table 1 Schedule of Events and Footnote 2 Section 6.1.1.3 - Tumor Diagnosis and Treatment History	Added in characterization of MSI/MMR and BRAF mutation in the Tumor Diagnosis and Treatment History assessment.
Table 1 Schedule of Events and Footnote 11 (footnote added) Section 6.1.1.12 - Blood Amylase and Lipase (section added)	Added assessments for amylase and lipase.
Table 1 Schedule of Events Section 6.1.1.16 - Pregnancy Test	Added "or an equivocal urine pregnancy test" in pregnancy testing requirements.
Table 2 Schedule of Events for Dense Pharmacokinetic and Electrocardiogram Evaluations for the Subset of Approximately 120 Patients Table 3 Schedule of Events for Sparse Pharmacokinetic and Electrocardiogram Evaluations for Patients Not Included in the Approximately 120 Patients in the Subset in Table 2	Added in a ±10-minute time window for acquisition of PK samples.
Section 4.1.1 - Enrollment in Study	Added additional rationale for 2:1 randomization.
Section 5.2 - Definitions	Additional details of randomization.
Section 6.1.1.17 - Electrocardiograms Monitoring	Added "All ECGs for the purposes of screening will be performed using standard, local equipment."
Section 6.1.1.3 - Tumor Diagnosis and Treatment History	Clarified requirements for RAS, BRAF, MSI/MMR status.
Section 6.2.1 - Permanent Discontinuation of Treatment reason #3	Added discontinuation details to intolerable toxicity
Section 7.1 - Study Drug Administration	Added instructions for study drug if subject vomits
Section 7.3.3.1 - Emergency Unblinding	Added language to request sponsor medical monitor notification if possible before emergency unblinding
Section 7.5.2 - Permitted Therapies – Permitted Therapies Table 13 Dose Adjustment for Hemorrhage at Any Site Appendix 6 Clinical Evaluation of Possible Drug-Induced Liver Injury (DILI)	Removed paragraph and footnote about monitoring subjects receiving anti-platelet and/or anti-thrombotic drugs.
Section 7.5.6.2 - Dose Modification for Important Identified Risks and Potential Risks	Changed title of section to "Dose Modification for Important Identified Risks and Potential Risks
Section 7.5.6.2 - Dose Modification for Important Identified Risks and Potential Risks Table 9 Dose Modification for Dermatological Toxicity (revised table heading)	Changed Palmar Plantar Erythrodysethesia and abbreviation of PPE to more broad term of Dermatological Toxicity.
Section 9.1.2 - Sample Size Rationale Section 9.2.1 - Primary Endpoint Section 9.2.2.1 - Key Secondary Endpoint: Progression-free Survival Section 9.2.5.1.1 - Primary Endpoint - Overall Survival Section 9.2.5.1.2 - Secondary Efficacy Endpoints (PFS, ORR, DCR, DoR)	Additional details added

Section 9.2.5.1.3 - Multiplicity Adjustment for the Primary Endpoint OS and Key Secondary Endpoint PFS Section 9.4 - Interim Analysis	
Section 11.3.2 – Protocol Deviations	Edited language
Table 1 Schedule of Events	Removed the visit window for cycle 1 day 21

Amendment 1 (08 April 2020)

Section	Summary of Change
Section 1 Synopsis - Inclusion Criteria, #3 Section 5.3 Inclusion Criteria, #3	Provided additional detail for molecular characterization of RAS, BRAF, and MSI/MMR status
Section 6.2.1 Permanent Discontinuation of Treatment	Added statement that patients may continue to receive treatment following progressive disease by RECIST
Section 1 Synopsis - Inclusion Criteria, #4 Section 5.3 Inclusion Criteria, #4	Modified requirement for prior treatment with TAS-102 or regorafenib
Section 7.5.6.2 Dose Modification for Important Identified Risks Table 9 Dose Modification for Dermatological Toxicity Table 10 Dose Modification for Proteinuria Table 11 Dose Modification for Hypertension Table 12 Dose Adjustment for Decreased Platelet Count Table 13 Dose Adjustment for Hemorrhage at Any Site	Edited “Dose Adjustment” requirements in Table 8, Table 9, Table 10, Table 11, and Table 12 to provide clear guidance
Section 1 Synopsis - Exclusion Criteria, #4 Section 5.4 Exclusion Criteria, #4 (deleted)	Removed exclusion criterion #4
Section 1 Synopsis - Inclusion Criteria, #5 Section 5.3 Inclusion Criteria, #5	Added additional detail regarding prior treatment with immune checkpoint inhibitors
Section 8.6.3 Persistent or Recurrent Adverse Events	Removed section

Statistical Analysis Plan for Interventional Studies
Text only

SAP Text Version Number: 1.0
SAP Text Date: 25-Mar-2021

Sponsor Name: Hutchison MediPharma Limited

Protocol Number: 2019-013-GLOB1

Protocol Title: 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 (FRESCO-2)

Protocol Version and Date: (DD-Mmm-YYYY): Amendment 2 – Version 1.0 dated 30-Oct-2020
Syneos Health Project Code: 7006046

Authors: [redacted]

Notice of Confidential and Proprietary Information:

Revision History

Version #	Date (DD Mmm YYYY)	Document Owner	Revision Summary
0.1	30-Jun-2020	[redacted]	In t a Re ease Vers on
0.2	18-Nov-2020	[redacted]	Update to address sponsor comments on v0.1 Update to nc ude changes from protoco amendment 2
0.3	14-Jan-2021	[redacted]	Update to address sponsor comments on v0.2
0.4	17-Feb-2021	[redacted]	Update to address sponsor comments on v0.3
0.5	15-Mar-2021	[redacted]	Update to address sponsor comments on v0.4
1.0	25-Mar-2021	[redacted]	Update to address sponsor comments on v1.0

I conf rm that I have rev ewed th s document and agree w th the content.

Approvals		
Syneos Health Approval		
[redacted] Name, T t e Lead B ostat st c an / Support B ostat st c an	S gnature	Date (DD Mmm YYYY)
[redacted] Name, T t e Lead Pharmacok net c st	S gnature	Date (DD Mmm YYYY)
[redacted] Name, T t e	S gnature	Date (DD Mmm YYYY)
Hutchison MediPharma Limited Approval		
[redacted] Sponsor Contact	S gnature	Date (DD Mmm YYYY)
[redacted] Sponsor Contact	S gnature	Date (DD Mmm YYYY)
[redacted] Sponsor Contact	S gnature	Date (DD Mmm YYYY)

Table of Contents

1. Glossary of Abbreviations

Abbreviation	Description
AE	Adverse event
ADaM	Analysis Data Model
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
aPTT	Activated Partial thromboplastin time
AST	Aspartate aminotransferase
ATC 2	Anatomical therapeutic class 2
AR (1)	Autoregressive (1)
BMI	Body mass index
BLQ	Below the lower limit of quantification
BRAF	B-Raf proto-oncogene
BSC	Best supportive care
CEA	Carcino-embryonic antigen
CI	Confidence interval
CMH	Cochran-Mantel Haenszel
COVID-19	Coronavirus 2019
ctDNA	Circulating tumor DNA
CTMS	Clinical trial management system
CR	Complete response
CS	Clinically significant
CSR	Clinical study report
CV	Coefficient of variation
CRO	Clinical research organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
dMMR	Deficient mismatch repair
DCR	Disease control rate
DoR	Duration of response

Abbreviation	Description
eCRF	Electronic case report form
ECHO	Echocardiogram
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of treatment
ERT	eResearchTechnology, Inc.
HR	Hazard ratio
ICF	Informed consent form
IDMC	Independent data monitoring committee
IND	Investigational new drug
INR	International normalized ratio
IRT	Interactive response technology
ITT	Intent-to-Treat
IWRS	Interactive web response system
JSMC	Japanese safety monitoring committee
LDH	Lactate dehydrogenase
LS	Least-square
mCRC	Metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
MSI	Microsatellite instability
MSI-H	Microsatellite instability-high
MID	Minimally important difference
MMR	Mismatch repair
MSS	Microsatellite stable
MMRM	Mixed model repeated measures
MRI	Magnetic resonance imaging
MUGA	Multigated acquisition

Abbreviation	Description
NA	Not available
NCS	Not clinically significant
NE	Not evaluable
ORR	Objective response rate
OS	Overall survival
pMMR	Proficient mismatch repair
PD	Progressive disease
PID	Percentage intended dose
PFS	Progression-free survival
PK	Pharmacokinetic
PO	Per os (oral administration)
PR	Partial response
PR	PR Interval (ECG Parameter)
PT	Preferred term
Q1	Lower quartile
Q3	Upper quartile
QoL	Quality of life
QD	Quaque die (once daily)
QTcB	QT correction Bazett formula
QTcF	QT correction Fridericia formula
QRS	A combination of the Q wave, R wave and S wave
RAS	Rat sarcoma
REML	Restricted maximum likelihood
RD	Relative dose
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SD	Stable disease

Abbreviation	Description
StdDev	Standard deviation
SDTM	Study Data Tabulation Model
SE	Standard error
SI	International System of Units
SOC	System organ class
TLFs	Tables, listings and figures
TSH	Thyroid-stimulating hormone
TTD	Time to deterioration
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
VAS	Visual analogue scale
VEGF	Vascular Endothelial Growth Factor
WHODD	World Health Organization Drug Dictionary

2. Purpose

The purpose of this statistical analysis plan (SAP) for the study is to ensure that the data listings, summary tables and figures that are to be produced, and the statistical methodologies that are used, are complete and appropriate to allow valid conclusions regarding the study objectives. The SAP adheres to the proper regulatory guidelines and most recent International Council for Harmonisation guidelines (E3, E6, E9). All decisions regarding the final analyses, as defined in this SAP document, have been made prior to locking the database; any deviations from these guidelines will be documented in the clinical study report (CSR).

A separate SAP is to be developed for the protocol Japanese Specific Addendum (Safety Lead-In for Japan).

2.1. Responsibilities

Syneos Health is to perform the statistical analyses and are responsible for the production and quality control of all Study Data Tabulation Model (SDTM) datasets, Analysis Data Model (ADaM) datasets, and the tables, listings, and figures (TLFs) for efficacy and safety, as well as tabulation of fruquintinib and M11 concentrations from PK (pharmacokinetic) plasma samples. Details for analysis of circulating tumor DNA and pharmacogenomics will be prepared in a separate document. The SAP for population PK, Electrocardiogram (ECG) (pharmacodynamics) and QTc-PK analysis will be prepared separately by another contract research organization (CRO).

2.2. Timings of Analyses

An independent data monitoring committee (IDMC) is to review descriptive summaries of accumulating safety and subject disposition every 6 months, or at a frequency recommended by the IDMC, as described in the IDMC Charter Final Version 1.0 dated 25-Aug-2020. An unblinded team from Syneos Health Biostatistics is to perform the analyses as described in Section 18, Content of Open and Closed Sessions of the IDMC Charter, in order to maintain the blinding of the study.

2.2.1. Interim Analyses

One interim non-binding futility analysis is to be performed once 1/3 of the total number of overall survival (OS) events (i.e., 160 OS events) have occurred. This interim analysis is for futility only, there are no plans to stop the study early for efficacy based on OS data at the interim analysis.

The IDMC is to be instructed to recommend stopping the study for futility if the 1-sided p-value from a stratified log-rank test is at least 0.772 (corresponding to an observed HR of 1.133). Otherwise, the study is to be continued with full enrollment.

There is a 22.8% chance of terminating the study for futility at the interim analysis if the true median OS in fruquintinib arm is 5 months, i.e., fruquintinib is ineffective. There is a 0.4% chance of stopping for futility, declaring fruquintinib ineffective at the interim if the true median OS in fruquintinib arm is 6.8 months, i.e., fruquintinib is effective in the study population.

2.2.2. Final Analysis

If the study does not stop based on the futility analysis, the final analysis for the CSR will be conducted when at least 480 OS events have been observed. All study data collected up through the time of the final analysis will be summarized, unless otherwise specified. Unblinding will occur at the time of the final analysis.

3. Study Objectives

3.1. Primary Objective

- To evaluate the overall survival (OS) of fruquintinib plus best supportive care (BSC) compared to placebo plus BSC in subjects with refractory metastatic colorectal cancer (mCRC).

3.2. Secondary Objective(s)

- To evaluate progression-free survival (PFS) of fruquintinib plus BSC compared to placebo plus BSC.
- To evaluate the objective response rate (ORR), disease control rate (DCR), and duration of response (DoR).
- To assess the safety and tolerability of fruquintinib plus BSC compared to placebo plus BSC.
- To characterize the PK exposure of fruquintinib and metabolite M11 in subjects with refractory mCRC.
- To evaluate the effect of fruquintinib on cardiac repolarization, as detected by changes in electrocardiogram (ECG) QTc intervals, and the potential relationship with fruquintinib and M11 plasma concentrations.
- To explore the relationship between fruquintinib exposure and endpoints for efficacy and safety.
- To evaluate quality of life (QoL) as assessed by using European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30: cancer-specific; and EQ-5D-5L questionnaires.
- To assess resource utilization (for example, hospitalizations, concomitant medications).

3.3. Exploratory Objective

- To assess potential predictive biomarkers of response to fruquintinib.

Details of the study objectives and correspondent endpoints is provided in Table 1.

Table 1. Objectives and Corresponding Endpoints

Tier	Objectives	Endpoints
Primary	To evaluate the overall survival of fruquintinib plus BSC compared to placebo plus BSC in subjects with refractory mCRC	OS
Secondary	To evaluate progression-free survival of fruquintinib plus BSC compared to placebo plus BSC	PFS
	To evaluate the objective response rate, disease control rate, and duration of response	• ORR • DCR • DoR

Tier	Objectives	Endpoints
	To assess the safety and tolerability of fruquintinib plus BSC compared to placebo plus BSC	Safety including treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), deaths, ECG's, and clinical laboratory abnormalities
	To characterize the PK profile of fruquintinib in subjects 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 electrocardiogram (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 (e.g., OS) and safety (e.g., adverse events [AEs]) endpoints
	To evaluate quality of life (QoL) as assessed by 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 (for example, hospitalizations, medications)	Resource utilization including all concomitant medications, days in hospital
Exploratory	To assess potential predictive biomarkers of response to fruquintinib	• Change from baseline in circulating tumor DNA (ctDNA) • Change from baseline in tumor markers (carcino-embryonic antigen [CEA]) • Pharmacogenomics

4. Study Details/Design

4.1. Brief Description

The study is a global, randomized, double-blind, placebo-controlled, multicenter phase 3 clinical trial to compare the efficacy and safety of fruquintinib plus BSC versus placebo plus BSC in subjects with mCRC. Approximately 687 subjects are to be randomized in a 2:1 ratio to either the fruquintinib plus BSC treatment group or the placebo plus BSC treatment group.

Randomization is stratified by the following factors:

- Prior therapy with trifluridine/tipiracil (TAS-102) versus regorafenib versus both trifluridine/tipiracil (TAS-102) and regorafenib.
- RAS (rat sarcoma) status (wild type versus mutant).
- Duration of metastatic disease (≤18 months versus >18 months).

Subjects are to receive study treatment, with each 4-week cycle consisting of 3 weeks of daily oral study medication and 1 week of study treatment interruption (3 weeks on/1 week off). Tumor evaluation is performed by imaging (computed tomography [CT] or magnetic resonance imaging [MRI] scan) every 8 weeks until there is progressive disease (PD), death, new anti-cancer treatment, study treatment discontinuation or study completion, whichever comes first. Safety parameters include assessment of adverse events (AE), laboratory tests, vital signs, ECG, Echocardiogram (ECHO), physical examination, Eastern Cooperative Oncology Group (ECOG) performance status, EORTC QLQ-C30 and EQ-5D-5L questionnaires. Post-discontinuation anti-tumor treatment and survival follow-up after PD is also recorded.

4.2. Subject Selection

The study is conducted at approximately 140 international study sites with a study population of subjects ≥18 years of age with histologically and/or cytologically documented metastatic colorectal adenocarcinoma who progressed on, or were intolerant to, all standard chemotherapies and relevant biologics and TAS-102 and/or regorafenib.

4.2.1. Inclusion Criteria

Refer to Section 5.3 Inclusion Criteria of the study protocol.

4.2.2. Exclusion Criteria

Refer to Section 5.4 Exclusion Criteria of the study protocol.

4.3. Statistical Hypothesis

This study is 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 is 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).

4.4. Determination of Sample Size

With regards to the study, the total sample size and number of OS events required for efficacy assessment in the intent-to-treat population is calculated based on the following assumptions:

- A one-sided significance level of 0.025;
- Assuming an OS hazard ratio (HR) of 0.73 (fruquintinib arm/placebo arm), this sample size yields approximately 90% statistical power to detect superiority of the fruquintinib arm over placebo arm. 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).
- An enrollment rate of 30 subjects per month during the first 3 months and 50 subjects per month thereafter;
- Yearly dropout rate of 10%;
- Randomization ratio = 2:1 (fruquintinib arm/placebo arm);
- Data maturity = 70%;
- One interim futility analysis when 1/3 of the total number of OS events (i.e., 160 OS events) have occurred, the Lan-DeMets spending function is used in the calculation.

Under the premise of these assumptions, approximately 687 subjects are to be randomized to this study over approximately 15 months in this study. OS is to be analyzed when 480 OS events have been observed, which is expected to occur in approximately 7 months after the end of enrollment. EAST version 6.5 was utilized for the calculation.

In clinical practice, TAS-102 is used more commonly than regorafenib. To ensure that the subject population is representative of clinical practice, post-regorafenib (regorafenib or both trifluridine/tipiracil (TAS-102) and regorafenib) subjects are to be capped at 344. This ensures that at least 50% of the subjects are post-TAS.

Subjects are considered in post-TAS-102 or post-regorafenib populations if they have received at least one dose of either agent, respectively, prior to entering the study. Based on the similar mechanisms of action between regorafenib and fruquintinib, it is to be of clinical interest to evaluate the magnitude of benefit in each of the populations when compared to the intent-to-treat population.

4.5. Treatment Assignment and Blinding

The study subject, investigators, and study site personnel are to remain blinded to all randomization assignments throughout the study. The sponsor's study director, study monitor, and any other sponsor and Syneos Health personnel who are in regular contact with the study site are to remain blinded to all subject randomization assignments, except sponsor pharmacovigilance personnel for the purpose of Investigational New Drug (IND) safety reports. Treatment is allocated using Interactive Web Response System (IWRS) randomization strategy and procedure defined in the IWRS manual.

Unblinding can occur in emergency cases. If unblinding is required for treatment of a subject for an SAE, the investigator must first contact the sponsor's medical monitor before unblinding, and then unblind the subject using the IWRS. Once unblinded, the subject should discontinue the treatment but continue to be followed for safety and efficacy. The investigator should record the event in the source document.

The interim futility analysis maintains blinding at IDMC meetings during the Open Sessions following the procedures described in Section 18, Content of Open and Closed Sessions of the latest version of the IDMC Charter.

4.6. Administration of Study Medication

Fruquintinib (HMPL-013) capsule 5 mg is administered orally (PO) once daily (QD), 3 weeks on, 1 week off (4-week cycles). Subjects are randomized into either fruquintinib in combination with BSC group (treatment group) or placebo in combination with BSC group (control group) in a 2:1 ratio (Figure 1).

If study treatment dose adjustment is required, the site must log into the IWRS, adjust the dose, reassign the drug serial number, and dispense new study treatment dose (in 1 mg capsules) to the subject. If the dose is adjusted a second time, i.e., from 4 mg QD to 3 mg QD, the site must log into the IWRS and record the second dose adjustment. On this occasion, it is not necessary to reassign a new drug serial number. If tumor evaluation shows PD during the previous cycle and new drug has been dispensed, the subject must return all unused study treatment on the 30-day safety visit after end of treatment (EOT).

- Treatment 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.

Subjects are allowed to have no more than 2 dose reductions: one reduction from 5 mg QD to 4 mg QD, and if not tolerated, then a second reduction from 4 mg QD to 3 mg QD. Once a dose has been reduced, it cannot be re-escalated. The dose reduction sequence by starting dose is shown in Table 2 below.

Table 2. Dose Modification Sequence by Starting Dose

Dose Level 0* (Original dose)	5 mg QD 3 weeks on, 1 week off	fruquintinib of 5 mg, 1 capsule, or 1 capsule of the matching placebo
Dose Level -1* (the 1st dose reduction)	4 mg QD 3 weeks on, 1 week off	fruquintinib of 1 mg, 4 capsules, or 4 capsules of the matching placebo
Dose Level -2* (the 2nd dose reduction)	3 mg QD 3 weeks on, 1 week off	fruquintinib of 1 mg, 3 capsules, or 3 capsules of the matching placebo

Reasons for dose modifications includes the following:

- Hematologic and non-hematologic toxicity.

- Palmar-Plantar Erythrodysethesia.
- Proteinuria.
- Hypertension.
- Decreased platelet count.
- Hemorrhage at any site.
- Abnormal live function.

Dose modification guidelines are detailed in Section 7.5.6 of the protocol.

4.7. Study Procedures and Flowchart

The study contains the following procedures.

- Screening Period: This period contains two visits windows of -28 to -1 days and -7 to -1.
- Study Treatment Period: This period contains treatment cycles, with a visit window of +/- 3 days for each scheduled visit starting at Cycle 2 day 1.
    - Cycle 1 includes cycle 1 day 1 and cycle 1 day 21 visits;
    - Cycle 2 includes cycle 2 day 1 and cycle 2 day 21 visits;
    - Cycle 3 includes cycle 3 day 1 and cycle 3 day 21 visits;
    - Cycle 4 and beyond include cycle 4 day 1, cycle 5 day 1, etc.
- Follow-Up: This period contains the following.
    - Post treatment: 7 days after last dose with a visit window of +/- 3 days,
    - Safety Follow-up: 30 days after EOT visit with a visit window of +/- 7 days, and
    - Survival Follow-up: 12 weeks from EOT visit with a visit window of +/- 14 days.
    - EOT: last non-missing assessment during the treatment period (treatment period is from the date of the first study drug administration until 37 days after last dose)

The protocol activities include the following throughout the periods listed above.

- Informed Consent.
- Demographics.

- Medical History, Disease History, and molecular characterization of RAS, B-Raf proto-oncogene (BRAF), Microsatellite Instability (MSI)/ Mismatch Repair (MMR) status.
- Prior and Concomitant Medication/Concomitant Procedure.
- Comprehensive Physical Examination.
- Limited Physical Examination.
- ECOG.
- Vital Signs.
- Hematology.
- Blood Chemistry.
- Blood amylase and lipase.
- Coagulation.
- Thyroid Function.
- Urinalysis.
- Serum Pregnancy Test.
- Urine Pregnancy Test.
- 12-lead ECG.
- ECHO/Multigated acquisition (MUGA).
- Tumor Evaluation/Imaging.
- Tumor Markers.
- Circulating Tumor DNA, excluded from Japanese Specific Addendum.
- PK Plasma Sampling.
- Subject Randomization, excluded from Japanese Specific Addendum.
- Drug/Dispense/Return.
- Study Treatment.
- Adverse Event.

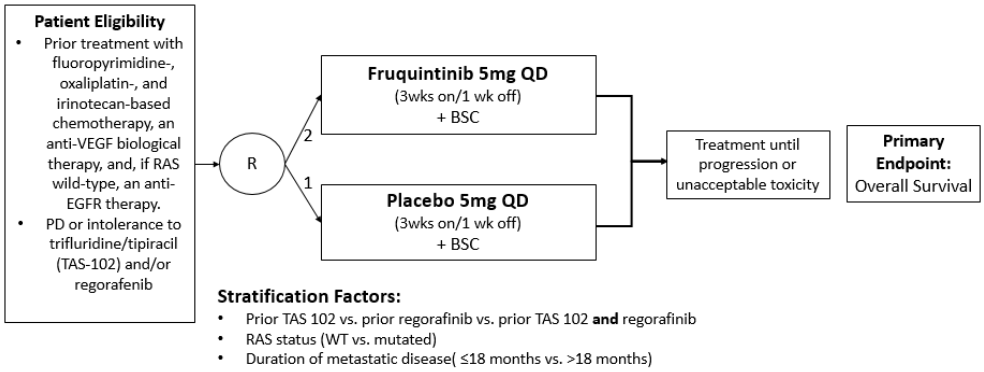
- Survival Follow-up.
- EORTC QLQ-C30 Questionnaire, excluded from Japanese Specific Addendum.
- EQ-5D-5L Questionnaire, excluded from Japanese Specific Addendum.

Details of study procedures can be found in the following tables within the protocols.

- Table 1. Schedule of Events.
- Table 2. Schedule of Events for Pharmacokinetic and Electrocardiogram Evaluations for the First Approximately 120 Subjects, and
- Table 3. Schedule of Events for Pharmacokinetic and Electrocardiogram Evaluations for Subjects Enrolled After the First Approximately 120.

The study schematic is presented in Figure 1.

Figure 1. Study Design Schema



5. Endpoints

5.1. Primary Efficacy Endpoint

The primary endpoint of the study is OS, defined as the time (months) from date of randomization to death from any cause. That is, OS is calculated as (date of death or last known alive – date of randomization + 1)/30.4375. Subjects without report of death at the time of analysis are censored at the date last known alive. Subjects lacking data beyond the date of randomization have their survival time censored at the date of randomization. OS will not be censored if a subject receives subsequent anticancer treatments after discontinuation of the study treatments. Date of last known alive defined in Section 7.2.4 and date of death is defined in Section 7.2.5 of the SAP.

5.2. Secondary Efficacy Endpoints

- Key secondary efficacy endpoint: PFS.

PFS is defined as the time (months) from randomization until the first radiographic documentation of objective progression as assessed by investigator using Response Evaluation Criteria In Solid Tumors (RECIST) v1.1, or death from any cause. More specifically, PFS will be determined using all the assessment data up until the last evaluable visit prior to or on the date of (i) disease progression as defined by RECIST Version 1.1 or death; or (ii) withdrawal of consent; or (iii) receiving subsequent anti-cancer therapy, whichever is earlier. Subjects without report of PD or death from any cause at the time of analysis are censored as described in Table 3 below.

The PFS time will always be derived based on scan dates not tumor assessment dates. If PD is documented between scheduled visits, the actual date of documented progression will be used as an uncensored value in the analysis of PFS. RECIST assessments/scans contributing towards a particular visit may be performed on different dates. The following rules are applied:

1. Date of progression is determined based on the earliest of the dates of the component that triggered the progression.

2. When censoring a subject for PFS, the subject is censored at the latest of the dates contributing to a particular overall visit assessment.

Table 3. Censoring Rules for PFS

Rule	Situation	Date of Progression or Censoring	Outcome
1	PD documented between schedule radiological assessment visits	Date of first documented disease progression	Event
2	Death between scheduled radiological assessment visits Death before first documented PD Death after one missing radiological assessment visit	Date of death	Event
3	Documented PD directly following a missing radiological assessment visit, if having not had disease progression observed previously	Date of first documented disease progression	Event
4	No baseline nor post-baseline radiological assessments available	Date of randomization	Censored
5	No death nor PD by the time of data cut-off for final analysis	Date of last adequate radiological assessment	Censored
6	Drops out before end of study	Date of last adequate radiological assessment	Censored
7	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
8	Death or PD occurred after two or more consecutive missed radiological assessment visits	Date of last adequate radiological assessment prior to missed visits	Censored

Note: An adequate rad o og c assessment s def ned as an assessment where the Invest gator determ ned rad o og ca response s comp ete response (CR), part a response (PR), stab e d sease (SD), or PD. If PD and new ant - cancer therapy occur on the same day, w assume that the progress on was documented f rst, e.g. outcome s progress on and the date s the date of the assessment of progress on

Note: Two consecut ve schedu ed tumor assessments s equa to 126 days (=2* (8 weeks *7+ 7 days)) s nce prev ous eva uab e RECIST 1.1 or base ne assessment f there s no post base ne tumor assessment.

Example of Situation #8,

Visit	Date of Assessment	Overall Response	PFS
C5D1	01JAN2020	SD	Censored
C7D1	29JAN2020 ± 3 days	Missing	
C9D1	26FEB2020 ± 3 days	Missing	
C11D1	25MAR2020 ± 3 days	PD or Death	

- The additional anti-tumor secondary efficacy endpoints include ORR, DCR, and DoR. The derivation of the best overall response is detailed in Section 9.2.3.

    - ORR is defined as the proportion of subjects achieving a best overall response of confirmed complete response (CR) or partial response (PR), per RECIST v1.1, as determined by the investigator.

    Objective response rate (ORR) will be calculated using two different ways:

        - Scenario #1: ORR will be calculated using a strict interpretation of RECIST Version 1.1. Objective response will be derived as no/yes variable. Subjects with a BOR of confirmed CR or PR will be assigned 'Yes'. Subjects not having a BOR of confirmed CR or PR will be assigned 'No'. Hence, ORR is defined as the proportion of subjects with objective response being "Yes".

        - Scenario #2: $ORR_{UNCONFIRMED}$ will be calculated using all responses regardless of confirmation. Objective response will be derived as no/yes variable. Subjects with a BOR of confirmed CR, confirmed PR, unconfirmed CR or unconfirmed PR will be assigned "Yes". All subjects with other BOR values will be assigned "No". Hence, $ORR_{UNCONFIRMED}$ is defined as the proportion of subjects with objective response being "Yes".

    - DCR is defined as proportion of subjects achieving a best overall response of confirmed CR, PR, or SD (for at least 7 weeks), within each treatment group, per RECIST v1.1, as determined by the investigator. To be qualified for SD, the duration of SD should last for at least 7 weeks.

    - DoR is defined as the time (months) from the first occurrence of PR or CR by RECIST Version 1.1, until the first date that progressive disease is documented by RECIST Version 1.1, or death, whichever comes first. Only those subjects with confirmed responses of CR or PR will be included in this analysis. Censoring will follow the rules outlined for PFS in Table 3 in this section for those subjects who do not have censored DoR, it is calculated as (date of death or PD or last assessment – date of first occurrence of confirmed CR or PR + 1)/30.4375.

- Changes in health status (QLQ-C30: cancer specific; and EQ-5D-5L).

- Resource utilization including all concomitant medications, days in hospital.

5.3. Exploratory Endpoints

- Change from baseline in circulating tumor DNA (ctDNA), analysis to be included in a separate document.

- Change from baseline in tumor markers (carcino-embryonic antigen [CEA]).

- Pharmacogenomics, analysis to be included in a separate document.

5.4. Safety Endpoints

- Safety including treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), deaths, ECG's, and clinical laboratory abnormalities.

5.5. Pharmacokinetic Endpoints

- Observed plasma concentrations, estimated population PK and exposure parameters of fruquintinib and M11.
- QTc interval and plasma concentrations of fruquintinib and M11 at specified time points.

5.6. Pharmacodynamic Endpoints

- Parameters describing exposure-response with efficacy (e.g., OS) and safety (e.g., AEs) endpoints.

6. Analysis Populations

6.1. Screened Population

The Screened population includes all subjects who signed informed consent form (ICF).

6.2. Intent-to-Treat Population

The Intent-to-Treat (ITT) population includes all randomized subjects. Subjects are analyzed by treatment group as randomized. The ITT population is the primary population for evaluating all efficacy endpoints and subject characteristics.

6.3. Safety Population

The Safety population includes all randomized subjects who received at least one dose of study treatment. Subjects in this population are analyzed according to the treatment they actually received. This population is used for all safety analyses.

6.4. Pharmacokinetic (PK) Population

The PK population includes all subjects who receive at least one dose of study treatment and have at least one post-dose PK sample obtained and analyzed. The PK population is used for tabulation of fruquintinib and M11 concentrations from PK plasma samples.

6.5. Non-COVID-19 Impacted Population

The Non-COVID-19 Impacted population includes all randomized subjects who do not have any Coronavirus 2019 (COVID-19)-related protocol deviations. The Non-COVID-19 Impacted population is used for sensitivity analyses for the primary and secondary efficacy endpoints.

6.6. Per Protocol (PP) Population

The per-protocol (PP) analysis set will include only those subjects in ITT who have no major protocol deviations (as described in Section 6.7) and who received the treatment to which they were randomized or assigned. For subjects who took the wrong treatment for part of the study, their data will be excluded from the PP population. PP population is used for sensitivity analyses of OS and PFS, and may be used to analyze selected endpoints to test the robustness of results. The criteria for inclusion in the PP subset will be finalized and documented prior to unblinding of the study.

6.7. Protocol Deviations

Protocol deviations are recorded in the clinical trial management system (CTMS) as outlined in the latest version of the Protocol Deviation and Non-compliance Management Plan. Protocol deviations are categorized as minor or major before database lock.

Protocol deviations including deviations that are related to COVID-19 are recorded in the CTMS as outlined within the Protocol Deviation and Non-Compliance Plan.

7. General Aspects for Statistical Analysis

7.1. General Methods

- Summaries are presented for each treatment group and overall for subjects' disposition, demographics and baseline characteristics, medical history, disease history, prior medications, and concomitant medications tables. Summaries are presented for each treatment group for other tables.
- All data listings that contain an evaluation date contains a relative study day as defined in Section 7.2.3.
- For categorical variables, summary tabulations of the number and percent of subjects within each category of the parameter as seen on the electronic case report form (eCRF) are to be presented. Percentage calculations are based on the number of subjects within treatment group and overall, unless otherwise specified. Percentages are rounded to 1 decimal place, unless otherwise specified. The category Missing is included in subject-level demographics and disease history tables when the count is greater than zero for missing subjects.
- For continuous variables, the number of subjects, mean, standard deviation (StdDev), median, lower quartile (Q1), upper quartile (Q3), minimum, and maximum values are presented. The precision of summary statistics, unless otherwise specified, is as follows:
    - Minimum, maximum: same decimal places as the raw data.
    - Mean, median, Q1, and Q3 : 1 more decimal place than the raw data.
    - Standard deviation, standard error: 2 decimal places more than the raw data.
- For results from a mixed model repeated measures, least-square (LS) mean and LS mean difference are presented with one decimal place, and standard error (SE) of LS means and SE of LS mean difference are presented with two decimal places.
- Comparison between treatment groups are calculated as fruquintinib plus BSC versus placebo plus BSC.
- Two-sided 95% confidence intervals (CI) are provided and rounded to 2 decimal places, unless otherwise specified.
- 2-sided p-values are presented with 3 decimal places.
- Any rounding will be done after all calculations are made.

7.2. Key Definitions

7.2.1. First Dose Date

First dose date is defined as the day of first dose of study treatment received after randomization.

7.2.2. Last Dose Date

Last dose date is defined as day of the last dose of study treatment.

For subjects ongoing for the treatment period at time of analysis prior to database lock, the last dose date is the date of the most recent study visit in the database for that subject.

7.2.3. Study Day

The study day is determined relative to the date of first dose of study treatment, unless otherwise specified. The day of the first dose of study treatment is defined as study day 1. The day prior to the first dose of study treatment is study day -1. There is no study day 0.

For events that occur before the first dose of study treatment,

study day = date of the event – first dose date;

for events that occur on or after the first dose of study treatment,

study day = date of the event – first dose date + 1.

7.2.4. Date of Last Known Alive

The date of last known alive is defined as the last alive date of contact from the Survival Follow-up page on the eCRF. For subjects ongoing at time of analysis, the date of last known alive is the date of the most recent study visit in the database for that subject.

More specifically, the last known alive date will be derived for subjects not known to have died at the analysis cut-off date using the latest date (including complete and partial date with Month and Year information) among the following data:

- All assessment dates (e.g. laboratory, vital signs assessments, ECG, ECOG, performance status assessment, tumor assessment dates etc.).
- Medication dates including study medication, concomitant medications, anticancer therapies administered after study treatment discontinuation.
- Adverse events start and end date, and the date of adverse event becoming serious.
- Date latest known alive collected during the survival follow-up.
- Randomization date.

7.2.5. Date of Death

Date of death is defined as the date of death from the Death Detail page on the eCRF. Date of death is cross-checked with AEs where outcome is ‘Fatal’, if applicable. In rare case, if year and month of death date are known but the day is unknown, day will be imputed as 15. For example, if a subject is reported to die on Dec2017, the death date will be imputed as 15 Dec2017.

7.2.6. Baseline and Change from Baseline

For all change from baseline variables, the baseline is defined as the last non-missing assessment prior to or on the day of randomization, and must be prior to the first administration of study treatment, including scheduled and unscheduled visits, unless otherwise specified. Hence, change from baseline = post-baseline value – baseline value.

The baseline value for analyses of qualitative parameters (e.g., normal/abnormal) is defined as the last evaluation prior to or on the day of randomization, and must be prior to the first administration of study treatment.

7.2.7. Treatment-emergent Events

An AE is considered a TEAE if the onset date is on or after the start of study treatment or if the onset date is missing, or if the AE has an onset date before the start of study treatment but worsened in severity after the study treatment until 37 days after the last dose of study treatment or a new treatment of anti-tumor therapy, whichever is earlier. After this period, treatment-related SAEs will also be considered as TEAEs. AEs with an unknown/not reported onset date will also be included.

7.3. Missing Data

All available data of the subjects who withdraw from the study for any reasons is analyzed. Missing data is assumed to be missing at random. Category 'Missing' is displayed for qualitative assessments, where applicable.

For demographic and baseline characteristics, each variable will be analyzed and/or summarized using the available data. Unless otherwise specified, subjects with missing data will be excluded only from analyses for which data are not available.

There is no imputation of missing data for the analysis purpose, unless otherwise stated.

7.3.1. Imputation of the Missing Dates

Imputation rules described in this section are applicable to partial dates of AEs, concomitant medications, anti-cancer therapy, primary diagnosis and metastatic disease diagnosis. However, imputation of missing AE and concomitant medication onset and stop dates will be used to determine the status of each AE and the prior/concomitant status of each medication, the imputed dates should not be shown in listings.

Incomplete Start Date of AEs:

- If the AE onset date is completely missing, the AE start date will be imputed as the reference start date (i.e. first dosing date);
- If the AE onset date is partial missing, then
  - If both the year and the month are available and the year and the month are the corresponding year and month of the reference start date, then the AE start date will be imputed as the reference start date;

- If both the year and the month are available and the year and the month are not equal to the corresponding year and month of the reference start date, then the AE start date will be imputed as the 1st day of the month;
- If only the year is available and the available year is the corresponding year of the reference start date, then the AE start date will be imputed as the reference start date;
- If only the year is available, and the available year is not equal to the corresponding year of the reference start date, then the AE start date will be imputed as the January 1st of the year.

Incomplete Stop Date of AEs:

AE end date will be imputed as below for the partial date only, the imputation rules only apply when the AE is not ongoing:

- If both the year and the month are available, AE end date will be imputed as the last day of the month;
- If only the year is available, AE end date will be imputed as the December 31st of the year.

If the imputed AE end date is after the death date for subjects is know to be dead at end of study or cut off date, the date of the death will be used for AE end date. If the imputed AE end date is after the last known alive date for subjects alive at the end of study or cut off date, the date of last known alive date will be use for AE end date.

For AE continuing at the cut-off date, the end date will not be imputed and instead will be reported as "ongoing".

Concomitant Medication/Procedure/Surgery with onset/end dates

Concomitant Medication/Procedure/Surgery with onset/end dates that are partially/completely missing will be imputed as follows.

(i) start date:

- 1st day of the month will be used to impute the start date if only the day is missing.
- January 1st will be used to impute the start date if both the day and month are missing.
- If the date is completely missing, then the day before the reference start date will be imputed as the start date.

(ii) end date:

- Last day of the month will be used to impute the end date if only the day is missing.
- December 31st of the year will be used to impute the end date if both the day and month are missing.
- If the date is completely missing, assign 'continuing' status to the end date.

If the imputed end date is after the death date or last known alive date, the date of the death or last known alive date will be imputed as the Concomitant medication/procedure/surgery end date.

Subsequent Anti-cancer Therapy Date (collected during Survival Follow-Up)

When a partial new anti-tumor therapy start date is reported, every effort will be made to identify the precedence relationship of starting date of new anti-tumor therapy relative to the reference end date (i.e. last dose date). Below rules will be used:

- If the date is completely missing, new anti-tumor therapy date will be imputed as reference end date + 1;
- If only the day is missing, 15th day will be imputed as the new anti-tumor therapy date;
- If both the day and the month are missing, then July 1st will be imputed as the new anti-tumor therapy.

If the imputed start date is prior to the reference end date for subjects, the reference end date + 1 will be used as the imputed start date of the subsequent anti-cancer therapy.

Primary Diagnosis Date and Metastatic Disease Diagnosis Date

When a partial date of primary diagnosis for advanced colorectal cancer or a partial date of first metastatic disease diagnosis is reported, the below imputation rules will be used:

- If the date is completely missing, no imputation will be conducted;
- If only the day is missing, 15th day will be assigned;
- If both the day and the month are missing, then July 1st will be assigned.

7.4. Visit Windows

It is expected that there will be a variation between subjects in the actual number of study days from the start of administration of study drug within each cycle – defined as Day 1 – to the dates that the scheduled visits occurs. To handle this, for tables and figures where data are grouped by visit, assessments will be categorized using visit windows based on study days (relative to the Day 1 of each cycle). The visit-window mapping is described in Table 4. Visit-based summaries will be based on the windowed visits. All data, whether or not within the visit windows, will be presented in subjects listings.

For windowed visits during the treatment cycles, if more than 1 visit occurs during a visit window, the visit closest to the scheduled day will be assigned to the windowed visit. If two visits are equidistant from the scheduled day, the later visit will be assigned to the windowed visit. If there are multiple assessments on the same day, the worst case will be used. For the treatment completion visit, the last assessment in the window will be included in the summary.

For a subject who prematurely discontinues the study, the premature visit will be slotted accordingly. The window for post treatment visit will be "last dose date of last cycle to last dose date of last cycle + 10 days" and the window for safety follow-up visit will be “Last dose date of last cycle + 11 days to last dose date of last cycle + 37 days”.

Table 4 Visit Windowing

	Cycle 1		Cycle 2-3		Cycle 4 and onwards	Post treatment	Safety follow-up
Visit	**C1D1**	**C1D21**	**CXD1**	**CXD21**	**CXD1**		
Scheduled Day [a]	1	21	1	21	1		
ECOG		1 to EOC	Day -3 to 3	4 to EOC	Day -3 to 3	Last dose date of last cycle to last dose date of last cycle + 10	Last dose date of last cycle + 11 to last dose date of last cycle + 37
Vital Sign		1 to EOC	Day -3 to 3	4 to EOC	Day -3 to 3		
Hematology		1 to EOC	Day -3 to 3	4 to EOC	Day -3 to 3		
Clinical Chemistry		1 to EOC	Day -3 to 3	4 to EOC	Day -3 to 3		
Blood amylase and lipase			Day -3 to 3		Day -3 to 3		
Coagulation		1 to EOC	Day -3 to 3	4 to EOC	Day -3 to 3		
Thyroid function			Day -3 to 3		Day -3 to 3		
Urinalysis			Day -3 to 3		Day -3 to 3		
ECG	Day 1	2 to EOC		1 to EOC			
CEA			Day -3 to 3		Day -3 to 3	Last dose date of last cycle to last dose date of last cycle + 10	
QLQ-C30			Day -3 to 3		Day -3 to 3		
EQ-5D-5L			Day -3 to 3		Day -3 to 3		

[a] The scheduled day is relative to the Day 1 of each cycle.

Note: The end date of a cycle (EOC) is defined as the one day earlier than the date of Day 1 study drug administration of its next cycle. For the last cycle (where no subsequent cycle is given), the end of cycle will be defined as Day 7 relative to the last dose of the cycle.

C1D1=cycle 1 day 1; C1D21= cycle 1 day 21; CEA= Carcino-embryonic antigen; CXD1=cycle X day 1; CXD21= cycle X day 21; ECG=electrocardiogram; ECOG= Eastern Cooperative Oncology Group; EOC= end date of a cycle.

7.5. Pooling of Centers

Data from all study centers is combined for analysis.

7.6. Outliers

Data Management are to be notified of outliers, if identified during TLF reviews, for query. Syneos Health Biostatistics and Programming do not change or remove outliers from the data.

7.7. Data Sources

Randomization numbers, stratification factors, and treatment assignments derived from IWRS are reconciled with the dummy randomization schedule prior to database lock and unblinding, and with the actual randomization schedule after database lock and unblinding.

After the study is unblinded, fruquintinib and M11 concentrations from PK plasma samples are provided by Covance and mapped onto SDTM PC domain. Syneos Health then transfers SDTM PC domain to Certara.

Protocol deviations are recorded in the clinical trial management system and provided as an Excel document. Protocol deviations are to be reviewed prior to database lock.

CRF data are extracted from Rave database.

Laboratory data are provided by local labs.

Imaging data are provided by eResearchTechnology, Inc. (ERT).

Interactive Response Technology (IRT) data are provided by Endpoint.

Quality of life data using EORTC QLQ-C30 and EQ-5D-5L questionnaires are collected via Electronic Clinical Outcome Assessment (eCOA) and provided by ERT.

8. Demographic, Other Baseline Characteristics and Medication

8.1. Subject Disposition and Withdrawals

The following summaries will be presented for all enrolled subjects to reflect the subject disposition:

- Number of subjects who signed the informed consent.
- Number of screen failures.
- Reason for screen failure.
- Number of subjects who are randomized.
- Number of subjects who do not receive study drug.
- Number of subjects who received study drug.
- Subjects still on treatment (i.e., missing end-of treatment information).
- Reason for study drug discontinuation (for study drug).
- Number of subjects going into Survival follow-up if there are any assessments after the last dose date + 37 days.
- Number and percentage of subjects still on study (i.e., missing end-of-study information).
- Number and percentage of subjects who discontinued the study.
- Reason for study discontinuation.

A separate table will be presented for the ITT population to show the subjects included in each analysis set and proper reasons for exclusion from an analysis set.

A separate table will be presented for the ITT population to show the concordance of randomization schedule stratification factors and CRF collected factors of prior therapy, duration of metastatic disease, and RAS status. The following summaries will be presented:

- Number of subjects with all randomization schedule stratification factors concordant with CRF collected factors.
- Number of subjects with at least one randomization schedule stratification factor discordant with CRF collected factors.
    - Number of subjects with discordance in prior therapy, duration of metastatic disease, and RAS status.
- Prior therapy (Trifluridine/Tipiracil (TAS-102), Regorafenib, or Both Trifluridine/Tipiracil (TAS-102) and Regorafenib) based on randomization schedule stratification factors and prior therapy based on CRF collected factors.
- Duration of metastatic disease (≤ 18 months, > 18 months) based on randomization schedule stratification factors, and duration of metastatic disease based on CRF collected factors.
- RAS status (Wild Type, Mutant) based on randomization schedule stratification factors, and RAS status based on CRF collected factors.

Subject discontinuation status and analysis population are also listed.

8.2. Protocol Deviations

Protocol deviations are summarized descriptively for subjects with at least 1 major protocol deviation and subjects with at least 1 minor protocol deviation for each treatment group and overall. Each protocol deviation is also summarized descriptively within major and minor protocol deviations for each treatment group and overall of the ITT population. A subject can have multiple major and/or minor deviations and

counted once per major and/or minor deviation. COVID-19-related protocol deviations are summarized descriptively for each treatment group and overall of the ITT population.

A listing of protocol deviations, including COVID-19-related protocol deviations, is provided.

8.3. Demographic and Baseline Characteristics

The following parameters are summarized descriptively for each treatment group and overall for the ITT population.

- Age (years) at ICF date, Age Categories (< 65 years, ≥ 65 years).
- Sex (Female, Male); If female, Child Bearing Potential.
- Race (American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other, Multiple Races, Not Reported, Unknown). A subject can have multiple races and is summarized in the multiple race category.
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown).
- Region (North America, Europe, and Asia).
- Baseline Height (cm).
- Baseline Weight (kg).
- Baseline body mass index [BMI] (kg/m^2): it is calculated as Weight at Baseline (kg)/ [Height at Baseline (m)]^2.
    - BMI category: < 18.5, ≥ 18.5 and < 24, ≥ 24 kg/m^2.
- Baseline ECOG Performance Status: 0, 1.

Age (years) at ICF date is calculated by site personnel as the number of years from date of birth up to date of informed consent. For example,

Date of Birth	Date of Informed Consent	Original Age	Age to be entered into IWRS
01MAR1985	01JUL2020	35 years 4 months	35
01AUG1985	01JUL2020	34 years 11 months	34

A separate table presenting number and percentage of subjects by site and country will be produced for the ITT population.

Demographic data and baseline characteristics, randomization scheme and codes, informed consent data, and inclusion/exclusion criteria are listed by subject.

8.4. Disease History

History of colorectal cancer of the ITT population is summarized descriptively for each treatment group and overall for the following.

- Time (months) since First Diagnosis of Colorectal Cancer: it is calculated as (date of randomization – date of first diagnosis of colorectal cancer)/30.4375.
- Stage of Colorectal Cancer at First Diagnosis (stage I, stage II, stage III, stage IV).
- Primary Tumor Location at First Diagnosis.
    - Colon.
        - Colon – Right (cecum, ascending colon, and hepatic flexure).
        - Colon – Left (splenic flexure, descending colon, transverse colon, sigmoid colon).
        - Colon – Right and Left.
        - Colon – Unknown.
    - Rectum.
    - Colon and Rectum.
        - Colon – Right (cecum, ascending colon, and hepatic flexure).
        - Colon – Left (splenic flexure, descending colon, transverse colon, sigmoid colon).
        - Colon – Right and Left.
        - Colon – Unknown.
    - Unknown.
- Primary Site at First Diagnosis (Colon Left, Colon Right, Both Colon Left and Right, Colon Unknown, Rectum Only, Unknown).
- Duration of Metastatic Disease (months): it is calculated as (date of randomization – date of diagnosis of metastasis disease)/30.4375.
    - Duration of Metastatic Disease Categories (≤ 18 months, > 18 months).
- Prior Oncology Treatments (Prior Anti-cancer Medication, Prior Anti-cancer Radiotherapy, Prior Anti-cancer Procedures).

- RAS Status (Wild Type, Mutant).
- BRAF Status (Wild Type, V600 E Mutation, Other).
- Microsatellite/Mismatch Repair Status (Microsatellite stable [MSS] and/or proficient mismatch repair [pMMR], microsatellite instability-high [MSI-H] and/or deficient mismatch repair [dMMR]).
- Prior Therapy with Trifluridine/Tipiracil (TAS-102) and/or Regorafenib (Trifluridine/Tipiracil (TAS-102), Regorafenib, Both Trifluridine/Tipiracil (TAS-102) and Regorafenib).
- Number of Prior Treatment Lines (≤ 3, > 3).
- Number of Prior Treatment Lines for Metastatic Disease (≤ 3, > 3).
- Prior Treatment with Vascular Endothelial Growth Factor (VEGF) Inhibitors (Yes, No).
- Prior Treatment with Epidermal Growth Factor Receptor (EGFR) Inhibitors (Yes, No).
- Prior Treatment with EGFR/VEGF Inhibitors.
    - No anti-VEGF and no anti-EGFR.
    - Anti-VEGF, or anti-EGFR, or both.
        - Anti-VEGF and no anti-EGFR.
        - Anti-EGFR and no anti-VEGF.
        - Both anti-VEGF and anti-EGFR.
- Prior Treatment with Immune Checkpoint Inhibitors for MSI-H/dMMR (Yes, No).
- Prior Treatment with BRAF Inhibitors for BRAF V600E Mutation (Yes, No).
- Liver Metastases at Baseline (Yes, No): obtained based on whether the liver organ was involved in the target and non-target lesion tumor scan assessment at the baseline.
- Number of Metastatic Sites Other than Colon or Rectum (Single, Multiple): obtained based on the number of sites/organs was involved in the target and non-target lesion tumor scan assessment at the baseline. If only one is involved, that would be single; if more than one are involved, it will be multiple. For this derivation, paired organs, such as lung, kidney, ovaries, and lymph nodes will be considered as one organ, irrespective of the number of parts they may be made up of (i.e. tumors in the left lung and right lung will be counted as in one site).
- Number of Metastatic Sites (Single, Multiple): obtained based on the number of sites/organs was involved in the target and non-target lesion tumor scan assessment at the baseline. If only one is involved, that would be single; if more than one are involved, it will be multiple. For this derivation, paired organs, such as lung, kidney, ovaries, and lymph nodes will be considered as one organ, irrespective of the number of parts they may be made up of (i.e. tumors in the left lung and right lung will be counted as in one site).

8.5. Medical History

The conditions/diseases from medical history are those conditions/diseases that stopped prior to the study entry. Medical history is coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 or higher. Medical history is summarized using discrete summary statistics for each MedDRA system organ class (SOC) and preferred term (PT) by treatment group and overall for the ITT population. Subjects with multiple medical histories in the same SOC or PT are counted only once for the respective SOC or PT.

Summaries are ordered in alphabetical order of SOC and then, within an SOC, in decreasing frequencies by PT in overall column. If the frequencies tie, an alphabetic order will be applied.

A listing of medical history by subject is provided.

8.6. Prior and Concomitant Medication

Prior and concomitant medications are classified by Anatomical Therapeutic Classification (ATC) therapeutic subgroup (Level 2) and PT using the World Health Organization Drug Dictionary (WHODD) version March2020 or later. Medications with partial start or stop dates are imputed as described in Section 7.3.1 prior to be determined whether the medication is prior or concomitant medication.

Medications taken prior to the first dose of study treatment are denoted “Prior”. Medications taken prior to the first dose of study treatment and continuing beyond the first dose of study treatment or those medications started on or after the first dose of study treatment but no later than 37 days after the last dose are denoted “Concomitant”. Medication with start date/time being partially or completely missing will be assumed to be concomitant if it cannot be definitely shown that the medication did not occur during the treatment period.

The use of prior and concomitant medications will be summarized using discrete summary statistics in each treatment group and overall for the ITT population. If a subject took a specific medication multiple times or took multiple medications within a specific ATC or PT, the subject is counted only once for the respective ATC or PT.

Summaries are ordered in alphabetical order of ATC and then, within an ATC , in decreasing frequencies by PT in overall column. If the frequencies tie, an alphabetic order will be applied.

A listing of prior medication and concomitant medication by subject is provided.

8.7. Concomitant Medical or Surgical Procedure

Medical or surgical procedures that occurs after first dose date but no later than 37 days after the last dose are denoted “Concomitant”. Concomitant medical or surgical procedures are classified using the MedDRA version 23.0 or higher.

The use of concomitant medical or surgical procedures will be summarized using discrete summary statistics in each treatment group and overall for the ITT population. If a subject took a specific medication multiple times or took multiple medications within a specific SOC or PT, the subject is counted only once for the respective SOC or PT.

Summaries are ordered in alphabetical order of SOC and then, within an SOC , in decreasing frequencies by PT in overall column. If the frequencies tie, an alphabetic order will be applied.

A listing of concomitant medical or surgical procedures by subject is provided.

8.8. Prior Oncology Treatment

Prior oncology treatments including prior anti-cancer mediation, prior anti-cancer radiotherapy, prior anti-cancer procedure or surgery are summarized descriptively for each treatment group and overall for the ITT population.

8.8.1. Prior Anti-cancer Medication

Summary of prior anti-cancer medication for the ITT population includes the following:

- The number and percent of subjects with at least one prior anti-cancer medication.
- The total number of prior anti-cancer medications.
- The number of prior lines of therapy and its categories of 0, 1, 2, 3, > 3.

Prior anti-cancer medications are classified using the WHODD version March 2020 or later.

The use of prior anti-cancer medications will be summarized by ATC and PT using discrete summary statistics in each line of therapy, each treatment group and overall for the ITT population. Within each line of therapy, a subject with multiple prior medication entries in the same ATC (PT) is only counted once within a particular ATC (PT).With each line of therapy, results are sorted by ATC followed by PT in decreasing order of frequency (by Total column). If the frequencies are tied, an alphabetic order is applied.

8.8.2. Prior Anti-cancer Radiotherapy

Summary of prior anti-cancer radiotherapy for the ITT population includes the following.

- The number and percent of subjects with at least one prior anti-cancer radiotherapy.
- The total number of prior anti-cancer radiotherapy.

8.8.3. Prior Anti-cancer Procedure or Surgery

Summary of prior anti-cancer procedure or surgery for the ITT population includes the following

- The number and percent of subjects with at least one prior anti-cancer procedure or surgery.
- The total number of prior anti-cancer procedures or surgery.

  The number and percent of subjects for each purpose of prior anti-cancer procedure or surgery. A subject with multiple occurrences of the same purpose will be counted only once for the purpose, and a subject with multiple purposes will be counted once in each category of purpose.

Prior anti-cancer procedure or surgery is coded (MedDRA) version 23.0 or higher.

The number and percent of subjects with each procedure or surgery will be summarized using discrete

summary statistics in each treatment group and overall for the ITT population by SOC and PT. If a subject had a procedure multiple times or had multiple procedures within a specific SOC or PT, the subject is counted only once for the respective SOC or PT. Summaries are ordered in alphabetical order of SOC and then, within an SOC, in decreasing frequencies by PT in overall column. If the frequencies tie, an alphabetic order will be applied.

8.9. Extent of Exposure

Exposure of study treatment is descriptively summarized for each treatment group as follows. Table 5 details the parameters of study treatment exposure.

Table 5. Extent of Exposure Parameters

Parameter	Definition
Duration of Exposure (days)	Last dose date of study drug – first dose date of study drug + 8.
Number of Days with Recorded Dose	Sum of days with recorded doses
Number of Cycles Treatment Received	Subjects are considered to have started a cycle if they have received at least one dose of any study treatment.
Number of Cycles Treatment Received Categories	1, 2, 3, 4, 5, 6 and > 6
Cumulative Dose (mg)	Sum of doses administered in all cycles. The total dose administered in each cycle is defined as: the sum of (number of 5 mg capsules taken × 5 + number of 1 mg capsules taken) where number of capsules taken = total capsules dispensed – total capsules returned.
Dose Intensity (mg/day)	Cumulative Dose (mg) / Duration of Exposure (day) Target dose intensity is 3.75 mg
Relative dose intensity (RDI) (%)	100 * [Dose Intensity (mg/day) / (5 × 21/28 (mg/day))]
RDI Categories	< 50% 50 - < 70% 70 - < 90% 90 - < 110% ≥ 110%.
Relative Dose (RD) (%)	100 * [Cumulative dose (mg) / (5×21× number of cycles treatment received (mg)]
RD Categories	< 50% 50 - < 70% 70 - < 90% 90 - < 110% ≥ 110%.
Percentage Intended Dose (PID) (%)	100 * [(number of days with any recorded doses) /duration of exposure] Target PID is 75%. Number of days with any recorded doses

The following summary for dose adjustment will be summarized for each treatment group.

- Study drug is administered orally on days 1-21 of each 28-day cycle. A cycle will be called cycle delay if the duration of the cycle is longer than 28 days. However, the last cycle will not be evaluated for cycle delay. Reason for delay is not collected. Hence, the total number of cycle delay will be calculated for each subject. Number of subjects with any cycle delay, and the frequency of cycle delay (0, 1, 2, 3, 4, 5, 6, > 6) will be summarized.
- Number of subjects with any dose modification (including both drug interruption and dose reduction);
- Frequency of dose modification: 0, 1, 2, 3, 4, 5, 6, > 6.
- Drug interrupted (number of subjects experienced drug interruption and reasons for drug interruption; frequency of drug interruptions: 0, 1, ≥ 2).
- Drug withdrawn (number of subjects experienced drug withdrawn and reasons for drug withdrawn).
- Dose reduced (Number of subjects with any dose reduction and reasons for dose reduction; and frequency of dose reduction: 0, 1, 2, ≥ 3), also the dose reduction category below will be summarized.
    - Reduction from 5mg to 4mg.
    - Reduction from 4mg to 3mg.

Study treatment accountability, study treatment administration are extent of exposure are listed by subject and visit.

9. Efficacy

Efficacy analyses are based on the ITT population. All secondary endpoints based on radiological assessments of tumor burden are derived from investigator assessment using Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 (Eisenhauer et al 2009).

9.1. Primary and Key Secondary Efficacy Endpoint and Analysis

9.1.1. Primary Efficacy Endpoint and Analysis

The primary endpoint of the study is OS, defined in Section 5.1 of the SAP and calculated as (date of death or last known alive – date of randomization + 1)/30.4375.

The Kaplan-Meier plots will be produced and the median, 25% and 75% percentile of time-to-event will be estimated using Kaplan-Meier method with their corresponding 95% CI which are calculated from a log-log transformation based on the method by Brookmeyer and Crowley (1982). Additionally, estimates will be provided for the survival probability along with their 95% CIs which are calculated using linear transformation based on the method by Brookmeyer and Crowley (1982) at selected landmarks, for example, at 3, 6, 9, 12, and 18 months. Example Statistical Analysis System (SAS) code is provided in Appendix 5.

The two-sided p-value to test the treatment effect will be calculated using a stratified log-rank test accounting for randomization schedule stratification factors. Example SAS code is provided in Appendix 6. The hazard ratio (HR) between the 2 treatment groups (fruquintinib vs placebo), together with its 95% CIs, will be calculated from a stratified Cox proportional hazard model (i.e. accounting for randomization schedule stratification factors) in which the treatment group is the only covariate in the model. A HR < 1 indicates a favorable clinical benefit from fruquintinib over the placebo group. Example SAS code is provided in Appendix 7.

Duration of follow-up is defined as the time (months) from date of randomization to the last date known to be alive for subjects who have not yet been reported to have died by the time of the analysis. Subjects who were reported to have died by the time of the analysis are censored at date of death. That is, duration of follow-up is calculated as (date of death or last known alive – date of randomization + 1)/30.4375. The duration of follow-up will be calculated using the Kaplan-Meier method.

All OS data are provided in listings by subject.

9.1.2. Key Secondary Efficacy Endpoint and Analysis

The key secondary efficacy endpoint is PFS. PFS is defined in Section 5.2 and calculated as (date of death or radiographic PD or last assessment – date of randomization + 1)/30.4375.

The number and percent of subjects who had progression-free events, the number and percent of subjects censored, and reasons for censoring are presented for each treatment group. Reasons for censoring include the following.

a. No baseline nor post-baseline assessment

b. No death nor PD

c. Drop-out before end of study

d. New anti-tumor therapy started prior to PD

e. Death or PD occurred after two or more consecutive missed assessment

The Kaplan-Meier plots will be produced and the median, 25% and 75% percentile of time-to-event will be estimated using Kaplan-Meier method with their corresponding 95% CI which are calculated from a log-log transformation based on the method by Brookmeyer and Crowley (1982). Additionally, estimates will be provided for the survival probability along with their 95% CIs which are calculated using linear transformation based on the method by Brookmeyer and Crowley (1982) at selected landmarks, for example, at 3, 6, 9, 12, and 18 months.

The two-sided p-value to test the treatment effect will be calculated using a stratified log-rank test accounting for randomization schedule stratification factors. The hazard ratio (HR) between the 2 treatment groups (fruquintinib vs placebo), together with its 95% CIs, will be calculated from a stratified Cox proportional hazard model (i.e. accounting for randomization schedule stratification factors) in which the treatment group is the only covariate in the model. A HR < 1 indicates a favorable clinical benefit from fruquintinib over the placebo group.

A Kaplan-Meier plot of the time to censoring, where the censoring indicator of the primary PFS analysis is reversed, will be presented.

All PFS data is provided in listings by subject.

9.1.3. Multiplicity Adjustments

The clinical trial evaluates the objectives defined in terms of the comparison of fruquintinib + BSC versus placebo + BSC on the primary and key secondary efficacy endpoints in Section 9.1.1 and Section 9.1.2. The multiplicity problem includes 2 hypotheses of no effect:

- Hypothesis H_1. Comparison of fruquintinib + BSC versus placebo + BSC for OS.
- Hypothesis H_2. Comparison of fruquintinib + BSC versus placebo + BSC for PFS.

The 2-sided p-values for the 2 comparisons will be used for the multiple testing procedure. Example SAS code in Appendix 6.

A fixed-sequence (hierarchical) testing procedure is 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 is ≤ 0.05, then, a superiority test of for PFS will be conducted at the two-sided significance level of 0.05.

9.1.4. Sensitivity Analysis for OS and PFS

The following sensitivity analyses for OS and PFS will be performed, in which the p-value will always be obtained from the stratified log-rank test and the hazard ratio (HR) between the 2 treatment groups (fruquintinib vs placebo), together with its 95% CIs will be calculated from the model in Section 9.1.1 and Section 9.1.2 for OS and PFS, respectively, unless otherwise specified.

- using ITT population, unstratified Cox proportional hazard model in which the randomization schedule stratification factors and treatment group are included in the model as covariates;
- using ITT population, stratified analysis for both log-rank test and Cox proportional hazard model, but using the stratification factors collected on the case report form (CRF);
- using ITT population, unstratified Cox proportional hazard model in which the stratification factors collected on the CRF and treatment group are included in the model as covariates;
- using Non-COVID-19 Impacted population,
- using ITT population, subjects with primary cause of death attributed to COVID-19 will be censored at the last known alive date prior to the death date for OS; and will follow the censoring rule defined in Table 3 for PFS and will use the data prior to the date of death.
- using PP population
- using PP population, unstratified Cox proportional hazard model in which the randomization schedule stratification factors and treatment group are included in the model as covariates;
- using PP population, stratified analysis for both log-rank test and Cox proportional hazard model using the stratification factors collected on the CRF;
- using ITT population, multivariate Cox's proportion hazard model with treatment and randomization schedule stratification factors (i.e. prior therapy, RAS status, and duration of metastatic disease) included in the model as covariate and, adjust for key prognostic factors using stepwise selection process with level of enter alpha= 0.15 and level of remove alpha= 0.15. Key prognostic factors include a set of potential prognostics/predictive factors as described in Section 9.1.5.

An additional sensitivity analyses for OS will be performed

- using ITT population, based on the first exact 480 deaths and the additional dead subjects will be censored at the date of last known alive before their death.
- using ITT population, subjects who take the subsequent anti-cancer therapy and are still alive will be censored at the date of initiating the subsequent anti-cancer therapy for OS.

The following additional sensitivity analyses for PFS will be performed, and all those sensitivity analyses defines the PFS event in an alternative way.

- For Rule 7 of Table 3, subjects who take new anti-cancer therapy are considered as a progression, and the date of progression is on the date of initiating the new anti-cancer therapy. However, if the new anti-cancer therapy is initiated after two or more consecutive missed/non-evaluable tumor assessments, the subjects will still be censored at date of last radiological assessment before the missed assessments. Then, the same analysis methods outlined in Section 9.1.2 will be conducted.

- For Rule 8 of Table 3, ignore the missing tumor assessments, that is, subjects with PD or death after two or more consecutive missed/non-evaluable tumor assessments will be considered as PFS event, and the event date for PD or death will be obtained as usual. Then, the same analysis methods outlined in Section 9.1.2 will be conducted.

9.1.5. Examination of Subgroups

Subgroup analyses will be conducted as stated in the OS analysis and progression free survival sections. 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 is not sufficient, analysis will not be performed.

The following subgroups will be assessed for OS and PFS:

- Age: < 65 years, >= 65 years
- Sex: Female, Male
- Region: North America, Europe, Asia
- Race: White, Asian, Black or African American, Other (including American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other as recorded on the Demographics eCRF, and subjects with multiple races selected)
- Baseline ECOG Performance Status: 0, 1
- Prior Therapy with Trifluridine/Tipiracil (TAS-102) and/or Regorafenib: Trifluridine/Tipiracil (TAS-102), Regorafenib, Both Trifluridine/Tipiracil (TAS-102) and Regorafenib
- RAS Gene Status: Wild Type, Mutant
- BRAF Status: Wild Type, V600 E Mutation, Other
- Microsatellite/Mismatch Repair Status: Microsatellite Stable (MSS) and/or proficient mismatch repair (pMMR), Microsatellite Instability-High (MSI-H) and/or deficient mismatch repair (dMMR)
- Duration of metastatic disease (time from 1st Metastatic Diagnosis to Randomization): ≤ 18 months, > 18 months
- Number of Prior Chemotherapy Treatment Lines: ≤ 3, > 3
- Number of Prior Chemotherapy Treatment Lines for Metastatic Disease: ≤ 3, > 3
- Prior Treatment with Vascular Endothelial Growth Factor (VEGF) Inhibitors: Yes, No
- Prior Epidermal Growth Factor Receptor (EGFR) Inhibitors: Yes, No
- Prior target treatment

  - No anti-VEGF and no anti-EGFR
  - Anti-VEGF, or anti-EGFR, or both
    - Anti-VEGF and no anti-EGFR
    - Anti-EGFR and no anti-VEGF
    - Both anti-VEGF and anti-EGFR

- Prior Treatment with Immune Checkpoint Inhibitors for MSI-H/dMMR: Yes, No
- Prior Treatment with BRAF Inhibitors for BRAF V600E Mutation: Yes, No
- Primary Tumor Location at First Diagnosis:
  - Colon, Rectum, Colon and Rectum, Unknown
- Primary Tumor Site at First Diagnosis:
  - Colon Left (Splenic flexure, descending colon, transverse colon, sigmoid colon and rectum), Colon Right (Cecum, ascending colon and hepatic flexure), Colon Left and Right, Colon Unknown, Rectum Only, Unknown
- Liver Metastases at Baseline: Yes, No
- Number of Metastatic Tumor Sites Other than Colon or Rectum: Single, Multiple
- Number of Metastatic Tumor Sites: Single, Multiple

The values of stratification factors used for subgroup analysis are actual values of strata collected through eCRF.

All the sensitivity and the subgroup analysis for both OS and PFS will be considered exploratory and may only be supportive of the primary analysis of OS and PFS. Forest plot will also be used to graphically show the results.

9.2. Secondary Efficacy Endpoints and Analyses

Secondary efficacy endpoints include ORR, DCR, and DoR.

9.2.1. Objective Response Rate and Disease Control Rate

The 95% CIs of ORR and $ORR_{UNCONFIRMED}$ are calculated using the Clopper-Pearson exact binomial method for each treatment group.

The adjusted proportion difference and along with its 95% CI in ORR between treatment groups will be calculated using the Wald method to account for the randomization schedule stratification factors, and p-value of comparing treatment groups is based on a stratified Cochran-Mantel Hanzel (CMH) test stratified by the randomization schedule stratification factors. If the number of objective responses is not sufficient to utilize the CMH test, a stratified exact CMH test is performed instead. Example SAS code is provided in Appendix 8 and Appendix 9.

Overall objective responses and best overall responses are summarized descriptively for each treatment group and provided in listings by subjects and visit.

The analysis methods outlined for ORR will be similarly applied to DCR.

9.2.2. Duration of Response

The descriptive analysis methods outlined in Section 9.1.1 and Section 9.1.2 for OS and PFS will be similarly applied to DoR. The median, 25% and 75% percentile of time-to-event will be estimated using Kaplan-Meier method with their corresponding 95% CI.

All DoR data is provided in listings by subject.

9.2.3. Best Overall Response

BOR will be determined using time point responses (TPRs) up until the last evaluable TPR prior to or on the date of (i) disease progression as defined by RECIST Version 1.1 (Eisenhauer et al., 2009) or death; or (ii) withdrawal of consent; or (iii) receiving subsequent anti-cancer therapy, whichever is earlier.

The timing of an overall TPR will always be derived based on scan dates not response assessment dates. For a scheduled tumor scan assessment, it is expected that there may be a variation for the actual timing of scans among target, non-target, and new lesions. In assigning a date for the overall response assessment at a visit, the earliest date collected at that visit will be used. Within a grouped timepoint, if there are multiple assessments on different dates for the same target lesions, the last assessment will be used.

A subject's BOR will be determined based on Table 7.

There are two ways of assigning BOR for a subject when the minimum interval for confirmation of CR and PR is not satisfied or if there are no confirmatory scans for CR and PR:

- Adding two more response categories as: unconfirmed CR, unconfirmed PR;
- Assigning BOR as SD, that is, both the unconfirmed CR and unconfirmed PR will be SD.

Both ways of assigning BOR will be implemented.

The number and percentage of subjects in each category of derived BOR (Confirmed CR, Confirmed PR, SD, PD, or not evaluable E]) will be summarized.

Table 7. Best Overall Response When Confirmation of CR and PR are Required

First TPR	Second TPR	Best overall response*^ for ORR	Best Overall Response for $ORR_{UNCONFIRMED}$
CR	CR	CR	CR
CR	PR	SD [b] or PD	Unconfirmed CR
CR	SD	SD [b] or PD	Unconfirmed CR
CR	PD	SD [b] or PD	Unconfirmed CR
CR	NE or NA	SD [c] or NE or NA	Unconfirmed CR
PR	CR	PR	Unconfirmed CR
PR	PR	PR	PR
PR	SD	SD [d]	Unconfirmed PR
PR	PD	SD [b] or PD	Unconfirmed PR

First TPR	Second TPR	Best overall response*^ for ORR	Best Overall Response for $ORR_{UNCONFIRMED}$
PR	NE or NA	SD [c] or NE or NA	Unconfirmed PR
NE	NE	NE	NE
NE	CR	SD	Unconfirmed CR
NE	PR	SD	Unconfirmed PR
NE	SD	SD	SD
NE or NA	PD	PD	PD
SD	PD	SD [b] or PD	SD [b] or PD
SD	CR	SD	SD
SD	PR	SD	SD
SD	SD	SD	SD
SD	NE or NA	SD [c] or NE or NA	SD [c] or NE
PD	No further evaluation	PD	PD

CR = Comp ete Response; NE = Not Eva uab e; NA = Not Ava ab e; ORR = Object ve Response Rate; PD = Progress ve D sease; PR= Part a Response; SD = Stab e D sease.
[a]The m n mum nterva for conf rmat on of CR and PR s 4 weeks.
[b]Best response w be SD f the f rst t me po nt overa response s after 49 days on study. Otherw se, the best response w be PD.
[c]Best response w be SD f the f rst t me po nt overa response f after 49 days on study. Otherw se, the best response w be NE.
[d]Best response w be SD prov ded the cr ter a for PD have not been met from the f rst to second assessment.
* A best overa response of SD can on y be made after the subject s on study for a m n mum of 49 days (counted from Cyc e 1 Day 1). If the subject s on study for ess than 49 days, any tumor assessment nd cat ng stab e d sease before th s t me per od w have a best response of NE un ess PD s dent f ed.
^ Subsequent documentat on of a CR may prov de conf rmat on of a prev ous y dent f ed CR even w th an nterven ng NE (e.g., CR NE CR). Subsequent documentat on of a PR may prov de conf rmat on of a prev ous y dent f ed PR even w th an nterven ng NE or SD (e.g., PR NE PR or PR SD PR). However, on y one (1) nterven ng NE or SD w be a owed between PRs for conf rmat on. Note: n the fo ow ng scenar o, PR SD NE PR, the second PR s not a conf rmat on of the f rst PR.

9.2.4. Tumor Assessment

Tumor assessments of target, non-target, and new lesions are listed by subject and visit.

Quality of life is assessed using EORTC QLQ-C30 (version 3.0) and EQ-5D-5L questionnaires. The assessments are performed during at Screening and day 1 of each cycle until treatment is discontinued. Analyses for quality of life assessment are performed for the ITT population, unless otherwise specified.

9.2.5. EORTC QLQ-C30 Questionnaire

The EORTC QLQ-C30 questionnaire, composed of both multi-item scales and single-item measures, is a 30-item cancer-specific instrument (Aaronson et al, 1993) which are grouped into 15 subscales as detailed below.

1. Global health status/QoL scale

2. Five functional scales: Physical functioning, Role functioning, Emotional functioning, Cognitive functioning, Social functioning

3. Three symptom scales: Fatigue, Nausea and vomiting, Pain

4. Six single items: Dyspnea, Insomnia, Appetite loss, Constipation, Diarrhea, Financial difficulties

Each subscale/single item is scored in accordance to the EORTC QLQ-C30 Scoring Manual (Aaronson et al, 1993). All scales and single-item measures range in score from 0 to 100 after linear transformation. A technical summary of scoring can be found in Appendix 1. Higher score for the Global health status/QoL and functioning scales represent higher functioning (i.e. a better state). However, the direction is opposite in symptom scales and single items. Higher scores on symptom and single-item scales represent higher levels of symptoms (i.e. a worse state).

The number and percent of subjects who completed the questionnaires are summarized by visit and each treatment group.

9.2.5.1. *Analysis of Change from Baseline in 15 Subscales*

Change from baseline in the scores of each of the 15 subscales are summarized by visit and each treatment group.

Analysis of change from baseline in the scores of each of the 15 subscales are performed by visit (i.e. cycle), using a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach. The MMRM model will include treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of scale, and randomization schedule stratification factors as fixed effects. An unstructured variance-covariance structure will be used to model within-subject errors. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. MMRM is based on the assumption of missing at random and the assumption that dropouts would behave similarly to other subjects in the same treatment group, and possibly with similar covariate values, had they not dropped out. Example SAS code is provided in Appendix 10. To ensure the proper amount of data utilized in the model for each visit, the following steps will be implemented to identify data to be included in the model.

(1) Calculate the number of subjects with non-missing assessments for each cycle.

(2) Identify the last cycle with at least 20 subjects in any of the treatment groups and no subsequent cycles having at least 20 subjects in any of the treatment groups.

(3) Assessments after the cycle identified in Step 2 will not be included in the model.

If there is a convergence issue with the unstructured covariance model, Toeplitz, Autoregressive (1) (AR (1)) covariance structure is used, following this sequence until convergence is achieved. If the model still does not converge with AR (1) structure, no results are reported. When the covariance structure is not unstructured, the sandwich estimator for the variance-covariance matrix is derived, using the EMPIRICAL option in the PROC MIXED statement in SAS.

The visit windowing rules defined in Section 7.4 will be applied to identify the record for a cycle of each subject, and hence to be included in the analysis. The comparison are between fruquintinib plus BSC to placebo plus BSC at each scheduled post-baseline visit. The tabulation of MMRM includes estimates of least-square (LS) means, standard errors (SE), and 2-sided 95% CIs for each treatment group. Estimates of the LS mean difference, SE of the difference, 2-sided 95% CI of the difference between treatment groups, and p-value are also presented. As a sensitivity analysis, subjects who have more than one assessment in a cycle (i.e., a quality of life assessment at an unscheduled visit), the worst score for that cycle is used in the analysis of change from baseline in the 15 subscales. The above analysis is replicated using these substituted values.

9.2.5.2. *Analysis of Minimally Important Difference and Time to Deterioration*

Depending on each scale and item, the minimally important difference (MID) cut-off for QoL improvement is defined as a change of at least 6.35 to 14.24 points from baseline, based on a recent validation study on subjects with mCRC (Musoro et al., 2020) and the study (Osoba et al., 1998) cited in the EORTC-QLQ-30 Scoring Manual. The MID cut-off for QoL deterioration, stable, and improvement and in each scale and item are listed in Table 8.

Table 8. Summary of MID for EORTC QLQ-C30 Questionnaire

Scale/item	Deterioration	Stable	Improvement
Global health status/QoL	-6.38	-6.38 < and < 8.34	8.43
Physical functioning	-7.47	-7.47 < and < 7.81	7.81
Role functioning	-10.66	-10.66 < and < 14.24	14.24
Emotional functioning*	-10	-10 < and <10	10
Cognitive functioning*	-10	-10 < and < 10	10
Social functioning	-6.18	-6.18 < and < 9.23	9.23
Fatigue	-7.38	-7.38 < and < 10.79	10.79
Nausea and vomiting	-6.62	-6.62 < and < 7.75	7.75
Pain*	-10	-10 < and < 10	10
Dyspnoea*	-10	-10 < and < 10	10
Insomnia*	-10	-10 < and < 10	10
Appetite loss	-9.78	-9.78 < and < 12.28	12.28
Diarrhea	-7.96	-7.96 < and 6.35	6.35
Constipation	-10*	-10* < and <12.75	12.75
Financial difficulties*	-10	-10 < and < 10	10

*The MID of these sca e/ tems were not reported n (Musoro et a ., 2020). Instead, the MID for these sca e/ tems were arb trar y determ ned at 10 po nts, fo ow ng the study (Osoba et a ., 1998) c ted n EORTC QLQ 30 Scor ng Manua . Osoba et a . reported "a tt e" change as a change of 5 10 po nts, and "moderate" change as 10 20 po nts.

The number and percent of subjects achieving MID for each scale (by categories defined in Table 8) are summarized by visit and treatment group.

In addition, for each scale and single item, time to deterioration (TTD) is defined as the time (months) from randomization until the first change of at least 6.18 to 10.66 points (depending on each scale and item) from baseline (Table 8), or death, whichever comes first. Any subject who does not experience TTD at the time of analysis is censored at the date of the most recent study visit in the database for that subject.

TTD is calculated as (date of the first reduction of at least 6.18 to 10.66 points from baseline, death or most recent visit – date of randomization + 1)/30.4375.

Kaplan-Meier estimates for TTD are tabulated by treatment group, using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% CIs. In addition, the two-sided p-value will be obtained from the stratified Kaplan-Meier method to account for the stratification factors. The hazard ratio (HR) between the two treatments (fruquintinib vs placebo), together with its 95% CIs will be calculated from a stratified (i.e. accounting for randomization schedule stratification factors) Cox hazard model in which treatment and baseline value of scale will be included as fixed effects.

Data of EORTC QLQ-C30 questionnaire and subscales are listed by subject and visit.

9.2.5.3. *Handling Missing Data for EORTC QLQ-C30 Questionnaire*

The number of and percent subjects of missing data on each of the 15 subscales are presented by visit and also for the overall trial. Subjects who have died are included in this count.

As a simple sensitivity analysis of the impact of intercurrent events such as death and drop-out, an analysis of covariance (ANCOVA) will be conducted using the change from baseline to the last available assessment for each subject during the period from the date of randomization to the 37 days after the date of last dose. The ANCOVA model, include baseline scale score, randomization schedule stratification factors, treatment, and a baseline score and treatment interaction as fixed-effect variables.

9.2.6. EQ-5D-5L Questionnaire

The EQ-5D is a generic preference-based measure that indirectly measures the utility for health that generates an index-based summary score based upon societal preference weights (Pickard et al 2007).The EQ-5D-5L consists of 5 items that cover 5 main dimensions including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and a general visual analogue scale (VAS) for health status. The range of VAS scoring is from 0 (the worst health imaginable) to 100 (the best health imaginable).

Each of the 5 dimensions comprising the EQ-5D descriptive system is divided into 5 levels of perceived problems as follows.

- Level 1: indicating no problem
- Level 2: indicating slight problems
- Level 3: indicating moderate problems
- Level 4: indicating severe problems
- Level 5: indicating extreme problems

The response levels collected from the EQ-5D-5L five dimensions as a health profile are converted into an EQ-5D-5L index (utility) scores to represent subjects' utility value. The EQ-5D-5L index-based score is typically interpreted along a continuum where a utility value of 1 represents perfect health, 0 represents a state equal to death and a negative value represents a state worse than dead.

The UK value set and scoring algorithm are used to derive the EQ-5D-5L index score for this analysis (Devlin et al., 2018). The detailed scoring algorithm can be found in Appendix 2.

The number and percent of subjects who completed the questionnaires are summarized by visit for each treatment group.

9.2.6.1. *Analysis of Change from Baseline in VAS and Index Scores*

Change from baseline in VAS and index scores are summarized by visit and for each treatment group. The MMRM analysis and the sensitivity analysis described in Section 9.2.5.1 can be similarly applied to the endpoints of

- change from baseline in VAS with the baseline VAS score as covariate;
- change from baseline in EQ-5D-5L index score with the baseline EQ-5D-5L index score as covariate

To ensure the proper amount of data utilized in the model for each visit, the following steps will be implemented to identify data to be included in the model.

(1) Calculate the number of subjects with non-missing assessments for each cycle.

(2) Identify the last cycle with at least 20 subjects in any of the treatment groups and no subsequent cycles having at least 20 subjects in any of the treatment groups.

(3) Assessments after the cycle identified in Step 2 will not be included in the model.

9.2.6.2. *Analysis of Minimally Important Difference and Time to Deterioration*

The appropriate MID cut-off for VAS is defined as a reduction of at least 7 points from baseline, based on a study of 534 cancer subjects evaluated by UK-based scoring algorithm (Pickard et al, 2007).

The appropriate MID cut-off for index score is defined as a reduction of at least 0.063 points from baseline, based on the study on the scoring algorithm from England (McClure et al., 2017). McClure et al. reported the MID in the England population has a mean (standard deviation) of 0.063 (0.013), and a median of 0.064 (interquartile range: 0.055 to 0.073).

The MID cut-off for VAS and index scores for QoL deterioration, stable, and improvement are listed in Table 9.

Table 9. Summary of MID for EQ-5D-5L Questionnaire

Scale/item	Deterioration	Stable	Improvement
VAS	-7	-7 < and < 7	7
Index Score	-0.063	-0.063 < and <0.063	0.063

The number and percent of subjects achieving MID are summarized by visit for each treatment group.

In addition, TTD of VAS is defined as the time (month) from randomization until the first reduction of at least 7 points from baseline or death, whichever comes first. TTD of index score is defined as the time (month)

from randomization until the first reduction of at least 0.063 points from baseline or death, whichever comes first.

TTD for VAS is calculated as (date of the first reduction of at least 7 points from baseline, PD, death or most recent visit – date of randomization + 1)/30.4375.

TTD for EQ-5D-5L index score is calculated as (date of the first reduction of at least 0.063 points from baseline, PD, death or most recent visit – date of randomization + 1)/30.4375.

Subjects who does not experience TTD at the time of analysis are censored at the last visit. Then, for the two time-to event endpoints

- TTD for VAS
- TTD for EQ-5D-5L index score

The Kaplan-Meier method will be used to obtain the descriptive statistics of median, 25% and 75% percentiles along with their 95% CIs by treatment group. In addition, the two-sided p-value will be obtained from the stratified Kaplan-Meier method to account for the randomization stratification factors. The hazard ratio (HR) between the two treatments (fruquintinib vs placebo), together with its 95% CIs will be calculated from a stratified (i.e. accounting for randomization schedule stratification factors) Cox hazard model in which treatment and baseline value of scale will be included as fixed effects.

Results from the descriptive system of 5 dimensions are summarized descriptively by visit for each treatment group. A shift table from baseline for the levels within each of the 5 dimensions is provided by visit and treatment group.

Data of EQ-5D-5L questionnaire are listed by subject and visit.

9.2.6.3. *Handling Missing Data for EQ-5D-5L Questionnaire*

The number of and percent subjects of missing data on the VAS and index score are presented by visit and for the overall trial. Subjects who have died are included in this count.

The sensitivity ANCOVA analysis described in Section 9.2.5.3 will be similarly applied to the endpoints of

- change from baseline in VAS for each subject during the period from the date of randomization to the 37 days after the date of last dose with the baseline VAS score as covariate;
- change from baseline in EQ-5D-5L index score for each subject during the period from the date of randomization to the 37 days after the date of last dose with the baseline EQ-5D-5L index score as covariate

9.2.7. Health Resource Utilization

Data of heath resource utilization including primary reason for visit, type of resource, duration of visit (days) which is calculated as stop date – start date +1, number of visits, concomitant medication prescribed (Yes/No), and special transportation required are summarized descriptively for each treatment group. Each subject may have multiple health care visit during the study period, and the non-missing value from each visit will be utilized in the analysis.

In addition, in the analysis of primary reason for visit, type of resource, concomitant medication prescribed (Yes/No), and special transportation required (Yes/No), only the unique response categories for a subject will be summarized. For example, a subject may have 10 health care visits, the response categories from those 10 visits are just 8 times of “Adverse Event” and 2 times of “Management of mCRC”, hence, this subject will only be counted in those two categories instead of summarizing 10 times in the aforementioned analysis.

Data of heath resource utilization are listed by subject.

9.3. Exploratory Efficacy Endpoints

9.3.1. Circulating Tumor DNA

The analysis of ctDNA will be documented separately, and is not covered in this SAP.

9.3.2. Tumor Marker

Change from baseline in serum CEA will be summarized by visit and for each treatment group.

Data of CEA is listed by subject and visit.

10. Pharmacokinetics

PK population is used for tabulation as specified in this section.

10.1. PK Sampling Schedule

The PK sampling schedule for the first approximately 120 subjects is displayed in Table 2 in the study protocol. Furthermore, the PK sampling schedule for subjects enrolled after the first approximately 120 subjects is displayed in Table 3 in the protocol.

10.2. Data Handling

10.2.1. Handling of Missing Data

Missing concentration data for all subjects who are administered scheduled study treatments is considered as non-informative missing and is not imputed. No concentration estimates are provided for missing sample values.

10.2.2. Handling of below the lower limit of quantification (BLQ) Data

For PK concentration summary, the following rules apply:

- PK concentrations below the lower limit of quantification (BLQ) in pre-dose samples and in samples taken before the time of the first quantifiable value are set to zero;
- The PK concentrations BLQ after quantifiable concentration are set to zero

10.2.3. Handling of the Difference between the Scheduled (nominal time) and the Actual Sampling Times (actual time)

For all sampling times, the actual sampling times relative to dosing are calculated as the difference between the actual clock time of sampling and the actual clock time of dosing. The actual post-dose sampling times relative to dosing expressed in hours and rounded off to two decimal digits are used, except for pre-dose samples occurring prior to dosing, which are reported as zero (0.00), regardless of the time difference. Scheduled sampling times are listed but will not be summarized. If the actual time of sampling is missing, it is reported as NR (not recorded) in the listing, the nominal time is used for summary statistics.

10.3. Listing and Presentation of Individual PK Data

PK data are presented by subject, cycle and day (for instance, C1D1, C1D21, C2D1, etc.), and time point.

1. Concentration data for fruquintinib and M11 are presented to the same decimal place and in original units as reported by the bioanalytical lab, e.g., ng/mL;
2. Listing of PK sampling times including nominal and actual time elapsed from dose with the deviation from the nominal time.

10.4. Summary of PK Concentration Data

The observed concentrations for fruquintinib and metabolite M11 are summarized descriptively at each scheduled timepoint and dose level including. Summaries are presented by cycle and day (for instance, C1D1, C1D21, C2D1, etc.) and time point using descriptive statistics.

- If the time deviation is greater than ± 20%, the PK concentration value is excluded from the summary descriptives.

PK plasma concentration data at each scheduled timepoint and dose level is presented using the following descriptive statistics.

- n
- arithmetic mean and StdDev
- coefficient of variation (CV)%
- median
- minimum and maximum
- geometric mean and geometric CV%
- number and percent of subject with BLQ

The conventions presented in Table 10 below are used for the presentation of the descriptive statistics of plasma concentrations.

Table 10. PK Reporting Precision

Variable	Summarized with:
Minimum, Maximum	3 significant digits or as needed based on actual measured values
Mean (arithmetic and geometric), Median	3 significant digits
StdDev	3 significant digits
CV% and Geometric CV%	1 decimal point

11. Safety

The Safety population is used to evaluate the safety endpoints including AEs, clinical laboratory data, vital signs, single 12-lead ECG parameters, ECHO/MUGA parameters, physical examinations, ECOG performance status, extent of exposure and compliance, survival follow-up, and death. Unless otherwise specified, the safety data during the treatment period will be evaluated, and the treatment period is defined as the duration from the date of the first study drug administration until 37 days after last dose.

11.1. Adverse Events

AEs are collected throughout the study, commencing from the time the ICF is signed until 30 ± 7 days after the last dose day of study treatment, or start of a new treatment of anti-tumor therapy, whichever is earlier. AEs related to COVID-19 are determined by sites and recorded in electronic data capture (EDC), as deemed appropriate.

AEs are coded by SOC and PT using MedDRA version 23.0 or higher. An AE is considered a TEAE if

1. the onset date is on or after the start of study treatment or if the onset date is missing, or
2. if the AE has an onset date before the start of study treatment but worsened in severity after the study treatment until 37 days after the last dose of study treatment or a new treatment of anti-tumor therapy, whichever is earlier. After this period, treatment-related SAEs will also be considered as TEAEs.

TEAEs related to COVID-19 are also flagged in AE analysis dataset.

An AE is considered treatment-related in the summaries if it is assessed as related to the study treatment by the investigator or if the assessment of relationship to study treatment is missing.

Severity of AEs is graded from Grade 1 to Grade 5 according to the National Cancer Institute Common Terminology Criteria for Adverse Event (CTCAE) version 5.0. Missing severity grade is imputed as Grade 3.

AESIs including hepatotoxicity, haemorrhage, hypertension, thyroid dysfunction, proteinuria, dermatological toxicity, cardiac ischemia and infarction, arterial or venous thromboembolic events, and gastrointestinal perforation are listed in Appendix 3.

11.1.1. Overview of TEAEs

An overall summary of the number and percent of subjects along with the total number of adverse events each treatment group is provided for the categories listed in Table 11.

Table 11. Overview of TEAEs

Category	Sub-category
All TEAEs	CTCAE Grade ≥3 Treatment-related Leading to Dose Reduction Leading to Dose Interruption Leading to Treatment Discontinuation Treatment-related Leading to Dose Reduction Treatment-related Leading to Dose Interruption Treatment-related Leading to Treatment Discontinuation Leading to Death
Serious TEAEs	CTCAE Grade ≥ 3 Treatment-related Leading to Dose Reduction Leading to Dose Interruption Leading to Treatment Discontinuation Treatment-related Leading to Dose Reduction Treatment-related Leading to Dose Interruption Treatment-related Leading to Treatment Discontinuation Leading to Death
Treatment-emergent AESIs	CTCAE Grade ≥ 3 Serious Treatment-related Leading to Dose Reduction Leading to Dose Interruption Leading to Treatment Discontinuation Treatment-related Leading to Dose Reduction Treatment-related Leading to Dose Interruption Treatment-related Leading to Treatment Discontinuation Leading to Death
COVID-19-related TEAEs	CTCAE Grade ≥ 3 Serious Treatment-related Leading to Dose Reduction Leading to Dose Interruption Leading to Treatment Discontinuation Treatment-related Leading to Dose Reduction Treatment-related Leading to Dose Interruption Treatment-related Leading to Treatment Discontinuation Leading to Death

A subject with two or more AEs in a category is counted only once for the subject count.

11.1.2. TEAEs by SOC and PT

The number and percent of subjects experiencing a TEAE within each of the categories and sub-categories listed in Table 11 are also summarized by SOC, PT, and highest CTCAE grade for each treatment group.

A subject with two or more adverse events for each combination of SOC and PT is counted only once for the combination.

The summary is sorted in descending order of frequency of SOC according to the sum of Fruquintinib + BSC and Placebo + BSC columns. Within SOC, sort by descending frequency of PT in according to the sum of Fruquintinib + BSC and Placebo + BSC columns.

In addition, the number and percent of subjects are summarized by PT and highest CTCAE grade and by PT and CTCAE grade >=3 for each treatment group.

11.1.3. Treatment-emergent Adverse Events of Special Interest

Treatment-emergent AESI are also summarized by highest CTCAE grade for each treatment group and the subgroups listed below.

Time (days) to onset of first treatment-emergent AESI are descriptively summarized for each AESI and treatment group. Time to first AESI is defined as time interval from date of first administration of study treatment to the earliest onset date among TEAEs within the same AESI categories. That is, if a subject has multiple AEs occurrences under the same AESI category, the earliest AE onset date will be used as the first onset date to the AESI category.

Adverse events of special interest (AESI) are summarized for the following subgroups.

- Age: < 65 years, >= 65 years
- Sex: Female, Male
- Region: North America (including USA), Europe (including Austria, Belgium, France, Germany, Hungary, Italy, Spain, and United Kingdom); Asia (including Japan)
- Race: White, Asian, Black or African American, Other
- BMI (kg/m^2): < 18.5, >= 18.5 to < 24, >= 24
- Prior Therapy: Trifluridine/Tipiracil (TAS-102), Regorafenib , Both Trifluridine/Tipiracil (TAS-102) and Regorafenib
- RAS Status: Wild Type, Mutant
- Duration of metastatic disease: <= 18 months, > 18 months
- Liver Metastases at Baseline: Yes, No

For AEs falling into the AESI category “hepatotoxicity”, a summary table will also be provided by SOC, PT, and highest CTCAE for subjects with the following liver function category at baseline. Each liver function category will be evaluated separately to identify the subjects meeting the criteria. A listing of hepatotoxicity AEs will also be produced for subjects who meet any of the liver function category criteria at baseline (i.e.

aspartate aminotransferase [AST] or alanine aminotransferase [ALT] >3x upper limit of normal [ULN] or total bilirubin >2xULN, or alkaline phosphatase [ALP] <2xULN).

- AST or ALT >3xULN & ≤ 5xULN;
- AST or ALT > 5xULN;
- Total bilirubin >2xULN;
- AST or ALT > 3xULN and Total bilirubin >2xULN;
- AST or ALT >3xULN, Total bilirubin >2xULN and ALP <2xULN

11.1.4. Subgroup analysis of AE

Analysis by BMI category (<18.5, ≥18.5 and <24 and ≥24) will be performed for the following AE summary:

- TEAE overview summary
- SAE summary
- Summary of TEAE leading to drug discontinuation
- Summary of TEAE with CTCAE grade ≥3.

11.2. Laboratory Evaluations

Blood and urine samples for the determination of clinical chemistry, hematology, and urinalysis laboratory variables described in Table 12 will be measured.

Clinical laboratory results will be graded according to CTCAE criteria, Version 5.0. Any graded changes that occurs following the initiation of study drug and represents at least a 1-grade change from the baseline assessment is defined as treatment emergent. Any assessment, for which CTCAE toxicity grades are not available, will not be included in any analyses for which toxicity grades are required. Grade 0 is assigned to all laboratory values except missing values and not already assigned another grade. Missing values are considered missing.

The non-protocol specified tests and urinalysis results will not be summarized; they will only be included in listings. Data recorded by the laboratory will be converted to the International System of Units (SI) and all presentations will use SI units. Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (LLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings. Quantitative data collected between after date of first dose administration and up to 37 days following the last dose of study medication will be used for analysis.

Table 12. List of Laboratory Parameters

Laboratory Category	Parameters
Hematology	Hemoglobin, Hematocrit, Red Blood Cell Count (RBC), Platelet Count, White Blood Cell Count (WBC), Absolute Neutrophil Count, Neutrophils %, Absolute Lymphocyte Count, Lymphocytes %, Absolute Monocyte Count, Monocytes %, Absolute Eosinophil Count, Eosinophils %, Absolute Basophil Count, Basophils %
Blood Chemistry	Albumin, Blood urea nitrogen (BUN), Creatinine, Aspartate transaminase (AST), Alanine aminotransferase (ALT), Alkaline phosphatase (ALP), Total Bilirubin, Lactate dehydrogenase (LDH), Uric acid, Sodium, Potassium, Chloride, Bicarbonate, Glucose, Calcium, Magnesium, Phosphorus, Total cholesterol, Triglycerides, Total Protein
Blood Chemistry – Thyroid Function	Free triiodothyronine (fT3), Serum free thyroxine (fT4), Thyroid-stimulating hormone (TSH)
Urinalysis	pH, Glucose, Protein, White blood cell, Red blood cell
Urinalysis Microscopy	Microscopic White Blood cell count, Microscopic Red Blood cell count, Other
Coagulation	Activated Partial thromboplastin time (aPTT), Prothrombin time, International normalized ratio (INR)

All summaries of hematology, blood chemistry (including thyroid function), urinalysis and coagulation parameters are based on the results of SI units, where applicable. Thyroid function parameters are analyzed under blood chemistry category.

Summary tables for hematology, blood chemistry, coagulation, and urinalysis (pH only) laboratory variables include descriptive statistics for result values and change from baseline for all continuous variables by visit and treatment group.

Toxicities for clinical labs will be characterized according to CTCAE, Version 5.0 (Table 18 of Appendix 4 when possible), and the frequency and percentage of subjects with each CTCAE grade for each visit during the treatment period will be described. Moreover, any occurrence of grade 3 or grade 4 during the treatment period will be summarized, and shift in grade from baseline to the worst post-baseline value will be summarized.

Summary table and listing are also provided for treatment-emergent hepatotoxicity and subjects with or without liver metastasis by each treatment group. Hepatotoxicity is based on the pre-specified thresholds below:

1. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3x upper limit of normal (ULN) and ≤ 5x ULN

2. AST > 3,5,8,10, and 20x ULN, AST > 5x ULN for more than 5 weeks
3. ALT > 3,5,8,10, and 20x ULN, ALT > 5x ULN for more than 5 weeks
4. AST and/or ALT > 3,5,8,10, and 20x ULN, > 5x ULN for more than 5 weeks
5. Total bilirubin elevations > 1.5x, 2x ULN
6. Potential Drug-Induced Liver Injury (DILI): AST and/or ALT > 3x ULN and total bilirubin > 2x ULN
7. Hy's Law criteria: AST and/or ALT > 3x ULN and total bilirubin > 2x ULN and ALP < 2x ULN

An edish plot presenting peak total bilirubin and peak ALT values will also be produced.

Qualitative assessments of urinalysis parameters are summarized for all subjects using the number of subjects with results of negative, trace, or positive.

Summary of clinical significance (Abnormal not clinically significant [NCS] and Abnormal clinically significant [CS]) is also provided by visit and treatment group. Shift from baseline to the worst post-baseline investigators' assessment (i.e. normal, NCS, and CS for quantitative measurements and categorical measurements) will be presented.

All laboratory results (including hematology, blood chemistry, blood chemistry – thyroid function, urinalysis, coagulation, hepatitis, amylase and lipase, and serum/urine pregnancy test data) in SI units are presented in data listings. Tests are listed in alphabetical order within their respective panels (hematology, blood chemistry, urinalysis, and coagulation).

11.3. Vital Signs

Vital signs include systolic blood pressure, diastolic blood pressure, respiratory rate, body temperature, pulse rate, weight, body mass index (BMI) will be computed as weight (kg)/[height (m)]2.

For vital signs, change from baseline to each post-baseline visit and timepoint will be calculated. The potentially clinically significant findings of vital signs will also be defined based on criteria defined in Table 13.

Vital signs are summarized with descriptive statistics for the observed values at each visit and change from baseline to post-baseline visits values by treatment group. The criteria of potentially clinically significant findings are defined in Table 13. The frequency and percentage of subjects with any potentially clinically significant findings during the treatment period will be presented.

Table 13. Potentially Clinically Significant Criteria for Vital Signs

Variable	Criterion value
SBP (mmHg)	Increase from baseline of > 0 - ≤ 20 > 20 - ≤ 40 > 40 Decrease from baseline of > 0 - ≤ 20 > 20 - ≤ 40 > 40
DBP (mmHg)	Increase from baseline of > 0 - ≤ 20 > 20 - ≤ 40 > 40 Decrease from baseline of > 0 - ≤ 20 > 20 - ≤ 40 > 40
Heart rate (bpm)	Increase from baseline of > 0 - ≤ 20 > 20 - ≤ 40 > 40 Decrease from baseline of > 0 - ≤ 20 > 20 - ≤ 40 > 40
Weight (kg)	Percentage increase from baseline of < 5% ≥ 5 – < 10% ≥ 10 - < 20% ≥ 20% Percentage decrease from baseline of < 5% ≥ 5 – < 10% ≥ 10 - < 20% ≥ 20%

Vital signs are listed by subject and visit.

11.4. Electrocardiogram

Electrocardiogram (ECG) parameters include heart rate, PR interval, and QT, QT correction Bazett formula (QTcB), QT correction Fridericia formula (QTcF) and a combination of the Q wave, R wave and S wave (QRS) intervals. Potentially clinically significant ECG findings will be identified using the criteria which are included in Table 14.

Table 14. Potentially Clinically Significant Criteria for ECG

Parameter (unit)	Criterion value
Heart Rate (bpm)	> 120
	< 50
PR Interval (msec)	≥ 210
RR Interval (msec)	> 1200
	< 500
QRS Interval (msec)	≥ 120
	≤ 50
QT Interval (msec)	≥ 500
	≤ 300
QTcF, QTcB (msec)	> 450
	> 480
	> 500
	≤ 300
	Increase from baseline > 30
	Increase from baseline > 60
	> 450 and increase from baseline > 30
	> 450 and increase from baseline > 60
	> 480 and increase from baseline > 30
	> 480 and increase from baseline > 60
	> 500 and increase from baseline > 30
	> 500 and increase from baseline > 60

Single 12-lead ECG are collected in all subjects using standardized equipment during cycles 1 to 3. From cycle 4 onward, ECG is only performed as clinically indicated.

For each ECG parameter, the observed values and change from baseline will be summarized. The 12-lead ECG interpretation by investigator are summarized at each visit descriptively, including the number and percent of subjects with normal, abnormal not clinically significant, and abnormal clinically significant results at baseline and each evaluation.

The criteria of potentially clinically significant findings are defined in Table 14. The frequency and percentage of subjects with any potentially clinically significant findings during the treatment period will be presented. Shift table from baseline to worst post-baseline ECG results is provided.

Single 12-lead ECG interpretations by investigator data are listed by subject and visit.

11.5. Echocardiogram

ECHOs are performed at Screening, cycle 2 day 1, and on day 1, every 3 cycles thereafter. Assessment parameters include left ventricular ejection fraction and overall interpretation of cardiac function. MUGAs are permitted if ECHOs cannot be performed.

Categorical summaries of overall interpretation and change from baseline of left ventricular ejection fraction of ECHO/MUGA results at each visit are summarized. A shift from baseline to the worst post-baseline table for overall interpretation is also provided.

ECHO/MUGA data is listed by subject and visit.

11.6. Physical Examination

A comprehensive physical examination at Screening includes subject general appearance, eyes, ears, nose and throat, head and neck, respiratory, cardiovascular, abdomen (gastrointestinal), skin, genitourinary system, lymph nodes, musculoskeletal, neurological assessments.

Limited physical examination at scheduled visits is a subset the comprehensive physical examination as deemed appropriate by the investigator.

Results of physical examination are listed by subject and visit.

11.7. ECOG Performance Status

ECOG performance status is be summarized descriptively using counts and percentages by visit for each treatment group. A shift from baseline to worst post-baseline value table is also provided.

ECOG performance status is listed by subject and visit.

11.8. Other Safety Endpoints

11.8.1. Survival Follow-up

Subjects received any anti-cancer medications, radiotherapy, and procedures during survival follow-up and survival status are summarized descriptively for each treatment group.

Data of survival follow-up are listed by subject and visit.

11.8.2. Anti-cancer Medication during Survival Follow-up

Anti-cancer medication during survival follow-up are classified using the WHODD version March 2020 or later.

The use of anti-cancer medication during survival follow-up will be summarized using discrete summary statistics, each treatment group and overall for the safety population. If a subject took a specific medication multiple times or took multiple medications within a specific ATC or PT, the subject is counted only once for the respective ATC or PT.

Summaries are ordered in alphabetical order of ATC and then, within an ATC, in decreasing frequencies by PT in overall column. If the frequencies tie, an alphabetic order will be applied.

Data of anti-cancer medication during survival follow-up are listed by subject.

11.8.3. Anti-cancer Procedure during Survival Follow-up

The anti-cancer procedures during survival follow-up are coded using MedDRA version 23.0 or higher.

The use of anti-cancer procedures during survival follow-up will be summarized using discrete summary statistics in each treatment group and overall for the safety population. If a subject had a specific procedure multiple times or had multiple procedures within a specific SOC or PT, the subject is counted only once for the respective SOC or PT.

Summaries are ordered in alphabetical order of SOC and then, within an SOC, in decreasing frequencies by PT in overall column. If the frequencies tie, an alphabetic order will be applied.

Data of anti-cancer procedure during survival follow-up are listed by subject.

11.8.4. Anti-cancer Radiotherapy during Survival Follow-up

The number and percent of subjects with at least one anti-cancer radiotherapy during survival follow-up are summarized for each treatment group.

Data of anti-cancer radiotherapy during survival follow-up are listed by subject.

11.8.5. Deaths

Primary cause of death and whether autopsy was performed are summarized descriptively for each treatment group. Similarly, the deaths happening during the treatment period, defined as the period from the date of the first study drug administration until 37 days after last dose, will also be tabulated. Data of deaths are listed by subject. On-treatment death will be flagged.

11.8.6. Impact of COVID-19

The study is conducted during the COVID-19 pandemic, additional data is collected for evaluating the impact of COVID-19.

To eliminate potential hazards to subjects and study staff due to the COVID-19 pandemic while ensuring subjects safety and maintaining data integrity, subjects are allowed remote visits during the pandemic. The planned protocol deviation analyses are described in Section 8.2; planned sensitivity analyses for the PFS and OS are described in Section 9.1.4, and the summary for COVID-19-related TEAEs are included in Section 11.1.1.

Additional summaries related to the COVID-19 pandemic from the following aspects will be produced for ITT:

- Type of impact on study visit (missing entire visit; Interrupted and/or out of window in-person visit at site; remote visit (virtual or telephone); or other)

- Reason related to COVID-19 (subject diagnosed with COVID-19; quarantined due to COVID-19; site closed or access restricted due to COVID-19; site open but subject unwilling or unable to come to site due to COVID-19; or other)
- Study drug discontinuation due to COVID-19

ITT population will be used for the planned analyses described above. The number of subjects impacted by COVID-19 during the study investigation period as well as at any time will be summarized by treatment group and overall. The study investigation period is defined as the period from the date of randomization to the 37 days after the date of last study treatment administration.

Supporting listings for the described analyses above will be provided.

11.8.7. Interstitial Lung Disease

Interstitial lung disease data collected, including chest x-ray results and oxygen saturation, are listed by subject.

12. IDMC Review

A subset of TLFs for the study final analysis will be used for IDMC meetings. The specific content of the TLFs submitted to the IDMC are determined by the IDMC members. The results to be reviewed by the IDMC will be primarily based on the safety data. Efficacy data is also provided for the purpose of the planned interim futility analysis after 1/3 of OS events has occurred.

For open sessions, the tables are presented with column Total only and the listings contains no treatment header. For closed sessions, the tables are presented with columns Treatment A + BSC, Treatment B + BSC, and Total, and the listings contain treatment headers. The unblended statistician to be involved in the closed sessions of the IDMC will share the actual treatment information for Treatment A an Treatment B.

The IDMC may request to be unblinded by treatment group or per-subject basis at any time. The unblinded biostatistician provides the information to unmask. These communications are maintained in the IDMC workspace and submitted to the Trial Master File at the end of the study.

The study is to be terminated in the case of confirmed futility after evaluation of 1/3 of OS events (i.e., 160 OS events).

At any time, the IDMC may request any other safety-related information deemed necessary to contribute to an appropriate review of safety.

Further details of content for open and closed sessions are provided in Section 18, “Content of Open and Closed Sessions”, of the IDMC Charter in order to maintain the blinding of the study.

13. Changes from Analysis Planned in Protocol

- Not applicable.

14. Reference List

Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JCJM, Kaasa S, Klee MC, Osoba D, Razavi D, Rofe PB, Schraub S, Sneeuw KCA, Sullivan M, Takeda F. The European Organisation for Research and Treatment of Cancer A quality-of-life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute* 1993; 85: 365-376.

Brookmeyer R., and Crowley J. (1982). A confidence interval for the median survival time. Biometrics, 29-41.

Devlin et al., Valuing health-related quality of life: An EQ-5D-5L value set for England. Health Economics. 2018;27:7–22. https://doi.org/10.1002/hec.3564

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer. 2009; 45:228-247.

European Organization for Research and Treatment of Cancer. EORTC QLQ-C30 Scoring Manual. https://www.eortc.org/app/uploads/sites/2/2018/02/SCmanual.pdf

EuroQol Research Foundation. EQ-5D-5L User Guide. Version 3.0; September 2019. https://euroqol.org/wp-content/uploads/2019/09/EQ-5D-5L-English-User-Guide_version-3.0-Sept-2019-secured.pdf

Kim, Y., & Won, S. (2013). Adjusted proportion difference and confidence interval in stratified randomized trials. PharmaSUG 2013. https://www.pharmasug.org/proceedings/2013/SP/PharmaSUG-2013-SP04.pdf

McClure et al., Instrument-Defined Estimates of the Minimally Important Difference for EQ-5D-5L Index Scores. Value Health. 2017 Apr;20(4):644-650. doi: 10.1016/j.jval.2016.11.015. Epub 2017 Jan 10. PMID: 28408007.

Musoro et al., Minimally important differences for interpreting European Organisation for Research and Treatment of Cancer (EORTC) Quality of life Questionnaire core 30 scores in subjects with ovarian cancer, Gynecologic Oncology, 10.1016/j.ygyno.2020.09.007, (2020).

Osoba et al., Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol. 1998 Jan;16(1):139-44. doi: 10.1200/JCO.1998.16.1.139. PMID: 9440735.

Pickard et al., Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes. 2007;5:70. doi: 10.1186/1477-7525-5-70.

Pickard AS, Wilke CT, Lin HW, Lloyd A. Health Utilities Using the EQ-5D in Studies of Cancer. *PharmacoEconomics* 2007;25:365–84

15. Programming Considerations

All TLFs and statistical analyses are generated using SAS for Windows, Release 9.4 (SAS Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure outputs adhere to the following specifications.

15.1. General Considerations

- One SAS program can create several outputs
- Each output is stored in a separate file
- Output files are delivered as follows
    - Two compiled pdf files (with bookmark and TOC) – one for tables and figures, and one for listings];
    - Individual rtf file for the TLFs (this is only applicable to the final delivery, e.g. final interim analysis delivery, final database lock delivery for clinical study report);
    - For figures, include the individual .tiff file (this is only applicable to the final delivery, e.g. final IA delivery, final DBL delivery for CSR)
- Numbering of TLFs follows ICH E3 guidance

15.2. Table, Listing, and Figure Format

15.2.1. General

- All TLFs are produced in landscape format on American letter paper size.
- All TLFs are produced using the Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- The data displays for all TLFs have a minimum blank 1-inch margin on all 4 sides.
- Headers and footers for figures are in Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- Legends are used for all figures with more than 1 variable, group, or item displayed.
- Table and listings are in black and white (no color). Figures are in colors, where applicable.
- Only standard keyboard characters are used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, are not used. Hexadecimal-derived characters are used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) are employed on a case-by-case basis.
- Mixed case is used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

15.2.2. Headers

- TLFs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

15.2.2.1. *Headers for Study*

- All output should have the following header at the top of each page:

```
Hutchison MediPharma Limited                                          Page X of Y
Protocol No.: 2019-013-GLOB1                          Data Cut-off Date: DDMMMYYYY
```

15.2.2.2. *Headers for Study – Interim Analysis*

- All output should have the following header at the top of each page:

```
Hutchison MediPharma Limited                                          Page X of Y
Protocol No.: 2019-013-GLOB1 – Interim Analysis       Data Cut-off Date: DDMMMYYYY
```

15.2.2.3. *Headers for IDMC Meeting*

- All output should have the following header at the top of each page:

```
Hutchison MediPharma Limited                                          Page X of Y
Protocol No.: 2019-013-GLOB1 - IDMC Meeting           Data Cut-off Date: DDMMMYYYY
```

15.2.2.4. *Headers for Japan Safety Lead-in Cohort*

- All output should have the following header at the top of each page:

```
Hutchison MediPharma Limited                                          Page X of Y
Protocol No.: 2019-013-GLOB1 - Japan Safety Lead-in Cohort  Data Cut-off Date: DDMMMYYYY
```

15.2.2.5. *Headers for Japan Safety Monitoring Committee (JSMC) Meeting*

- All output should have the following header at the top of each page:

```
Hutchison MediPharma Limited                                          Page X of Y
Protocol No.: 2019-013-GLOB1 – JSMC Meeting           Data Cut-off Date: DDMMMYYYY
```

15.2.3. Display Titles

- Each TLF are identified by the designation and a numeral. (i.e., Table 14.1.1). A decimal system (x.y and x.y.z) are used to identify TLFs with related contents. The title is centered. The analysis set are identified on the line immediately following the title. The title and table designation are single-spaced. A solid line spanning the margins separate the display titles from the column headers. There is 1 blank line between the last title and the solid line. Parameters or Visits, if applicable, are between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(Intent-to-Treat Population)

15.2.4. Column Headers

- Column headings are displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column is on the far left followed by the treatment group columns. P-values are presented under the 'Fruquintinib + BSC' column.
- For numeric variables, include "unit" in column or row heading when appropriate.
- Analysis set sizes are presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of subjects in the analysis set.
- The order of treatments in the tables and listings is 'Placebo + BSC' first then 'Fruquintinib + BSC', followed by a 'Total' column, where applicable.

15.2.5. Body of the Data Display

15.2.5.1. *General Conventions*

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values are left-justified;
- Whole numbers (e.g., counts) are right-justified; and
- Numbers containing fractional portions are decimal aligned.

15.2.5.2. *Table Conventions*

- Units are included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category are presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages are presented and so counts of 0 are presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups are included.

- An Unknown or Missing category are added to each parameter for which information is not available for 1 or more subjects.

- Unless otherwise specified, the estimated mean, median, Q1, and Q3 for a set of values are printed out to 1 more significant digit than the original values, and standard deviations are printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean (StdDev)	XXX.X (X.XX)
Median	XXX.X
Min, Max	XXX, XXX
Q1, Q3	XXX, XXX
Missing	XXX

- P-values are output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. Every p-value less than 0.001 is presented as <0. If the p-value is returned as >0.999, then present as >0.999.

- Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8), 13 (5.4)). Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation is the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% are presented as 100, without decimal places.

- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of AE data are presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC 2 code), and AEs (by preferred term) are displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically.

- Missing descriptive statistics or p-values which cannot be estimated are reported as “-”.

- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.

- For categorical summaries (number and percent of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject are included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont.)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

15.2.5.3. *Listing Conventions*

- Listings are sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time.

- Missing data are represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.

- Dates are printed in SAS DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates are represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.

- All observed time values are to be presented using a 24-hour clock HH:MM. Time is reported if it was measured as part of the study.

- Units are included where available

15.2.5.4. *Figure Conventions*

- Unless otherwise specified, for all figures, study visits are displayed on the X-axis and endpoint (e.g., treatment mean change from baseline) values are displayed on the Y-axis.

15.2.6. Footnotes

- A solid line spanning the margins separates the body of the data display from the footnotes.

- All footnotes are left justified with single-line spacing immediately below the solid line underneath the data display. Each footnote will end with a period ".".

- Footnotes should always begin with "Note:" if an informational footnote, or a, b, c, etc. if a reference footnote. Each new footnote should start on a new line, where possible.

- Subject specific footnotes are avoided, where possible.

- Footnotes are used sparingly and add value to the table, figure, or listing. If more than six lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data are repeated on each page.

- The order of different types of footnotes need to follow the proper order as shown below

    1. Subject specific footnote, such as [a], [b], *, 1, 2, 3, and etc.;
    2. General footnote starting with “Note: …”, also the text of the footnotes will be properly aligned at the place after the phrase “Note:” if the line of footnote will wrap to the next row.
    3. Abbreviation footnote. The abbreviation of the footnote will be ordered alphabetically, In addition, each word spelling the abbreviation will use uppercase for the first letter unless it is the convention to use lowercase, e.g. “of”, “and”, etc. Each abbreviation will be separated by a “;”
    4. The last line of the footnote section is standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source. For example,

    ```
    Source: Listing 16.2.x.x                    Table Generation: DDMMMYYYY HH:MM
    Program: xxxx.sas
    ```

16. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in Syneos Health SOP Developing Statistical Programs (3907).

Syneos Health SOPs Developing Statistical Programs (3907) and Conducting the Transfer of Biostatistical Deliverables (3908) describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

Syneos Health SOP Pharmacokinetic and Related Data Analyses (3913.01) describes the procedure for the generation and reporting of PK and pharmacodynamics data.

17. Appendix

17.1. Appendix 1. EORTC QLQ-C30 Scoring Algorithm

The principle for scoring these scales is the same in all cases. The steps for scoring are: 1) Estimate the average of the items that contribute to the scale. (i.e. the raw score);
2) Use a linear transformation to standardize the raw score, so that scores range from 0 to 100.

More specifically, if items $I_1, I_2, \ldots, I_n$ are included in a scale, the *RawScore*, *RS*, is the mean of the component items:

$$RawScore \quad RS \quad (I_1 + I_2 + \cdots + I_n)/n$$

Then apply the linear transformation to 0-100 to obtain the desired score for the scale, i.e.

- for **Functional scales**:

$$Score \quad \left\{1 \quad \frac{(RS \quad 1)}{range}\right\} \times 100$$

- for **Symptom scales/items** and **Global health status/QoL**:

$$Score \quad \left\{\frac{(RS \quad 1)}{range}\right\} \times 100$$

where *Range* in the formula is the difference between the maximum possible value of *RS* and the minimum possible value. The QLQ-C30 has been designed so that all items in any scale take the same range of values. Therefore, the range of *RS* equals the range of the item values. Most items are scored 1 to 4, giving *range* = 3. The exceptions are the items contributing to the global health status / QoL, which are 7-point questions with *range* = 6. More detailed information about the items to be included in each scale is summarized in Table 15 below.

To calculate the score for a scale following the aforementioned principles, it is required to at least half of the items have been answered, otherwise, the score will be set as missing. However, for single-item scale, set the score to missing if it is not answered. For example, role functioning and cognitive functioning each contain 2 items, and so these scales can be estimated whenever one of their constituent items is present; physical functioning contains 5 items, and so at least 3 need to have been completed.

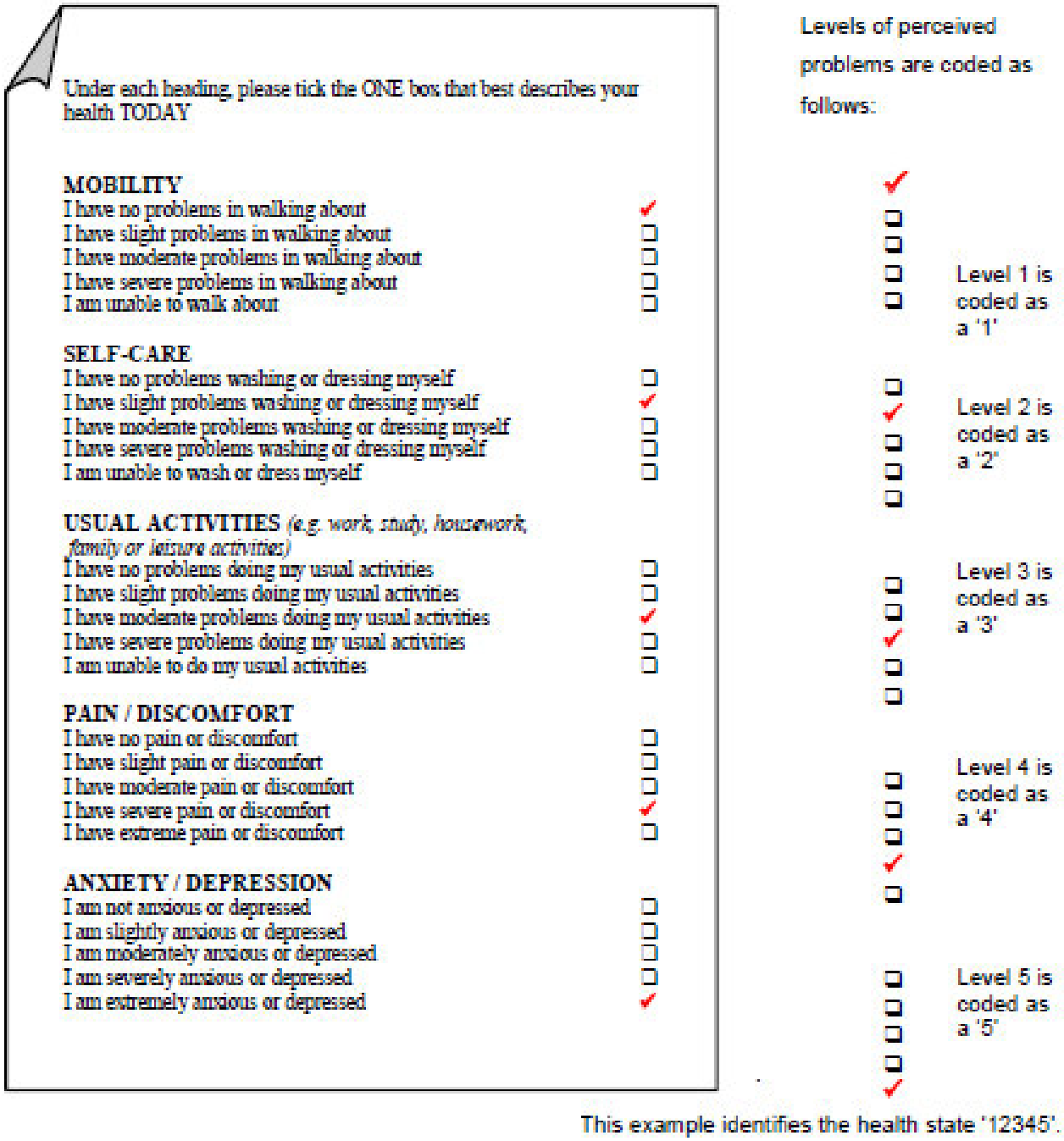
Table 15. Scoring the EORTC QLQ-C30 version 3.0

	Scale	Number of items	Item range	**Version 3.0** Item numbers
Global health status / QoL				
Global health status/QoL (revised)	QL2	2	6	29, 30
Functional scales				
Physical functioning (revised)	PF2	5	3	1 to 5
Role functioning (revised)	RF2	2	3	6, 7
Emotional functioning	EF	4	3	21 to 24
Cognitive functioning	CF	2	3	20, 25
Social functioning	SF	2	3	26, 27
Symptom scales / items				
Fatigue	FA	3	3	10, 12, 18
Nausea and vomiting	NV	2	3	14, 15
Pain	PA	2	3	9, 19
Dyspnoea	DY	1	3	8
Insomnia	SL	1	3	11
Appetite loss	AP	1	3	13
Constipation	CO	1	3	16
Diarrhoea	DI	1	3	17
Financial difficulties	FI	1	3	28

17.2. Appendix 2. Scoring the EQ-5D-5L Descriptive System

The EQ-5D-5L descriptive system can be scored as an example in Figure 2 below. There should be only one response for each dimension.

Figure 2. Example of Scoring the EQ-5D-5L Descriptive System



Then, the EQ-5D-5L index score is a weighted linear combination over 5 dimensions of health status. The coefficient for the weighting for each level of domains are presented in Table 16.

Table 16. EQ-5D-5L weighting coefficient scheme from England for the response of each dimension (Devlin et al., 2018)

Score level of dimension	Coefficient for each level of dimension				
	Mobility	Self-care	Usual activities	Pain/ discomfort	Anxiety/ depression
Level 1: no problem	0	0	0	0	0
Level 2: slight	0.027	0.023	0.023	0.029	0.036
Level 3: moderate	0.035	0.037	0.029	0.039	0.048
Level 4: severe	0.096	0.076	0.075	0.128	0.132
Level 5: unable or extreme [a]	0.127	0.094	0.085	0.155	0.134

[a] For dimensions (Mobility, Self-care, and Usual activities), it takes value “Unable”. For dimensions (Pain/discomfort and Anxiety/depression), it takes value “Extreme”.

The EQ-5D-5L index score is calculated using the equation

$$\text{EQ-5D-5L index score} \quad 1 \quad 2.159 \times \sum \text{coefficient value assigned to the response of each dimention}$$

If any of the 5 dimension scores is missing, the index score will be set to missing.

For example, for a value of health state 23245, the EQ-5D-5L index score is calculated as

$$\text{EQ-5D-5L index score} = 1 - 2.159 \times \sum \text{coefficient value assigned to the response of each dimention} = 1 - 2.159 \times \sum(0.027 + 0.037 + 0.023 + 0.128 + 0.134) = 0.247$$

17.3. Appendix 3. AESI Categories and Preferred Term

Table 17. AESI Categories and Preferred Term list

AESI category	Description and Analysis
Hepatotoxicity	Analysis methods: Hepatic adverse events are evaluated by the standardized categories of Hepatic failure, fibrosis, and cirrhosis and other liver damage-related conditions with corresponding PT listed as in “Preferred Terms” column, categorized by CTCAE grades.

Preferred Terms: Acute hepatic failure, Acute yellow liver atrophy, Ascites, Asterixis, Bacterascites, Biliary cirrhosis, Biliary cirrhosis primary, Biliary fibrosis, Cholestatic liver injury, Chronic hepatic failure, Coma hepatic, Cryptogenic cirrhosis, Diabetic hepatopathy, Drug-induced liver injury, Duodenal varices, Gallbladder varices, Gastric varices, Gastric varices haemorrhage, Hepatectomy, Hepatic atrophy, infiltration eosinophilic, Hepatic lesion,	Hepatic necrosis, Gastroduodenal haemorrhage, Gastric ulcer haemorrhage, Duodenal ulcer haemorrhage, Gastrointestinal ulcer haemorrhage, Hepatic calcification, Hepatic cirrhosis, Hepatic encephalopathy, Hepatic encephalopathy prophylaxis, Hepatic failure, Hepatic fibrosis, Hepatic hydrothorax, Hepatic Hepatic steatosis, Hepatitis fulminant, Hepatobiliary disease, Hepatocellular foamy cell syndrome, Hepatocellular injury, Hepatopulmonary syndrome, Hepatorenal failure,	Hepatorenal syndrome, Hepatotoxicity, Intestinal varices, Liver and small intestine transplant, Liver disorder, Liver injury, Liver operation, Liver transplant, Lupoid hepatic cirrhosis, Mixed liver injury, Nodular regenerative hyperplasia, Non-alcoholic steatohepatitis, Oedema due to hepatic disease, Oesophageal varices haemorrhage, Peripancreatic varices, Portal fibrosis, Portal hypertension, Portal hypertensive enteropathy, Portal hypertensive gastropathy, Portal triaditis,	Portal vein cavernous transformation, Portal vein dilatation, Portopulmonary hypertension, Renal and liver transplant, Retrograde portal vein flow, Reye's syndrome, Reynold's syndrome, Splenic varices, Splenic varices haemorrhage, Subacute hepatic failure, Varices oesophageal, Varicose veins of abdominal wall, Anorectal varices, Anorectal varices haemorrhage, Intrahepatic portal hepatic venous fistula, Peritoneovenous shunt, Portal shunt, Small-for-size liver syndrome, Spider naevus.

Haemorrhage	Description: Any bleeding event, including skin, respiratory, gastrointestinal, genitourinary tracts, brain, tumor or any other site bleeding, or PLT decreased or PT\APTT\INR prolongation with corresponding PT as listed in "Preferred Term" column, without a bleeding symptom. Analysis method: The overall incidence of the risk of hemorrhage with Fruquintinib compared to placebo will be evaluated using the standardized categories of Hemorrhages, and categorized by CTCAE grades.

Preferred Terms:

Blood urine present,	Anal haemorrhage,	Metrorrhagia,	Retroperitoneal haematoma,
Blood urine,	Haematochezia,	Postmenopausal haemorrhage,	Blood blister,
Gastric occult blood positive,	Melaena,	Uterine haemorrhage,	Bloody discharge,
Occult blood positive,	Gingival bleeding,	Vaginal haemorrhage,	Ecchymosis,
Haemorrhage,	Lip haemorrhage,	Skin haemorrhage,	Contusion,
Haematoma,	Mouth haemorrhage,	Skin ulcer haemorrhage,	Purpura,
Haemorrhagic diathesis,	Mucosal haemorrhage,	Soft tissue haemorrhage,	Thrombocytopenic purpura,
Haemorrhagic disorder,	Epistaxis,	Subcutaneous haematoma,	Injection site haemorrhage,
Spontaneous haemorrhage,	Haemoptysis,	Haemorrhage subcutaneous,	Injection site haematoma,
Haemorrhagic stroke,	Pulmonary haemorrhage,	Nail bed bleeding,	Injection site bruising,
Gastrointestinal haemorrhage,	Respiratory tract haemorrhage,	Ear haemorrhage,	Infusion site haemorrhage,
Upper gastrointestinal haemorrhage,	Haemothorax,	Eye contusion,	Infusion site haematoma,
	Pericardial haemorrhage,	Eye haemorrhage,	Infusion site bruising,
Lower gastrointestinal haemorrhage,	Haematuria,	Eyelid bleeding,	Traumatic haemorrhage,
	Renal haemorrhage,	Retinal haemorrhage,	Wound haemorrhage,
Gastric haemorrhage,	Urethral haemorrhage,	Hepatic haemorrhage,	Tumor haemorrhage,
Ulcer haemorrhage,	Urinary bladder haemorrhage,	Splenic haemorrhage,	Disseminated intravascular coagulation.
Rectal haemorrhage,	Menorrhagia,	Haemarthrosis,	

Hypertension	Description: Any event of hypertension or blood pressure increased, with or without any sign or symptom, corresponding PT are listed in "Preferred Term" column. Analysis method: The overall incidence of hypertension with Fruquintinib compared to placebo will be evaluated using the standardized categories of Hypertension. It will be categorized by CTCAE grades.		
Preferred Terms: Hypertension, Blood pressure increased, Blood pressure diastolic increased, Blood pressure systolic increased, Blood pressure inadequately controlled,	Blood pressure management, Blood pressure orthostatic increased, Orthostatic hypertension, Essential hypertension, Hypertensive crisis,	Hypertensive emergency, Malignant hypertension, Hypertensive encephalopathy, Labile hypertension, Prehypertension, Procedural hypertension,	Renal hypertension, Secondary hypertension, Systolic hypertension, Withdrawal hypertension, Blood pressure fluctuation.
Thyroid Dysfunction	Description: Any event of hypothyroidism or other thyroid dysfunction; or Lab TSH increase with T3 or T4 decrease, with or without any symptom. Corresponding PT are listed in "Preferred Term" column Analysis method: The overall incidence of thyroid dysfunction with Fruquintinib compared to placebo will be evaluated using the MedDRA SMQ of Hypothyroidism. It will be categorized by CTCAE grades.		

Preferred Terms: Hypothyroidism, Thyroid disorder, Thyroxine therapy, Thyroid therapy, Thyroid atrophy,	Thyroid function test abnormal, Thyroxine abnormal, Thyroxine decreased, Thyroxine free abnormal, Thyroxine free decreased,	Tri-iodothyronine abnormal, Tri-iodothyronine free decreased, Iodine uptake abnormal, Iodine uptake decreased, Tri-iodothyronine uptake abnormal,	Tri-iodothyronine uptake decreased, Anti-thyroid antibody positive, Anti-thyroid antibody.
Proteinuria	Description: Any event of proteinuria, 24hrs urinary protein high, urinary protein test positive, corresponding PT are listed in "Preferred Term" column. Analysis method: The overall incidence of proteinuria with Fruquintinib compared to placebo will be evaluated using a group of MedDRA PTs regarding proteinuria (PT listing will be defined upon the cleaned and coded AE data). It will also be categorized by CTCAE grades.		
Preferred Terms:	Protein urine present,	Proteinuria.	
Dermatological Toxicity	Description: Any event of hand-foot syndrome or other severe skin reactions, corresponding PT are listed in "Preferred Term" column. Analysis method: The overall incidence of HFS and rash with Fruquintinib compared to placebo will be evaluated using a group of MedDRA PTs regarding HFS and rash (PT listing will be defined upon the cleaned and coded AE data). It will also be categorized by CTCAE grades.		

Preferred Terms: Palmar-plantar erythrodysaesthesia syndrome, Palmar erythema, Dermatitis bullous, Dermatitis allergic, Dermatitis psoriasiform, Dermatitis acneiform, Blister, Rash, Rash erythematous,	Rash maculo-papular, Skin reaction, Skin disorder, Skin exfoliation, Erythrosis, Nail disorder, Nail bed bleeding, Acute generalised exanthematous pustulosis, Cutaneous vasculitis,	Dermatitis exfoliative generalized, Dermatitis exfoliative, Drug reaction with eosinophilia and systemic symptoms, Epidermal necrosis, Erythema multiforme, Exfoliative rash, Oculomucocutaneous syndrome, Skin necrosis, Stevens-johnson syndrome,	Toxic epidermal necrolysis, Toxic skin eruption, Acquired epidermolysis bullosa, Blister rupture, Bullous impetigo, Drug eruption, Epidermolysis bullosa, Epidermolysis, Skin erosion.
Cardiac Ischemia and Infarction	Description: A group of Acute Cardiac Syndrome (ACS) relevant symptoms, such as chest pain, tightness or discomfort, accompanied with dyspnoea, nausea, vomiting…, OR Any diagnosis event of angina, ACS ,or cardiac ischemia or infarction. Corresponding PT are listed in "Preferred Term" column. Analysis method: The overall incidence of cardiac ischemia and infarction with Fruquintinib compared to placebo will be evaluated using the MedDRA SMQ of Ischaemic heart disease. It will be categorized by CTCAE grades.		

Preferred Terms: Acute coronary syndrome, Acute myocardial infarction, Angina unstable, Blood creatine phosphokinase MB abnormal, Blood creatine phosphokinase MB increased, Coronary artery embolism, Coronary artery occlusion, Coronary artery thrombosis, Myocardial infarction,	Myocardial necrosis , Troponin increased, Troponin I increased, Troponin T increased, Infarction, Blood creatine phosphokinase abnormal, Blood creatine phosphokinase increased, Cardiac enzymes increased,	Electrocardiogram ST segment elevation, Electrocardiogram ST-T segment elevation, Angina pectoris, Angina unstable, Arteriosclerosis coronary artery, Arteriospasm coronary, Coronary angioplasty, Coronary arterial stent insertion, Coronary artery bypass,	Percutaneous coronary intervention, Coronary artery disease, Coronary artery insufficiency, Coronary artery stenosis, ECG signs of myocardial ischaemia, Ischaemic cardiomyopathy, Myocardial ischaemia, Prinzmetal angina, Subendocardial ischaemia.
Arterial/Venous Thromboembolic Events	Description: Any arterial or venous thromboembolic event, including but not limited to, arterial thrombosis, pulmonary embolism, deep vein thrombosis, retinal vein occlusion or thrombosis. Corresponding PT are listed in "Preferred Term" column Analysis method: The overall incidence of thromboembolic events with Fruquintinib compared to placebo will be evaluated using the MedDRA SMQ of Embolic and thrombotic events. It will be categorized by CTCAE grades.		
Preferred Terms: Acute aortic syndrome, Acute myocardial infarction, Aortic embolus, Aortic thrombosis, Arterial occlusive disease, Arterial thrombosis, Basal ganglia infarction, Basilar artery occlusion,	Ischaemic stroke, Lacunar infarction, Leriche syndrome, Mesenteric arterial occlusion, Mesenteric arteriosclerosis, Mesenteric artery embolism, Mesenteric artery stenosis, Mesenteric artery thrombosis,	Subclavian artery occlusion, Subclavian artery thrombosis, Superior mesenteric artery syndrome, Thrombotic microangiopathy, Thrombotic thrombocytopenic purpura, Transient ischaemic attack,	Portal vein thrombosis, Post procedural pulmonary embolism, Post thrombotic syndrome, Postoperative thrombosis, Pulmonary embolism, Pulmonary infarction, Pulmonary microemboli,

Basilar artery thrombosis, Blindness transient, Brachiocephalic artery occlusion, Carotid arterial embolus, Carotid artery occlusion, Carotid artery thrombosis, Cerebellar artery occlusion, Cerebellar artery thrombosis, Cerebral artery embolism, Cerebral artery occlusion, Cerebral artery thrombosis, Cerebral hypoperfusion, Cerebrovascular insufficiency, Cerebrovascular stenosis, Coeliac artery occlusion, Coronary artery embolism, Coronary artery occlusion, Coronary artery reocclusion, Coronary artery thrombosis, Embolism arterial, Femoral artery embolism, Femoral artery occlusion, Hepatic artery embolism, Hepatic artery occlusion, Hepatic artery thrombosis, Iliac artery embolism, Iliac artery occlusion, Intraoperative cerebral artery occlusion, Ischaemic cerebral infarction,	Myocardial infarction, Myocardial necrosis, Papillary muscle infarction, Penile artery occlusion, Peripheral arterial occlusive disease, Peripheral arterial reocclusion, Peripheral artery thrombosis, Peripheral embolism, Popliteal artery entrapment syndrome, Post procedural myocardial infarction, Pulmonary artery thrombosis, Renal artery occlusion, Renal artery thrombosis, Renal embolism, Retinal artery embolism, Retinal artery occlusion, Retinal artery thrombosis, Silent myocardial infarction, Spinal artery embolism, Spinal artery thrombosis, Splenic artery thrombosis, Splenic embolism, Stress cardiomyopathy, Subclavian artery embolism, Subclavian artery occlusion, Stress cardiomyopathy, Subclavian artery embolism,	Truncus coeliacus thrombosis, Vertebral artery occlusion, Vertebral artery thrombosis, Visual acuity reduced transiently, Axillary vein thrombosis, Cavernous sinus thrombosis, Cerebral venous thrombosis, Deep vein thrombosis, Deep vein thrombosis postoperative, Embolism venous, Hepatic vein occlusion, Hepatic vein thrombosis, Iliac vein occlusion, Inferior vena cava syndrome, Inferior vena caval occlusion, Intracranial venous sinus thrombosis, Jugular vein thrombosis, May-Thurner syndrome, Mesenteric vein thrombosis, Mesenteric venous occlusion, Obstetrical pulmonary embolism, Obstructive shock, Ophthalmic vein thrombosis, Ovarian vein thrombosis, Paget-Schroetter syndrome, Pelvic venous thrombosis, Penile vein thrombosis, Portal vein occlusion,	Pulmonary thrombosis, Pulmonary vein occlusion, Pulmonary veno-occlusive disease, Pulmonary venous thrombosis, Renal vein embolism, Renal vein occlusion, Renal vein thrombosis, Retinal vein occlusion, Retinal vein thrombosis, Splenic vein occlusion, Splenic vein thrombosis, Subclavian vein thrombosis, Superior sagittal sinus thrombosis, Superior vena cava occlusion, Superior vena cava syndrome, Thrombophlebitis, Thrombophlebitis migrans, Thrombophlebitis neonatal, Thrombophlebitis superficial, Thrombosed varicose vein, Thrombosis corpora cavernosa, Transverse sinus thrombosis, Vena cava embolism, Vena cava thrombosis, Venogram abnormal, Venoocclusive disease, Venoocclusive liver disease, Venous occlusion, Venous thrombosis, Venous thrombosis limb.

Gastrointestinal Perforation	Description: Any event of gastrointestinal perforation. Analysis method: The overall incidence of gastrointestinal perforation with Fruquintinib compared to placebo will be evaluated using the MedDRA SMQ of Gastrointestinal perforation. It will be categorized by CTCAE grades.		
Preferred Terms: Abdominal abscess, Abdominal hernia perforation, Abdominal wall abscess, Abscess intestinal, Acquired tracheo-oesophageal fistula, Anal abscess, Anal fistula, Anal fistula excision, Anastomotic ulcer perforation, Anovulvar fistula, Aorto-duodenal fistula, Aorto-oesophageal fistula, Appendiceal abscess, Appendicitis perforated, Chemical peritonitis, Colon fistula repair, Colonic abscess, Colonic fistula, Diverticular fistula, Diverticular perforation, Douglas' abscess,	Duodenal fistula, Duodenal perforation, Duodenal ulcer perforation, Duodenal ulcer perforation, obstructive, Duodenal ulcer repair, Enterocolonic fistula, Enterocutaneous fistula, Enterovesical fistula, Gastric fistula, Gastric fistula repair, Gastric perforation, Gastric ulcer perforation, Gastric ulcer perforation, obstructive, Gastrointestinal anastomotic leak, Gastrointestinal fistula, Gastrointestinal fistula repair, Gastrointestinal perforation, Gastrointestinal ulcer perforation, Gastropleural fistula,	Ileal fistula, Ileal perforation, Ileal ulcer perforation, Intestinal fistula, Intestinal fistula repair, Intestinal perforation, Intestinal ulcer perforation, Jejunal fistula, Jejunal perforation, Jejunal ulcer perforation, Large intestinal ulcer perforation, Large intestine perforation, Neonatal intestinal perforation, Oesophageal fistula, Oesophageal fistula repair, Oesophageal perforation, Oesophageal rupture, Oesophageal ulcer perforation, Oesophagobronchial fistula, Paraoesophageal abscess,	Peptic ulcer perforation, Peptic ulcer perforation, obstructive, Perforated peptic ulcer oversewing, Perforated ulcer, Perineal abscess, Perirectal abscess, Peritoneal abscess, Peritonitis, Peritonitis bacterial, Procedural intestinal perforation, Rectal abscess, Rectal fistula repair, Rectal perforation, Rectoprostatic fistula, Rectourethral fistula, Retroperitoneal abscess, Small intestinal perforation, Small intestinal ulcer perforation.

17.4. Appendix 4. Clinical Laboratory Parameters CTCAE Criteria

Table 18. Clinical Laboratory Parameters CTCAE Criteria

			ATOXGR			
PARAM (SI Unit)	**Hypo**	**Hyper**	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
Hemoglobin (g/L)		Hemoglobin increased	Increase in >0 - 2 g/dL	Increase in >2 - 4 g/dL	Increase in >4 g/dL	~
	Anemia		Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L	~
Platelets (10^9/L)	Platelet count decreased		<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L
Leukocytes (10^9/L)	White blood cell decreased		<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L
Neutrophils (10^9/L)	Neutrophil count decreased		<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L
Lymphocytes (10^9/L)	Lymphocyte count decreased		<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L
		Lymphocyte count increased	~	>4000/mm3 - 20,000/mm3	>20,000/mm3	~
Eosinophils (%)		Eosinophilia	>ULN and >Baseline	-	-	-
Activated Partial Thromboplastin Time (s)		Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN	~

			ATOXGR			
PARAM (SI Unit)	**Hypo**	**Hyper**	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
International Normalized Ratio		INR increased	>1.2 - 1.5	>1.5 - 2.5	>2.5	~
Albumin (g/L)	Hypoalbuminemia		<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	~
Glucose (mmol/L)	Hypoglycemia		<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L
Creatinine (umol/L)		Creatinine increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline if baseline was abnormal; >1.5 - 3.0 x ULN if baseline was normal	>3.0 x baseline-6.0xULN if baseline was abnormal; >3.0 - 6.0 x ULN if baseline is normal	>6.0 x ULN
Alkaline Phosphatase (uKat/L)		Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Aspartate Aminotransferase (uKat/L)		Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Alanine Aminotransferase (uKat/L)		Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal

			ATOXGR			
PARAM (SI Unit)	**Hypo**	**Hyper**	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
Serum Calcium (mmol/L)		Hypercalcemia	>ULN - 2.9 mmol/L	>2.9 - 3.1 mmol/L	>3.1 - 3.4 mmol/L	>3.4 mmol/L
	Hypocalcemia		<LLN - 2.0 mmol/L	<2.0 - 1.75 mmol/L	<1.75 - 1.5 mmol/L	<1.5 mmol/L
Magnesium (mmol/L)	Hypomagnesemia	Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	~	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L
			<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L
Potassium (mmol/L)		Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L
	Hypokalemia		<LLN - 3.0 mmol/L	~	<3.0 - 2.5 mmol/L	<2.5 mmol/L
Sodium (mmol/L)		Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
	Hyponatremia		<LLN - 130 mmol/L	125-129 mmol/L	120-124 mmol/L	<120 mmol/L
Total cholesterol (mmol/L)		Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L
Bilirubin (umol/L)		Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
Triglycerides (mmol/L)		Hypertriglyceridemia	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L

			ATOXGR			
PARAM (SI Unit)	**Hypo**	**Hyper**	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
Urinary protein		Proteinuria	1+ proteinuria; urinary protein ≥ULN - <1.0 g/24 hrs	2+ and 3+ proteinuria; urinary protein 1.0-<3.5g/24hrs	4+ proteinuria; urinary protein >= 3.5g/24hrs	~

17.5. Appendix 5. Kaplan Meier Estimates and 95% CI from Brookmeyer and Crowley method

17.5.1. SAS Code example for KM estimates and 95% CI from a log-log transformation based on Brookmeyer-Crowley method

Example SAS code for 95% CI calculated from a log-log transformation based on the method by Brookmeyer and Crowley, for median, 25th and 75th percentiles:

```
*** KM Estimates - Quartiles ***;
ods output quartiles=quartiles1;
proc lifetest
      data=ADTTE(where=(PARAMCD="OS"))
      conftype=loglog;
      time AVAL*CNSR(1);
      strata TRTPN;
run;
```

AVAL is the time in months, CNSR is the censoring variable, TRTPN is the treatment group variable.

The output dataset (quartiles1) contains by treatment group, the estimate for median (ESTIMATE, where PERCENT=50), 25% (ESTIMATE, where PERCENT=25), and 75% (ESTIMATE, where PERCENT=75), along with the corresponding 95% CI calculated from a log-log transformation (for each corresponding PERCENT=25, =50 and =75, the CI values are stored in LowerLimit and UpperLimit).

17.5.2. SAS Code example for KM estimates and 95% CI from a linear transformation based on Brookmeyer-Crowley method at selected landmarks

Example SAS code for 95% CI calculated from a linear transformation based on the method by Brookmeyer and Crowley at selected landmarks, for example, at 3, 6, 9, 12, and 18 months:

```
*** KM Estimates - Timelist ***;
proc lifetest
      data=ADTTE(where=(PARAMCD="OS"))
      conftype=linear method=km atrisk timelist=(3, 6, 9, 12, 18)
reduceout outsurv=tlist;
      time AVAL*CNSR(1);
      strata TRTPN;
run;
```

AVAL is the time in months, CNSR is the censoring variable, TRTPN is the treatment group variable.

The outsurv dataset (tlist) will provide by treatment group, the estimate (SURVIVAL*100) at specified time points (variable TIMELIST) and the corresponding 95% CIs (SDF_LCL*100, SDF_UCL*100).

17.6. Appendix 6. Stratified Log-Rank Test

Example SAS code for Stratified Log-Rank Test, accounting for randomization schedule stratification factors.

```
*** Stratified Log rank test ***;
ods output LogUniChisq=logunichisq1;
proc lifetest
      data=ADTTE(where=(PARAMCD="OS"))
      method=km;
      time AVAL*CNSR(1);
      strata STRAT1RN STRAT2RN STRAT3RN;
      test TRTPN;
run;
```

AVAL is the time in months, CNSR is the censoring variable, TRTPN is the treatment group variable, and STRAT1RN, STRAT2RN and STRAT3RN are placeholder variables representing the randomization schedule stratification factors.

The output dataset (logunichisq1) contains the p-value for the Log-Rank Test (ProbChiSq) comparing the treatment groups.

17.6.1. Multiplicity Adjustment for Log-Rank Tests for OS and PFS

A fixed-sequence (hierarchical) testing procedure is 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 is ≤ 0.05, then, a superiority test of for PFS will be conducted at the two-sided significance level of 0.05.

If the resulting p-value from the analysis of primary endpoint OS is ≤ 0.05 then the adjusted p-values are the maximum value between the p-values produced for the OS and PFS procedures.

```
data pvalue;
   input p @@;
   if (_n_ = 1) then
      pseq = 0;
   pseq = max(pseq, p);
   retain pseq;
   cards;
0.021 0.043;
run;
```

The raw p-values used to calculate the adjusted p-value will be obtained from the SAS programming for OS and PFS, then, this sample program will be tailored in the production.

17.7. Appendix 7. Stratified Cox Proportional Hazard Model

Example SAS code for hazard ratio between the 2 treatment groups (fruquintinib vs placebo), and corresponding 95% CIs, calculated from a stratified Cox proportional hazard model (i.e. accounting for randomization schedule stratification factors) in which the treatment group is the only covariate in the model:

```
*** Hazard ratio ***;
ods output hazardratios=hazrat1;
proc phreg
      data=ADTTE(where=(PARAMCD="OS"))
      alpha=0.05;
      model AVAL*CNSR(1)=TRTPN;
      strata STRAT1RN STRAT2RN STRAT3RN;
      hazardratio TRTPN;
run;
```

AVAL is the time in months, CNSR is the censoring variable, TRTPN is the treatment group variable, and STRAT1RN, STRAT2RN and STRAT3RN are placeholder variables representing the randomization schedule stratification factors.

The output dataset (hazrat1) contains the hazard ratio (HazardRatio) and the corresponding 95% CI (WaldLower, WaldUpper). Confirm the order of TRTPN variables is coded so HR < 1 indicates a favorable clinical benefit from fruquintinib over the placebo group.

17.8. Appendix 8. Cochran-Mantel Haenszel test stratified by randomization schedule stratification factors

Example SAS code for p-value of comparing treatment groups based on a Cochran-Mantel Hanzel test stratified by the randomization schedule stratification factors.

```
 *** stratified Cochran-Mantel Haenszel (CMH) test ***;
ods output CMH=cmh1;
proc freq
      data=ADEFF(where=(PARAMCD="ORR"));
      table STRAT1RN*STRAT2RN*STRAT3RN*TRTPN*AVAL/cmh;
run;
```

TRTPN is the treatment group variable and STRAT1RN, STRAT2RN and STRAT3RN are placeholder variables representing the randomization schedule stratification factors.

The output dataset (cmh1) contains the p-value (Prob, corresponding to the Statistic=3, for General Association). If the number of objective responses is not sufficient to utilize the CMH test, a stratified exact CMH test will be performed instead.

17.9. Appendix 9. Adjusted proportion difference between treatment groups with 95% CI using the Wald method to account for randomization schedule stratification factors

Example SAS code for adjusted proportion difference between treatment groups with 95% CI using the Wald method to account for randomization schedule stratification factors:

```
ods output CommonPdiff=pdiff1;
proc freq data = ADEFF(where=(PARAMCD="ORR"));
   tables STRAT1RN*STRAT2RN*STRAT3RN*TRTPN*AVAL/riskdiff(column=2
common cl=wald);
run;
```

Using ADEFF and variable AVAL, the outcome of interest is ORR (i.e. Objective response rate), TRTPN is the treatment group variable and STRAT1RN, STRAT2RN and STRAT3RN are placeholder variables representing the randomization schedule stratification factors. The above example assumes the response is coded in column 2 (i.e. AVAL is coded as 0, 1, where 1 is response), and that fruquintinib is presented in row 1, and placebo is presented in row 2. The above code will be adjusted for correct presentation based on the actual coding in ADEFF if necessary.

The output (pdiff1) provides an adjusted proportion difference between treatment groups (the variable Value, when Method="Mantel-Haenszel") with a 95% CI (the variables LowerCL, UpperCL, when Method="Mantel-Haenszel") using the Wald method to account for randomization schedule stratification factors.

17.10. Appendix 10. REML-based MMRM

Example SAS code for REML-based MMRM:

```
proc mixed
     data=ADQS(where=(PARAMCD="PHYSF" and ANL20FL="Y"))
     method=reml;
     class USUBJID TRTPN AVISITN STRAT1RN STRAT2RN STRAT3RN;
     model CHG = BASE TRTPN AVISITN TRTPN*AVISITN STRAT1RN STRAT2RN
     STRAT3RN/solution ddfm=kr;
     repeated AVISITN/subject=USUBJID type=UN;
     lsmeans TRTPN*AVISITN/diff cl slice = AVISITN;
run;
```

CHG is the change from baseline in score of the subscale, USUBJID is the subject identification variable, TRTPN is the treatment group variable, AVISITN is a placeholder variable for visit, TRTPN*AVISITN is the treatment group-by-visit interaction, BASE is a placeholder variable for baseline value of scale, and STRAT1RN, STRAT2RN, and STRAT3RN are placeholder variables representing the randomization schedule stratification factors.

Prior to performing this analysis, the visits for each subject are limited within the dataset up to the last cycle with at least 20 subjects in any of the treatment groups (i.e. all subsequent cycles have less than 20 patients in each of the treatment groups). If there is a convergence issue with the unstructured covariance model, Toeplitz, Autoregressive (1) (AR (1)) covariance structure is used, following this sequence until convergence is achieved. If the model still does not converge with AR (1) structure, no results are reported. When the covariance structure is not unstructured, the sandwich estimator for the variance-covariance matrix is derived, using the EMPIRICAL option in the PROC MIXED statement in SAS.

Statistical Analysis Plan for Interventional Studies
Text only

SAP Text Version Number: 1.4
SAP Text Date: 21-Jul-2022

Sponsor Name: Hutchison MediPharma Limited

Protocol Number: 2019-013-GLOB1

Protocol Title: 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 (FRESCO-2)

Protocol Version and Date: Amendment 4 – Version 1.0 dated 24 June 2021
Syneos Health Project Code: 7006046

Authors: [redacted]

Notice of Confidential and Proprietary Information:

Revision History

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I conf rm that I have rev ewed th s document and agree w th the content.

Approvals		
Syneos Health Approval		
[redacted]		
Name, T t e Lead B ostat st c an / Support B ostat st c an	S gnature	Date (DD Mmm YYYY)
[redacted]		
Name, T t e	S gnature	Date (DD Mmm YYYY)
Hutchison MediPharma Limited Approval		
[redacted]		
Sponsor Contact	S gnature	Date (DD Mmm YYYY)
[redacted]		
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[redacted]		
Sponsor Contact	S gnature	Date (DD Mmm YYYY)

Table of Contents

1. Glossary of Abbreviations

Abbreviation	Description
AE	Adverse event
ADaM	Analysis Data Model
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
aPTT	Activated Partial thromboplastin time
AST	Aspartate aminotransferase
ATC 2	Anatomical therapeutic class 2
AR (1)	Autoregressive (1)
BMI	Body mass index
BLQ	Below the lower limit of quantification
BRAF	B-Raf proto-oncogene
BSC	Best supportive care
CEA	Carcino-embryonic antigen
CI	Confidence interval
CMH	Cochran-Mantel Haenszel
COVID-19	Coronavirus 2019
ctDNA	Circulating tumor DNA
CTMS	Clinical trial management system
CR	Complete response
CS	Clinically significant
CSR	Clinical study report
CV	Coefficient of variation
CRO	Clinical research organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
dMMR	Deficient mismatch repair
DCR	Disease control rate
DoR	Duration of response

Abbreviation	Description
eCRF	Electronic case report form
ECHO	Echocardiogram
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of treatment
ERT	eResearchTechnology, Inc.
HR	Hazard ratio
ICF	Informed consent form
IDMC	Independent data monitoring committee
IND	Investigational new drug
INR	International normalized ratio
IRT	Interactive response technology
ITT	Intent-to-Treat
IWRS	Interactive web response system
JSMC	Japanese safety monitoring committee
LDH	Lactate dehydrogenase
LS	Least-square
mCRC	Metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
MSI	Microsatellite instability
MSI-H	Microsatellite instability-high
MID	Minimally important difference
MMR	Mismatch repair
MSS	Microsatellite stable
MMRM	Mixed model repeated measures
MRI	Magnetic resonance imaging
MUGA	Multigated acquisition

Abbreviation	Description
NA	Not available
NCS	Not clinically significant
NE	Not evaluable
ORR	Objective response rate
OS	Overall survival
pMMR	Proficient mismatch repair
PD	Progressive disease
PID	Percentage intended dose
PFS	Progression-free survival
PK	Pharmacokinetic
PO	Per os (oral administration)
PR	Partial response
PR	PR Interval (ECG Parameter)
PT	Preferred term
Q1	Lower quartile
Q3	Upper quartile
QoL	Quality of life
QD	Quaque die (once daily)
QTcB	QT correction Bazett formula
QTcF	QT correction Fridericia formula
QRS	A combination of the Q wave, R wave and S wave
RAS	Rat sarcoma
REML	Restricted maximum likelihood
RD	Relative dose
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SD	Stable disease

Abbreviation	Description
StdDev	Standard deviation
SDTM	Study Data Tabulation Model
SE	Standard error
SI	International System of Units
SOC	System organ class
TLFs	Tables, listings and figures
TSH	Thyroid-stimulating hormone
TTD	Time to deterioration
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
VAS	Visual analogue scale
VEGF	Vascular Endothelial Growth Factor
WHODD	World Health Organization Drug Dictionary

2. Purpose

The purpose of this statistical analysis plan (SAP) for the study is to ensure that the data listings, summary tables and figures that are to be produced, and the statistical methodologies that are used, are complete and appropriate to allow valid conclusions regarding the study objectives. The SAP adheres to the proper regulatory guidelines and most recent International Council for Harmonisation guidelines (E3, E6, E9). All decisions regarding the final analyses, as defined in this SAP document, have been made prior to locking the database; any deviations from these guidelines will be documented in the clinical study report (CSR).

A separate SAP is to be developed for the protocol Japanese Specific Addendum (Safety Lead-In for Japan).

2.1. Responsibilities

Syneos Health is to perform the statistical analyses and are responsible for the production and quality control of all Study Data Tabulation Model (SDTM) datasets, Analysis Data Model (ADaM) datasets, and the tables, listings, and figures (TLFs) for efficacy and safety, as well as tabulation of fruquintinib and M11 concentrations from PK (pharmacokinetic) plasma samples. Details for analysis of circulating tumor DNA and pharmacogenomics will be prepared in a separate document. The SAP for population PK, Electrocardiogram (ECG) (pharmacodynamics) and QTc-PK analysis will be prepared separately by another contract research organization (CRO).

2.2. Timings of Analyses

An independent data monitoring committee (IDMC) is to review descriptive summaries of accumulating safety and subject disposition every 6 months, or at a frequency recommended by the IDMC, as described in the IDMC Charter Final Version 1.0 dated 25-Aug-2020. An unblinded team from Syneos Health Biostatistics is to perform the analyses as described in Section 18, Content of Open and Closed Sessions of the IDMC Charter, in order to maintain the blinding of the study.

2.2.1. Interim Analyses

One interim non-binding futility analysis is to be performed once 1/3 of the total number of overall survival (OS) events (i.e., 160 OS events) have occurred. This interim analysis is for futility only, there are no plans to stop the study early for efficacy based on OS data at the interim analysis.

The IDMC is to be instructed to recommend stopping the study for futility if the 1-sided p-value from a stratified log-rank test is at least 0.772 (corresponding to an observed HR of 1.133). Otherwise, the study is to be continued with full enrollment.

There is a 22.8% chance of terminating the study for futility at the interim analysis if the true median OS in fruquintinib arm is 5 months, i.e., fruquintinib is ineffective. There is a 0.4% chance of stopping for futility, declaring fruquintinib ineffective at the interim if the true median OS in fruquintinib arm is 6.8 months, i.e., fruquintinib is effective in the study population.

2.2.2. Final Analysis

If the study does not stop based on the futility analysis, the final analysis for the CSR will be conducted when at least 480 OS events have been observed. All study data collected up through the time of the final analysis will be summarized, unless otherwise specified. Unblinding will occur at the time of the final analysis.

3. Study Objectives

3.1. Primary Objective

- To evaluate the overall survival (OS) of fruquintinib plus best supportive care (BSC) compared to placebo plus BSC in subjects with refractory metastatic colorectal cancer (mCRC).

3.2. Secondary Objective(s)

- To evaluate progression-free survival (PFS) of fruquintinib plus BSC compared to placebo plus BSC.
- To evaluate the objective response rate (ORR), disease control rate (DCR), and duration of response (DoR).
- To assess the safety and tolerability of fruquintinib plus BSC compared to placebo plus BSC.
- To characterize the PK exposure of fruquintinib and metabolite M11 in subjects with refractory mCRC.
- To evaluate the effect of fruquintinib on cardiac repolarization, as detected by changes in electrocardiogram (ECG) QTc intervals, and the potential relationship with fruquintinib and M11 plasma concentrations.
- To explore the relationship between fruquintinib exposure and endpoints for efficacy and safety.
- To evaluate quality of life (QoL) as assessed by using European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30: cancer-specific; and EQ-5D-5L questionnaires.
- To assess resource utilization (for example, hospitalizations, concomitant medications).

3.3. Exploratory Objective

- To assess potential predictive biomarkers of response to fruquintinib.

Details of the study objectives and correspondent endpoints is provided in Table 1.

Table 1. Objectives and Corresponding Endpoints

Tier	Objectives	Endpoints
Primary	To evaluate the overall survival of fruquintinib plus BSC compared to placebo plus BSC in subjects with refractory mCRC	OS
Secondary	To evaluate progression-free survival of fruquintinib plus BSC compared to placebo plus BSC	PFS
	To evaluate the objective response rate, disease control rate, and duration of response	• ORR • DCR • DoR

Tier	Objectives	Endpoints
	To assess the safety and tolerability of fruquintinib plus BSC compared to placebo plus BSC	Safety including treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), deaths, ECG's, and clinical laboratory abnormalities
	To characterize the PK profile of fruquintinib in subjects 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 electrocardiogram (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 (e.g., OS) and safety (e.g., adverse events [AEs]) endpoints
	To evaluate quality of life (QoL) as assessed by 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 (for example, hospitalizations, medications)	Resource utilization including all concomitant medications, days in hospital
Exploratory	To assess potential predictive biomarkers of response to fruquintinib	• Change from baseline in circulating tumor DNA (ctDNA) • Change from baseline in tumor markers (carcino-embryonic antigen [CEA]) • Pharmacogenomics

4. Study Details/Design

4.1. Brief Description

The study is a global, randomized, double-blind, placebo-controlled, multicenter phase 3 clinical trial to compare the efficacy and safety of fruquintinib plus BSC versus placebo plus BSC in subjects with mCRC. Approximately 687 subjects are to be randomized in a 2:1 ratio to either the fruquintinib plus BSC treatment group or the placebo plus BSC treatment group.

Randomization is stratified by the following factors:

- Prior therapy with trifluridine/tipiracil (TAS-102) versus regorafenib versus both trifluridine/tipiracil (TAS-102) and regorafenib.
- RAS (rat sarcoma) status (wild type versus mutant).
- Duration of metastatic disease (≤18 months versus >18 months).

Subjects are to receive study treatment, with each 4-week cycle consisting of 3 weeks of daily oral study medication and 1 week of study treatment interruption (3 weeks on/1 week off). Tumor evaluation is performed by imaging (computed tomography [CT] or magnetic resonance imaging [MRI] scan) every 8 weeks until there is progressive disease (PD), death, new anti-cancer treatment, study treatment discontinuation or study completion, whichever comes first. Safety parameters include assessment of adverse events (AE), laboratory tests, vital signs, ECG, Echocardiogram (ECHO), physical examination, Eastern Cooperative Oncology Group (ECOG) performance status, EORTC QLQ-C30 and EQ-5D-5L questionnaires. Post-discontinuation anti-tumor treatment and survival follow-up after PD is also recorded.

4.2. Subject Selection

The study is conducted at approximately 140 international study sites with a study population of subjects ≥18 years of age with histologically and/or cytologically documented metastatic colorectal adenocarcinoma who progressed on, or were intolerant to, all standard chemotherapies and relevant biologics and TAS-102 and/or regorafenib.

4.2.1. Inclusion Criteria

Refer to Section 5.3 Inclusion Criteria of the study protocol.

4.2.2. Exclusion Criteria

Refer to Section 5.4 Exclusion Criteria of the study protocol.

4.3. Statistical Hypothesis

This study is 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 is 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).

4.4. Determination of Sample Size

With regards to the study, the total sample size and number of OS events required for efficacy assessment in the intent-to-treat population is calculated based on the following assumptions:

- A one-sided significance level of 0.025;
- Assuming an OS hazard ratio (HR) of 0.73 (fruquintinib arm/placebo arm), this sample size yields approximately 90% statistical power to detect superiority of the fruquintinib arm over placebo arm. 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).
- An enrollment rate of 30 subjects per month during the first 3 months and 50 subjects per month thereafter;
- Yearly dropout rate of 10%;
- Randomization ratio = 2:1 (fruquintinib arm/placebo arm);
- Data maturity = 70%;
- One interim futility analysis when 1/3 of the total number of OS events (i.e., 160 OS events) have occurred, the Lan-DeMets spending function is used in the calculation.

Under the premise of these assumptions, approximately 687 subjects are to be randomized to this study over approximately 15 months in this study. OS is to be analyzed when 480 OS events have been observed, which is expected to occur in approximately 7 months after the end of enrollment. EAST version 6.5 was utilized for the calculation.

In clinical practice, TAS-102 is used more commonly than regorafenib. To ensure that the subject population is representative of clinical practice, post-regorafenib (regorafenib or both trifluridine/tipiracil (TAS-102) and regorafenib) subjects are to be capped at 344. This ensures that at least 50% of the subjects are post-TAS.

Subjects are considered in post-TAS-102 or post-regorafenib populations if they have received at least one dose of either agent, respectively, prior to entering the study. Based on the similar mechanisms of action between regorafenib and fruquintinib, it is to be of clinical interest to evaluate the magnitude of benefit in each of the populations when compared to the intent-to-treat population.

4.5. Treatment Assignment and Blinding

The study subject, investigators, and study site personnel are to remain blinded to all randomization assignments throughout the study. The sponsor's study director, study monitor, and any other sponsor and Syneos Health personnel who are in regular contact with the study site are to remain blinded to all subject randomization assignments, except sponsor pharmacovigilance personnel for the purpose of Investigational New Drug (IND) safety reports. Treatment is allocated using Interactive Web Response System (IWRS) randomization strategy and procedure defined in the IWRS manual.

Unblinding can occur in emergency cases. If unblinding is required for treatment of a subject for an SAE, the investigator must first contact the sponsor's medical monitor before unblinding, and then unblind the subject using the IWRS. Once unblinded, the subject should discontinue the treatment but continue to be followed for safety and efficacy. The investigator should record the event in the source document.

The interim futility analysis maintains blinding at IDMC meetings during the Open Sessions following the procedures described in Section 18, Content of Open and Closed Sessions of the latest version of the IDMC Charter.

4.6. Administration of Study Medication

Fruquintinib (HMPL-013) capsule 5 mg is administered orally (PO) once daily (QD), 3 weeks on, 1 week off (4-week cycles). Subjects are randomized into either fruquintinib in combination with BSC group (treatment group) or placebo in combination with BSC group (control group) in a 2:1 ratio (Figure 1).

If study treatment dose adjustment is required, the site must log into the IWRS, adjust the dose, reassign the drug serial number, and dispense new study treatment dose (in 1 mg capsules) to the subject. If the dose is adjusted a second time, i.e., from 4 mg QD to 3 mg QD, the site must log into the IWRS and record the second dose adjustment. On this occasion, it is not necessary to reassign a new drug serial number. If tumor evaluation shows PD during the previous cycle and new drug has been dispensed, the subject must return all unused study treatment on the 30-day safety visit after end of treatment (EOT).

- Treatment 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.

Subjects are allowed to have no more than 2 dose reductions: one reduction from 5 mg QD to 4 mg QD, and if not tolerated, then a second reduction from 4 mg QD to 3 mg QD. Once a dose has been reduced, it cannot be re-escalated. The dose reduction sequence by starting dose is shown in Table 2 below.

Table 2. Dose Modification Sequence by Starting Dose

Dose Level 0* (Original dose)	5 mg QD 3 weeks on, 1 week off	fruquintinib of 5 mg, 1 capsule, or 1 capsule of the matching placebo
Dose Level -1* (the 1st dose reduction)	4 mg QD 3 weeks on, 1 week off	fruquintinib of 1 mg, 4 capsules, or 4 capsules of the matching placebo
Dose Level -2* (the 2nd dose reduction)	3 mg QD 3 weeks on, 1 week off	fruquintinib of 1 mg, 3 capsules, or 3 capsules of the matching placebo

Reasons and guidelines for dose modifications are detailed in Section 7.5.6 of the protocol.

4.7. Study Procedures and Flowchart

The study contains the following procedures.

- Screening Period: This period contains two visit windows of -28 to -1 days and -7 to -1.
- Study Treatment Period: This period contains treatment cycles, with a visit window of +/- 3 days for each scheduled visit starting at Cycle 2 day 1.
    - Cycle 1 includes cycle 1 day 1 and cycle 1 day 21 visits;
    - Cycle 2 includes cycle 2 day 1 and cycle 2 day 21 visits;
    - Cycle 3 includes cycle 3 day 1 and cycle 3 day 21 visits;
    - Cycle 4 and beyond include cycle 4 day 1, cycle 5 day 1, etc.
- Follow-Up: This period contains the following.
    - Post treatment: 7 days after last dose with a visit window of +/- 3 days,
    - Safety Follow-up: 30 days after EOT visit with a visit window of +/- 7 days, and
    - Survival Follow-up: 12 weeks from EOT visit with a visit window of +/- 14 days.
    - EOT: last non-missing assessment during the treatment period (treatment period is from the date of the first study drug administration until 37 days after last dose)

The protocol activities include the following throughout the periods listed above.

- Informed Consent.
- Demographics.
- Medical History, Disease History, and molecular characterization of RAS, B-Raf proto-oncogene (BRAF), Microsatellite Instability (MSI)/ Mismatch Repair (MMR) status.
- Prior and Concomitant Medication/Concomitant Procedure.
- Comprehensive Physical Examination.
- Limited Physical Examination.
- ECOG.
- Vital Signs.
- Hematology.

- Blood Chemistry.
- Blood amylase and lipase.
- Coagulation.
- Thyroid Function.
- Urinalysis.
- Serum Pregnancy Test.
- Urine Pregnancy Test.
- 12-lead ECG.
- ECHO/Multigated acquisition (MUGA).
- Tumor Evaluation/Imaging.
- Tumor Markers.
- Circulating Tumor DNA, excluded from Japanese Specific Addendum.
- PK Plasma Sampling.
- Subject Randomization, excluded from Japanese Specific Addendum.
- Drug/Dispense/Return.
- Study Treatment.
- Adverse Event.
- Survival Follow-up.
- EORTC QLQ-C30 Questionnaire, excluded from Japanese Specific Addendum.
- EQ-5D-5L Questionnaire, excluded from Japanese Specific Addendum.

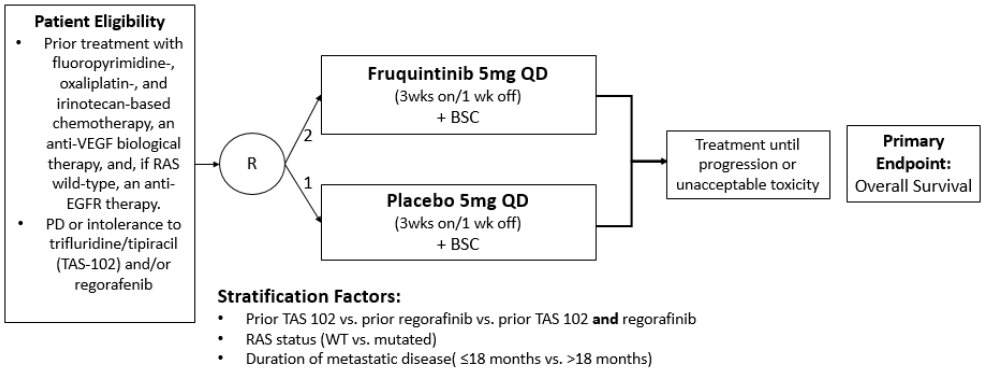
Details of study procedures can be found in the following tables within the protocols.

- Table 1. Schedule of Events.
- Table 2. Schedule of Events for Pharmacokinetic and Electrocardiogram Evaluations for the First Approximately 120 Subjects, and
- Table 3. Schedule of Events for Pharmacokinetic and Electrocardiogram Evaluations for Subjects

Enrolled After the First Approximately 120.

The study schematic is presented in Figure 1.

Figure 1. Study Design Schema



5. Endpoints

5.1. Primary Efficacy Endpoint

The primary endpoint of the study is OS, defined as the time (months) from date of randomization to death from any cause. That is, OS is calculated as (date of death or last known alive – date of randomization + 1)/30.4375. Subjects without report of death at the time of analysis are censored at the date last known alive. Subjects lacking data beyond the date of randomization have their survival time censored at the date of randomization. OS will not be censored if a subject receives subsequent anticancer treatments after discontinuation of the study treatments. Date of last known alive defined in Section 7.2.4 and date of death is defined in Section 7.2.5 of the SAP.

5.2. Secondary Endpoints

- Key secondary efficacy endpoint: PFS.

PFS is defined as the time (months) from randomization until the first radiographic documentation of objective progression as assessed by investigator using Response Evaluation Criteria In Solid Tumors (RECIST) v1.1, or death from any cause. More specifically, PFS will be determined using all the assessment data up until the last evaluable visit prior to or on the date of (i) disease progression as defined by RECIST Version 1.1 or death; or (ii) withdrawal of consent or lost to follow-up; or (iii) receiving subsequent anti-cancer therapy, whichever is earlier. Subjects without report of PD or death from any cause at the time of analysis are censored as described in Table 3 below.

The PFS time will always be derived based on scan dates not tumor assessment dates. RECIST assessments/scans contributing towards a particular visit may be performed on different dates. The following rules are applied:

1. Date of progression is determined based on the earliest of the dates of the component that triggered the progression.

2. When censoring a subject for PFS, the subject is censored at the latest of the dates contributing to a particular overall visit assessment.

Table 3. Censoring Rules for PFS

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

Note: An adequate rad o og c assessment s def ned as an assessment where the Invest gator determ ned rad o og ca response s comp ete response (CR), part a response (PR), stab e d sease (SD), or PD. If PD and new ant - cancer therapy occur on the same day, w assume that the progress on was documented f rst, e.g. outcome s progress on and the date s the date of the assessment of progress on

Note: Two consecut ve schedu ed tumor assessments s equa to 126 days (=2* (8 weeks *7+ 7 days)) s nce prev ous eva uab e RECIST 1.1 or base ne assessment f there s no post base ne tumor assessment.

Example of Situation #8,

Visit	Date of Assessment	Overall Response	PFS
C5D1	01JAN2020	SD	Censored
C7D1	29JAN2020 ± 3 days	Missing	
C9D1	26FEB2020 ± 3 days	Missing	
C11D1	25MAR2020 ± 3 days	PD or Death	

- The additional anti-tumor secondary efficacy endpoints include ORR, DCR, and DoR. The derivation of the best overall response is detailed in Section 9.2.3.
    - ORR is defined as the proportion of subjects achieving a best overall response of confirmed complete response (CR) or partial response (PR), per RECIST v1.1, as determined by the investigator.

Objective response rate (ORR) will be calculated using two different ways:

- Scenario #1: ORR will be calculated using a strict interpretation of RECIST Version 1.1. Objective response will be derived as no/yes variable. Subjects with a BOR of confirmed CR or PR will be assigned 'Yes'. Subjects not having a BOR of confirmed CR or PR will be assigned 'No'. Hence, ORR is defined as the proportion of subjects with objective response being "Yes".
- Scenario #2: $ORR_{UNCONF\ RMED}$ will be calculated using all responses regardless of confirmation. Objective response will be derived as no/yes variable. Subjects with a BOR of confirmed CR, confirmed PR, unconfirmed CR or unconfirmed PR will be assigned "Yes". All subjects with other BOR values will be assigned "No". Hence, $ORR_{UNCONF\ RMED}$ is defined as the proportion of subjects with objective response being "Yes".

- DCR is defined as proportion of subjects achieving a best overall response of confirmed CR, PR, or SD (for at least 7 weeks)per RECIST v1.1, as determined by the investigator. To be qualified for SD, the duration of SD should last for at least 7 weeks.
- DoR is defined as the time (months) from the first occurrence of PR or CR by RECIST Version 1.1, until the first date that progressive disease is documented by RECIST Version 1.1, or death, whichever comes first. Only those subjects with confirmed responses of CR or PR will be included in this analysis. Censoring will follow the rules outlined for PFS in Table 3 in this section. For those subjects who do not have censored DoR, it is calculated as (date of death or PD or last assessment – date of first occurrence of confirmed CR or PR + 1)/30.4375.

- Changes in health status (QLQ-C30: cancer specific; and EQ-5D-5L).
- Resource utilization including all concomitant medications, days in hospital.

5.3. Exploratory Endpoints

- Change from baseline in circulating tumor DNA (ctDNA), analysis plan to be included in a separate document.
- Change from baseline in tumor markers (carcino-embryonic antigen [CEA]).
- Pharmacogenomics, analysis plan to be included in a separate document.

5.4. Safety Endpoints

- Safety including treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), deaths, ECG's, and clinical laboratory abnormalities.

5.5. Pharmacokinetic Endpoints

- Observed plasma concentrations, estimated population PK and exposure parameters of fruquintinib and M11.
- QTc interval and plasma concentrations of fruquintinib and M11 at specified time points.

5.6. Pharmacodynamic Endpoints

- Parameters describing exposure-response with efficacy (e.g., OS) and safety (e.g., AEs) endpoints.

6. Analysis Populations

6.1. Screened Population

The Screened population includes all subjects who signed informed consent form (ICF).

6.2. Intent-to-Treat Population

The Intent-to-Treat (ITT) population includes all randomized subjects. Subjects are analyzed by treatment group as randomized. The ITT population is the primary population for evaluating all efficacy endpoints and subject characteristics.

6.3. Safety Population

The Safety population includes all randomized subjects who received at least one dose of study treatment. Subjects in this population are analyzed according to the treatment they actually received. This population is used for all safety analyses.

In the event that there are protocol deviations reported during the conduct of the study leading to a patient receiving mixed treatment (ie, receiving both placebo and fruquintinib), the actual treatment assigned for the patient will be the most frequently used treatment. For example, if a patient received 42 days of placebo and 21 days of fruquintinib during the treatment period, then the actual treatment for the patient will be PLACEBO. However, if the duration of treatment for placebo and fruquintinib tie, then the assigned treatment at the time of randomization for the patient will be the actual treatment used for the patient in the summary. For example, a patient was randomized to fruquintinib, but received 21 days of placebo and 21 days of fruquintinib during the treatment period, then the actual treatment for the patient will be FRUQUINTINIB which is the assigned treatment at randomization.

6.4. Per Protocol (PP) Population

The per-protocol (PP) analysis set will include only those subjects in ITT who received the treatment to which they were randomized to and have no major protocol deviations that preclude the assessment of efficacy and/or data integrity. Subjects who took the wrong treatment at any time during the study will be excluded from the PP population. PP population is used for sensitivity analyses of OS and PFS, and may be used to analyze selected endpoints to test the robustness of results. The criteria for inclusion in the PP subset will be finalized and documented prior to unblinding of the study.

6.5. Pharmacokinetic (PK) Population

The PK population includes all subjects who receive at least one dose of study treatment and have at least one post-dose PK sample obtained and analyzed (i.e. valid result being available). The PK population is used for tabulation of fruquintinib and M11 concentrations from PK plasma samples.

6.6. Protocol Deviations

Protocol deviations including deviations that are related to COVID-19 are recorded in the clinical trial management system (CTMS) as outlined in the latest version of the Protocol Deviation and Non-compliance Management Plan. During the course of the study, a list of key programmable PDs will be produced and reviewed periodically, these PDs will be reconciled into the CTMS. These programmable PDs include but

not limited to the (i) programmable inclusion criteria 1-5, 7-9, 12, exclusion criteria 1-7, 13, 21, 26; (ii) randomized but failed to receive treatment; (iii) treated without randomization; (iv) other PDs that may affect efficacy evaluation. All major and minor protocol deviations will be reviewed and confirmed during blind data review meeting prior to database lock. Out of all major protocol deviations identified, a subset of protocol deviations leading to exclusion of subjects from PP population will be determined.

7. General Aspects for Statistical Analysis

7.1. General Methods

- Summaries are presented for each treatment group and overall for subjects' disposition, demographics and baseline characteristics, medical history, disease history, prior medications, and concomitant medications tables. Summaries are presented for each treatment group for other tables.
- All data listings that contain an evaluation date contains a relative study day as defined in Section 7.2.3.
- For categorical variables, summary tabulations of the number and percent of subjects within each category of the parameter as seen on the electronic case report form (eCRF) are to be presented. Percentage calculations are based on the number of subjects within treatment group and overall, unless otherwise specified. Percentages are rounded to 1 decimal place, unless otherwise specified. The category Missing is included in subject-level demographics and disease history tables when the count is greater than zero for missing subjects.
- For continuous variables, the number of subjects, mean, standard deviation (StdDev), median, lower quartile (Q1), upper quartile (Q3), minimum, and maximum values are presented. The precision of summary statistics, unless otherwise specified, is as follows:
    - Minimum, maximum: same decimal places as the raw data.
    - Mean, median, Q1, and Q3 : 1 more decimal place than the raw data.
    - Standard deviation, standard error: 2 decimal places more than the raw data.
- For results from a mixed model repeated measures, least-square (LS) mean and LS mean difference are presented with one decimal place, and standard error (SE) of LS means and SE of LS mean difference are presented with two decimal places.
- Comparison between treatment groups are calculated as fruquintinib plus BSC versus placebo plus BSC.
- Two-sided 95% confidence intervals (CI) are provided and rounded to 2 decimal places, unless otherwise specified.
- 2-sided p-values are presented with 3 decimal places.
- Any rounding will be done after all calculations are made.

7.2. Key Definitions

7.2.1. First Dose Date

First dose date is defined as the day of first dose of study treatment received on or after date of

randomization.

7.2.2. Last Dose Date

Last dose date is defined as day of the last non-zero dose of study treatment. The last dose date is typically obtained from the study drug administration records. For the situation that the last non-zero dose record has a partial end date (i.e. only missing day) for a patient, the following algorithm will be implemented to impute the partial end date.

1. Calculate the date that is 21 days after the start date of the record;
2. Obtain the end date of the month for the month of partial end date;
3. Get the end of study date;
4. Get the death date;
5. The partial end date will be imputed to be the earliest among those dates from Item 1 to 4.

For example, for a patient, the last non-zero dosing record has the start date being 19 Aug 2020, and the end date being partial as Sep 2020. With the end of study and death date being 13 Sep 2020, after implementing the algorithm above, the partial end date will be imputed to be 08 Sep 2020 which is the earliest date among (08 Sep 2020, 30 Sep 2020, and 13 Sep 2020).

For subjects ongoing for the treatment period at time of analysis prior to database lock, the last dose date is the date of the most recent study visit in the database for that subject.

7.2.3. Study Day

The study day is determined relative to the date of first dose of study treatment, unless otherwise specified. The day of the first dose of study treatment is defined as study day 1. The day prior to the first dose of study treatment is study day -1. There is no study day 0.

For events that occur before the first dose of study treatment,

study day = date of the event – first dose date;

for events that occur on or after the first dose of study treatment,

study day = date of the event – first dose date + 1.

7.2.4. Date of Last Known Alive

The date of last known alive is defined as the last alive date of contact from the Survival Follow-up page on the eCRF. For subjects ongoing at time of analysis, the date of last known alive is the date of the most recent study visit in the database for that subject.

More specifically, the last known alive date will be derived for subjects not known to have died at the analysis cut-off date using the latest date (including complete and partial date with Month and Year information) among the following data:

- All assessment dates (e.g. laboratory, vital signs assessments, ECG, ECOG, performance status assessment, tumor assessment dates etc.).
- Medication dates including study medication, concomitant medications, anticancer therapies administered after study treatment discontinuation.
- Adverse events start and end date, and the date of adverse event becoming serious.
- Date latest known alive collected during the survival follow-up.
- Randomization date.

After sorting properly for all those available dates, if the last last known alive date is a partial date with Month and Year information, day will be imputed as 15, unless this is after the cut off date in which case the cut off date will be used as last alive date.

7.2.5. Date of Death

Date of death is defined as the date of death from the Death Detail page on the eCRF. Date of death is cross-checked with AEs where outcome is 'Fatal', if applicable. In rare case, if year and month of death date are known but the day is unknown, day will be imputed as 15. For example, if a subject is reported to die on Dec2017, the death date will be imputed as 15 Dec2017. In the case of the imputed death date being after the end of study date and the death date and end of study date being the same month, the death date will be assigned to be the date of end of study.

7.2.6. Baseline and Change from Baseline

For all change from baseline variables, the baseline is defined as the last non-missing assessment prior to or on the day of randomization, and must be prior to the first administration of study treatment, including scheduled and unscheduled visits, unless otherwise specified. Hence, change from baseline = post-baseline value – baseline value.

The baseline value for analyses of qualitative parameters (e.g., normal/abnormal) is defined as the last evaluation prior to or on the day of randomization, and must be prior to the first administration of study treatment.

7.2.7. Treatment-emergent Events

An AE is considered a TEAE if the onset date is on or after the start of study treatment or if the onset date is missing, or if the AE has an onset date before the start of study treatment but worsened in severity after the study treatment until 37 days after the last dose of study treatment or a new treatment of anti-tumor therapy, whichever is earlier. After this period, treatment-related SAEs will also be considered as TEAEs. AEs with an unknown/not reported onset date will also be included.

7.3. Missing Data

All available data of the subjects who withdraw from the study for any reason is analyzed. Missing data is assumed to be missing at random. Category 'Missing' is displayed for qualitative assessments, where applicable.

For demographic and baseline characteristics, each variable will be analyzed and/or summarized using the available data. Unless otherwise specified, subjects with missing data will be excluded only from analyses for which data are not available.

There is no imputation of missing data for the analysis purpose, unless otherwise stated.

7.3.1. Imputation of the Missing Dates

Imputation rules described in this section are applicable to partial dates of AEs, concomitant medications, anti-cancer therapy, primary diagnosis and metastatic disease diagnosis. However, imputation of missing AE and concomitant medication onset and stop dates will be used to determine the status of each AE and the prior/concomitant status of each medication, the imputed dates should not be shown in listings.

Incomplete Start Date of AEs:

- If the AE onset date is completely missing, the AE start date will be imputed as the reference start date (i.e. first dosing date);
- If the AE onset date is partial missing, then
  - If both the year and the month are available and the year and the month are the corresponding year and month of the reference start date, then the AE start date will be imputed as the reference start date;
  - If both the year and the month are available and the year and the month are not equal to the corresponding year and month of the reference start date, then the AE start date will be imputed as the 1st day of the month;
  - If only the year is available and the available year is the corresponding year of the reference start date, then the AE start date will be imputed as the reference start date;
  - If only the year is available, and the available year is not equal to the corresponding year of the reference start date, then the AE start date will be imputed as the January 1st of the year.

Incomplete Stop Date of AEs:

AE end date will be imputed as below for the partial date only, the imputation rules only apply when the AE is not ongoing:

- If both the year and the month are available, AE end date will be imputed as the last day of the month;
- If only the year is available, AE end date will be imputed as the December 31st of the year.

If the imputed AE end date is after the death date for subjects is know to be dead at end of study or cut off date, the date of the death will be used for AE end date. If the imputed AE end date is after the last

known alive date for subjects alive at the end of study or cut off date, the date of last known alive date will be use for AE end date.

For AE continuing at the cut-off date, the end date will not be imputed and instead will be reported as "ongoing".

Concomitant Medication/Procedure/Surgery with onset/end dates

Concomitant Medication/Procedure/Surgery with onset/end dates that are partially/completely missing will be imputed as follows.

(i) start date:

- 1st day of the month will be used to impute the start date if only the day is missing.
- January 1st will be used to impute the start date if both the day and month are missing.
- If the date is completely missing, then the day before the reference start date will be imputed as the start date.

(ii) end date:

- Last day of the month will be used to impute the end date if only the day is missing.
- December 31st of the year will be used to impute the end date if both the day and month are missing.
- If the date is completely missing, assign 'continuing' status to the end date.

If the imputed end date is after the death date or last known alive date, the date of the death or last known alive date will be imputed as the Concomitant medication/procedure/surgery end date.

Subsequent Anti-cancer Therapy Date (collected during Survival Follow-Up)

When a partial new anti-tumor therapy start date is reported, every effort will be made to identify the precedence relationship of starting date of new anti-tumor therapy relative to the reference end date (i.e. last dose date). Below rules will be used:

- If the date is completely missing, new anti-tumor therapy date will be imputed as reference end date + 1;
- If only the day is missing, 15th day will be imputed as the new anti-tumor therapy date;
- If both the day and the month are missing, then July 1st will be imputed as the new anti-tumor therapy.

If the imputed start date is prior to the reference end date for subjects, the reference end date + 1 will be used as the imputed start date of the subsequent anti-cancer therapy.

Primary Diagnosis Date and Metastatic Disease Diagnosis Date

When a partial date of primary diagnosis for advanced colorectal cancer or a partial date of first metastatic disease diagnosis is reported, the below imputation rules will be used:

- If the date is completely missing, no imputation will be conducted;
- If only the day is missing, 15th day will be assigned;
- If both the day and the month are missing, then July 1st will be assigned.

7.4. Visit Windows

It is expected that there will be a variation between subjects in the actual number of study days from the start of administration of study drug within each cycle defined as Day 1 to the dates that the scheduled visits occurs. To handle this, for tables and figures where data are grouped by visit, assessments will be categorized using visit windows based on study days (relative to the Day 1 of each cycle). The visit-window mapping is described in Table 4. Visit-based summaries will be based on the windowed visits. All data, whether or not within the visit windows, will be presented in subjects listings.

For windowed visits during the treatment cycles, if more than 1 visit occurs during a visit window, the visit closest to the scheduled day will be assigned to the windowed visit. If two visits are equidistant from the scheduled day, the later visit will be assigned to the windowed visit. If there are multiple assessments on the same day, the worst case will be used. For the treatment completion visit, the last assessment in the window will be included in the summary.

For a subject who prematurely discontinues the study, the premature visit will be slotted accordingly. The window for post treatment visit will be "last dose date of last cycle + 4 days to last dose date of last cycle + 10 days" and the window for safety follow-up visit will be “Last dose date of last cycle + 11 days to last dose date of last cycle + 37 days”.

Table 4 Visit Windowing

	Cycle 1		Cycle 2-3		Cycle 4 and onwards	Post treatment	Safety follow-up
Visit	**C1D1**	**C1D21[c]**	**CXD1**	**CXD21[c]**	**CXD1**		
Scheduled Day [a]	1	21	1	21	1		
ECOG		1 to EOC-3	Day -3 to 3	4 to EOC-3	Day -3 to 3	Last dose date of last cycle + 4 days to last dose date of last cycle + 10	Last dose date of last cycle + 11 to last dose date of last cycle + 37
Vital Sign		1 to EOC-3	Day -3 to 3	4 to EOC-3	Day -3 to 3		
Hematology		1 to EOC-3	Day -3 to 3	4 to EOC-3	Day -3 to 3		
Clinical Chemistry		1 to EOC-3	Day -3 to 3	4 to EOC-3	Day -3 to 3		
Blood amylase and lipase			Day -3 to 3		Day -3 to 3		
Coagulation		1 to EOC-3	Day -3 to 3	4 to EOC-3	Day -3 to 3		
Thyroid function			Day -3 to 3		Day -3 to 3		
Urinalysis			Day -3 to 3		Day -3 to 3		
ECG	Day 1	2 to EOC		1 to EOC			
ECHO/MUGA [b]			Day -3 to 3		Day -3 to 3		
CEA			Day -3 to 3		Day -3 to 3	Last dose date of last cycle + 4 days to last dose date of last cycle + 10	
QLQ-C30			Day -3 to 3		Day -3 to 3		
EQ-5D-5L			Day -3 to 3		Day -3 to 3		

[a] The schedu ed day s re at ve to the Day 1 of each cyc e.
[b] An echocard ogram s schedu ed at C2D1, and on the f rst day, every 3 cyc es thereafter, e.g. cyc e 2 day 1, cyc e 5 day 1, cyc e 8 day 1, and etc.
[c] In the case that the Cyc e 1, 2 or 3 become the ast cyc e, the v s t w ndow upper bound w be EOC 4.
Note: The end date of a cyc e (EOC) s def ned as the one day ear er than the date of Day 1 study drug adm n strat on of ts next cyc e. For the ast cyc e (where no subsequent cyc e s g ven), the end of cyc e w be def ned as Day 7 re at ve to the ast dose of the cyc e.

Table 4 Visit Windowing

	Cycle 1		Cycle 2-3		Cycle 4 and onwards	Post treatment	Safety follow-up
Visit	**C1D1**	**C1D21[c]**	**CXD1**	**CXD21[c]**	**CXD1**		

C1D1=cyc e 1 day 1; C1D21= cyc e 1 day 21; CEA= Carc no embryon c ant gen; CXD1=cyc e X day 1; CXD21= cyc e X day 21; ECG=e ectrocard ogram; ECOG= Eastern Cooperat ve Onco ogy Group; EOC= end date of a cyc e.

7.5. Pooling of Centers

Data from all study centers is combined for analysis.

7.6. Outliers

Data Management are to be notified of outliers, if identified during TLF reviews, for query. Syneos Health Biostatistics and Programming do not change or remove outliers from the data.

7.7. Data Sources

Randomization numbers, stratification factors, and treatment assignments derived from IWRS are reconciled with the dummy randomization schedule prior to database lock and unblinding, and with the actual randomization schedule after database lock and unblinding.

After the study is unblinded, fruquintinib and M11 concentrations from PK plasma samples are provided by Covance and mapped onto SDTM PC domain. Syneos Health then transfers SDTM PC domain to Certara.

Protocol deviations are recorded in the CTMS and provided as an Excel document. Protocol deviations are to be reviewed prior to database lock.

CRF data are extracted from Rave database.

Laboratory data are provided by local labs.

Imaging data are provided by eResearchTechnology, Inc. (ERT).

Interactive Response Technology (IRT) data are provided by Endpoint.

Quality of life data using EORTC QLQ-C30 and EQ-5D-5L questionnaires are collected via Electronic Clinical Outcome Assessment (eCOA) and provided by ERT.

8. Demographic, Other Baseline Characteristics and Medication

8.1. Subject Disposition and Withdrawals

The following summaries will be presented for all enrolled subjects to reflect the subject disposition:

- Number of subjects who signed the informed consent.
- Number of screen failures.
- Reason for screen failure.
- Number of subjects who are randomized.
- Number of subjects who do not receive study drug.
- Number of subjects who received study drug.
- Subjects still on treatment (i.e., missing end-of treatment information).
- Reason for study drug discontinuation (for study drug).
- Number of subjects going into Survival follow-up if there are any assessments after the last dose date + 37 days.
- Number and percentage of subjects still on study (i.e., missing end-of-study information).
- Number and percentage of subjects who discontinued the study.
- Reason for study discontinuation.

Since there is no designated CRF field to collect the reasons at the end of Study (EoS) page of the CRF, the following algorithm will be implemented to derive the reason for EoS.

1. If a patient died on the study, the reason for EoS will be “death.”
2. If a patient did not die on the study,
   a. Check the Survival Follow-Up (SFU) page, extract the value (eg, Lost to Follow-up and Withdrawal of Consent) in the field of Survival Status from the last available SFU page, and it will be assigned as the EoS reason.
   b. When 2.a is not available, check the Visit Information page where SFU visit was not performed, extract the last available value in the field of reason not conducting the visit, and it will be assigned as the EoS reason or “Missing” if the visit information is there but reason is missing before proceeding to the next step.
   c. When 2.a and 2.b are both not available, check the End of Treatment (EoT), extract the reason of EoT, and it will be assigned as the EoS reason.

A separate table will be presented to show the subjects included in each analysis set and proper reasons for exclusion from an analysis set.

A separate table will be presented for the ITT population to show the concordance of randomization schedule stratification factors and CRF collected factors of prior therapy [i.e. Trifluridine/Tipiracil (TAS-102), Regorafenib, or Both Trifluridine/Tipiracil (TAS-102) and Regorafenib], duration of metastatic disease (≤ 18 months, > 18 months), and RAS status (Wild Type, Mutant). The following summaries will be presented:

- Number of subjects with all randomization schedule stratification factors concordant with CRF collected factors.
- Number of subjects with at least one randomization schedule stratification factor discordant with CRF collected factors.
    - Number of subjects with discordance in prior therapy [i.e. Trifluridine/Tipiracil (TAS-102), Regorafenib, or Both Trifluridine/Tipiracil (TAS-102) and Regorafenib], duration of metastatic disease, and RAS status.

Subject discontinuation status and analysis population are also listed.

8.2. Protocol Deviations

Protocol deviations are summarized descriptively for subjects with at least 1 major protocol deviation and subjects with at least 1 minor protocol deviation for each treatment group and overall. Each protocol deviation is also summarized descriptively by categories within major and minor protocol deviations for each treatment group and overall for the ITT population. A subject can have multiple major and/or minor deviations and counted once per major and/or minor deviation. COVID-19-related protocol deviations are summarized descriptively for each treatment group and overall for the ITT population.

A listing of protocol deviations, including COVID-19-related protocol deviations, is provided.

8.3. Demographic and Baseline Characteristics

The following parameters are summarized descriptively for each treatment group and overall for the ITT population.

- Age (years) at ICF date, Age Categories (< 65 years, ≥ 65 years).
- Sex (Female, Male); If female, Child Bearing Potential.
- Race (American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other, Multiple Races, Not Reported, Unknown). A subject can have multiple races and is summarized in the multiple race category.
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown).
- Region (North America, Europe, and Asia).
- Baseline Height (cm).
- Baseline Weight (kg).
- Baseline body mass index [BMI] (kg/m^2): it is calculated as Weight at Baseline (kg)/ [Height at Baseline (m)]^2.
    - BMI category: < 18.5, ≥ 18.5 and < 24, ≥ 24 kg/m^2.
- Baseline ECOG Performance Status: 0, 1.

Age (years) at ICF date is calculated by site personnel as the number of years from date of birth up to date of informed consent. For example,

Date of Birth	Date of Informed Consent	Original Age	Age to be entered into IWRS
01MAR1985	01JUL2020	35 years 4 months	35

01AUG1985	01JUL2020	34 years 11 months	34

A separate table presenting number and percentage of subjects by site and country will be produced for the ITT population.

Demographic data and baseline characteristics, randomization scheme and codes, informed consent data, and inclusion/exclusion criteria are listed by subject.

8.4. Disease History

History of colorectal cancer of the ITT population is summarized descriptively for each treatment group and overall for the following:

- Time (months) since First Diagnosis of Colorectal Cancer: it is calculated as (date of randomization – date of first diagnosis of colorectal cancer)/30.4375.
- Stage of Colorectal Cancer at First Diagnosis (stage I, stage II, stage III, stage IV).
- Primary Tumor Location at First Diagnosis.
    - Colon.
        - Colon – Right (cecum, ascending colon, and hepatic flexure).
        - Colon – Left (splenic flexure, descending colon, transverse colon, sigmoid colon).
        - Colon – Right and Left.
        - Colon – Unknown.
    - Rectum.
    - Colon and Rectum.
        - Colon – Right (cecum, ascending colon, and hepatic flexure).
        - Colon – Left (splenic flexure, descending colon, transverse colon, sigmoid colon).
        - Colon – Right and Left.
        - Colon – Unknown.
    - Unknown.
- Primary Site at First Diagnosis (Colon Left, Colon Right, Both Colon Left and Right, Colon Unknown, Rectum Only, Unknown).

- Duration of Metastatic Disease (months): it is calculated as (date of randomization – date of diagnosis of metastasis disease)/30.4375.
    - Duration of Metastatic Disease Categories (≤ 18 months, > 18 months).
- Prior Oncology Treatments (Prior Anti-cancer Medication, Prior Anti-cancer Radiotherapy, Prior Anti-cancer Procedures).
- RAS Status (Wild Type, Mutant).
- BRAF Status (Wild Type, V600 E Mutation, Other).
- Microsatellite/Mismatch Repair Status (Microsatellite stable [MSS] and/or proficient mismatch repair [pMMR], microsatellite instability-high [MSI-H] and/or deficient mismatch repair [dMMR]).
- Prior Therapy with Trifluridine/Tipiracil (TAS-102) and/or Regorafenib (Trifluridine/Tipiracil (TAS-102), Regorafenib, Both Trifluridine/Tipiracil (TAS-102) and Regorafenib).
- Number of Prior Treatment Lines (≤ 3, > 3).
- Number of Prior Treatment Lines for Metastatic Disease (≤ 3, > 3).
- Prior Treatment with Vascular Endothelial Growth Factor (VEGF) Inhibitors (Yes, No).
- Prior Treatment with Epidermal Growth Factor Receptor (EGFR) Inhibitors (Yes, No).
- Prior Treatment with EGFR/VEGF Inhibitors.
    - No anti-VEGF and no anti-EGFR.
    - Anti-VEGF, or anti-EGFR, or both.
        - Anti-VEGF and no anti-EGFR.
        - Anti-EGFR and no anti-VEGF.
        - Both anti-VEGF and anti-EGFR.
- Prior Treatment with Immune Checkpoint Inhibitors for MSI-H/dMMR (Yes, No).
- Prior Treatment with BRAF Inhibitors for BRAF V600E Mutation (Yes, No).
- Liver Metastases at Baseline (Yes, No): obtained based on whether the liver organ was involved in the target and non-target lesion tumor scan assessment at the baseline.
- Number of Metastatic Sites Other than Colon or Rectum (Single, Multiple): obtained based on the number of sites/organs was involved in the target and non-target lesion tumor scan assessment at the baseline. If only one is involved, that would be single; if more than one are involved, it will be multiple. For this derivation, paired organs, such as lung, kidney, ovaries, and lymph nodes will be considered as one organ, irrespective of the number of parts they may be made up of (i.e. tumors in the left lung and right lung will be counted as in one site).

- Number of Metastatic Sites (Single, Multiple): obtained based on the number of sites/organs was involved in the target and non-target lesion tumor scan assessment at the baseline. If only one is involved, that would be single; if more than one are involved, it will be multiple. For this derivation, paired organs, such as lung, kidney, ovaries, and lymph nodes will be considered as one organ, irrespective of the number of parts they may be made up of (i.e. tumors in the left lung and right lung will be counted as in one site).

8.5. Medical History

The conditions/diseases from medical history are those conditions/diseases that stopped prior to the study entry. Medical history is coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.0. Medical history is summarized using discrete summary statistics for each MedDRA system organ class (SOC) and preferred term (PT) by treatment group and overall for the ITT population. Subjects with multiple medical histories in the same SOC or PT are counted only once for the respective SOC or PT.

Summaries are ordered in alphabetical order of SOC and then, within an SOC, in decreasing frequencies by PT in overall column. If the frequencies tie, an alphabetic order will be applied.

A listing of medical history by subject is provided.

8.6. Prior and Concomitant Medication

Prior and concomitant medications are classified by Anatomical Therapeutic Classification (ATC) therapeutic subgroup (Level 2) and PT using the World Health Organization Drug Dictionary (WHODD) version March2020 or later. Medications with partial start or stop dates are imputed as described in Section 7.3.1 prior to be determined whether the medication is prior or concomitant medication.

Medications taken prior to the first dose of study treatment are denoted “Prior”. Medications taken prior to the first dose of study treatment and continuing beyond the first dose of study treatment or those medications started on or after the first dose of study treatment but no later than 37 days after the last dose are denoted “Concomitant”. Medication with start date/time being partially or completely missing will be assumed to be concomitant if it cannot be definitely shown that the medication did not occur during the treatment period.

The use of prior and concomitant medications will be summarized using discrete summary statistics in each treatment group and overall for the ITT population. If a subject took a specific medication multiple times or took multiple medications within a specific ATC or PT, the subject is counted only once for the respective ATC or PT.

Summaries are ordered in alphabetical order of ATC and then, within an ATC , in decreasing frequencies by PT in overall column. If the frequencies tie, an alphabetic order will be applied.

A listing of prior medication and concomitant medication by subject is provided.

8.7. Concomitant Medical or Surgical Procedure

Medical or surgical procedures that occurs after first dose date but no later than 37 days after the last dose are denoted “Concomitant”. Concomitant medical or surgical procedures are classified using the MedDRA version 25.0.

The use of concomitant medical or surgical procedures will be summarized using discrete summary statistics in each treatment group and overall for the ITT population. If a subject took a specific medication or surgical procedures multiple times or took multiple medications or surgical procedures within a specific SOC or PT, the subject is counted only once for the respective SOC or PT.

Summaries are ordered in alphabetical order of SOC and then, within an SOC , in decreasing frequencies by PT in overall column. If the frequencies tie, an alphabetic order will be applied.

A listing of concomitant medical or surgical procedures by subject is provided.

8.8. Prior Oncology Treatment

Prior oncology treatments including prior anti-cancer mediation, prior anti-cancer radiotherapy, prior anti-cancer procedure or surgery are summarized descriptively for each treatment group and overall for the ITT population.

8.8.1. Prior Anti-cancer Medication

Summary of prior anti-cancer medication for the ITT population includes the following:

- The number and percent of subjects with at least one prior anti-cancer medication.
- The total number of prior anti-cancer medications.
- The number of prior lines of therapy and its categories of 0, 1, 2, 3, > 3.

Prior anti-cancer medications are classified using the WHODD version March 2022.

The use of prior anti-cancer medications will be summarized by ATC and PT using discrete summary statistics, each treatment group and overall for the ITT population. A subject with multiple prior medication entries in the same ATC (PT) is only counted once within a particular ATC (PT).Results are sorted by ATC followed by PT in decreasing order of frequency (by Total column). If the frequencies are tied, an alphabetic order is applied.

8.8.2. Prior Anti-cancer Radiotherapy

Summary of prior anti-cancer radiotherapy for the ITT population includes the following.

- The number and percent of subjects with at least one prior anti-cancer radiotherapy.
- The total number of prior anti-cancer radiotherapy.

8.8.3. Prior Anti-cancer Procedure or Surgery

Summary of prior anti-cancer procedure or surgery for the ITT population includes the following

- The number and percent of subjects with at least one prior anti-cancer procedure or surgery.
- The total number of prior anti-cancer procedures or surgery.

  The number and percent of subjects for each purpose of prior anti-cancer procedure or surgery. A subject with multiple occurrences of the same purpose will be counted only once for the purpose, and a subject with multiple purposes will be counted once in each category of purpose.

Prior anti-cancer procedure or surgery is coded (MedDRA) version 25.0.

The number and percent of subjects with each procedure or surgery will be summarized using discrete summary statistics in each treatment group and overall for the ITT population by SOC and PT. If a subject had a procedure multiple times or had multiple procedures within a specific SOC or PT, the subject is counted only once for the respective SOC or PT. Summaries are ordered in alphabetical order of SOC and then, within an SOC, in decreasing frequencies by PT in overall column. If the frequencies tie, an alphabetic order will be applied.

8.9. Extent of Exposure

Exposure of study treatment is descriptively summarized for each treatment group as follows. Table 5 details the parameters of study treatment exposure.

Table 5. Extent of Exposure Parameters

Parameter	Definition
Duration of Exposure (days)	(Last dose date of study drug or death, whichever comes earlier) – first dose date of study drug + 8 or the date of death while on study, whichever comes first.
Number of Days with Recorded Dose	Sum of days with recorded doses
Number of Cycles Treatment Received	Subjects are considered to have started a cycle if they have received at least one dose of any study treatment.
Number of Cycles Treatment Received Categories	1, 2, 3, 4, 5, 6 and > 6
Cumulative Dose (mg)	Sum of doses administered in all cycles. The total dose administered in each cycle is defined as: the sum of (number of 5 mg capsules taken × 5 + number of 1 mg capsules taken) where number of capsules taken = total capsules dispensed – total capsules returned.
Dose Intensity (mg/day)	Cumulative Dose (mg) / Duration of Exposure (day) Target dose intensity is 3.75 mg
Relative dose intensity (RDI) (%)	100 * [Dose Intensity (mg/day) / (5 × 21/28 (mg/day))]
RDI Categories	< 50% 50 - < 70% 70 - < 90% 90 - < 110% ≥ 110%.
Relative Dose (RD) (%)	100 * [Cumulative dose (mg) / (5×21× number of cycles treatment received (mg)]

Parameter	Definition
RD Categories	< 50% 50 - < 70% 70 - < 90% 90 - < 110% ≥ 110%.
Percentage Intended Dose (PID) (%)	100 * [(number of days with any recorded doses) /duration of exposure] Target PID is 75%. Number of days with any recorded doses

The following summary for dose adjustment will be summarized for each treatment group.

- Study drug is administered orally on days 1-21 of each 28-day cycle. A cycle will be called cycle delay if the duration of the cycle is longer than 28 days. However, the last cycle will not be evaluated for cycle delay. Reason for delay is not collected. Hence, the total number of cycle delay will be calculated for each subject. Number of subjects with any cycle delay, and the frequency of cycle delay (0, 1, 2, 3, 4, 5, 6, > 6) will be summarized.
- Number of subjects with any dose modification (including both drug interruption and dose reduction);
- Frequency of dose modification: 0, 1, 2, 3, 4, 5, 6, > 6.
- Drug interrupted (number of subjects experienced drug interruption and reasons for drug interruption; frequency of drug interruptions: 0, 1, ≥ 2).
- Drug withdrawn (number of subjects experienced drug withdrawn and reasons for drug withdrawn).
- Dose reduced (Number of subjects with any dose reduction and reasons for dose reduction; and frequency of dose reduction: 0, 1, 2, ≥ 3), also the dose reduction category below will be summarized.
    - Reduction from 5mg to 4mg.
    - Reduction from 4mg to 3mg.

Study treatment accountability, study treatment administration are extent of exposure are listed by subject and visit.

9. Efficacy

Efficacy analyses are based on the ITT population. All secondary endpoints based on radiological assessments of tumor burden are derived from investigator assessment using Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 (Eisenhauer et al 2009).

9.1. Primary and Key Secondary Efficacy Endpoint and Analysis

9.1.1. Primary Efficacy Endpoint and Analysis

The primary endpoint of the study is OS, defined in Section 5.1 of the SAP and calculated as (date of death or last known alive – date of randomization + 1)/30.4375.

The Kaplan-Meier plots will be produced and the median, 25% and 75% percentile of time-to-event will be estimated using Kaplan-Meier method with their corresponding 95% CI which are calculated from a log-log transformation based on the method by Brookmeyer and Crowley (1982). Additionally, estimates will be provided for the survival probability along with their 95% CIs which are calculated using linear transformation based on the method by Brookmeyer and Crowley (1982) at selected landmarks, for example, at 3, 6, 9, 12, and 18 months. Example Statistical Analysis System (SAS) code is provided in Appendix 6.

The two-sided p-value to test the treatment effect will be calculated using a stratified log-rank test accounting for randomization schedule stratification factors. Example SAS code is provided in Appendix 7. The hazard ratio (HR) between the 2 treatment groups (fruquintinib vs placebo), together with its 95% CIs, will be calculated from a stratified Cox proportional hazard model (i.e. accounting for randomization schedule stratification factors) in which the treatment group is the only covariate in the model. A HR < 1 indicates a favorable clinical benefit from fruquintinib over the placebo group. Example SAS code is provided in Appendix 8.

Duration of follow-up is defined as the time (months) from date of randomization to the last date known to be alive for subjects who have not yet been reported to have died by the time of the analysis. Subjects who were reported to have died by the time of the analysis are censored at date of death. That is, duration of follow-up is calculated as (date of death or last known alive – date of randomization + 1)/30.4375. The duration of follow-up will be calculated using the Kaplan-Meier method.

All OS data are provided in listings by subject.

9.1.2. Key Secondary Efficacy Endpoint and Analysis

The key secondary efficacy endpoint is PFS. PFS is defined in Section 5.2 and calculated as (date of death or radiographic PD or last assessment – date of randomization + 1)/30.4375.

The number and percent of subjects who had progression-free events, the number and percent of subjects censored, and reasons for censoring are presented for each treatment group. Reasons for censoring include the following.

a. No baseline nor post-baseline assessment

b. No death nor PD

c. Lost to follow-up without death or PD

d. Withdrawal of consent without death or PD

e. New anti-tumor therapy started prior to PD

f. Death or PD occurred after two or more consecutive missed assessment

The Kaplan-Meier plots will be produced and the median, 25% and 75% percentile of time-to-event will be estimated using Kaplan-Meier method with their corresponding 95% CI which are calculated from a log-log transformation based on the method by Brookmeyer and Crowley (1982). Additionally, estimates will be provided for the survival probability along with their 95% CIs which are calculated using linear transformation based on the method by Brookmeyer and Crowley (1982) at selected landmarks, for example, at 3, 6, 9, 12, and 18 months.

The two-sided p-value to test the treatment effect will be calculated using a stratified log-rank test accounting for randomization schedule stratification factors. The hazard ratio (HR) between the 2 treatment groups (fruquintinib vs placebo), together with its 95% CIs, will be calculated from a stratified Cox proportional hazard model (i.e. accounting for randomization schedule stratification factors) in which the treatment group is the only covariate in the model. A HR < 1 indicates a favorable clinical benefit from fruquintinib over the placebo group.

A Kaplan-Meier plot of the time to censoring, where the censoring indicator of the primary PFS analysis is reversed, will be presented.

All PFS data is provided in listings by subject.

9.1.3. Multiplicity Adjustments

The clinical trial evaluates the objectives defined in terms of the comparison of fruquintinib + BSC versus placebo + BSC on the primary and key secondary efficacy endpoints in Section 9.1.1 and Section 9.1.2. The multiplicity problem includes 2 hypotheses of no effect:

- Hypothesis H_1. Comparison of fruquintinib + BSC versus placebo + BSC for OS.
- Hypothesis H_2. Comparison of fruquintinib + BSC versus placebo + BSC for PFS.

The 2-sided p-values for the 2 comparisons will be used for the multiple testing procedure. Example SAS code in Appendix 7.

A fixed-sequence (hierarchical) testing procedure is 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 is ≤ 0.05, then, a superiority test of for PFS will be conducted at the two-sided significance level of 0.05.

9.1.4. Sensitivity Analysis for OS and PFS

The following sensitivity analyses for OS and PFS will be performed, in which the p-value will always be obtained from the stratified log-rank test and the hazard ratio (HR) between the 2 treatment groups

(fruquintinib vs placebo), together with its 95% CIs will be calculated from the model in Section 9.1.1 and Section 9.1.2 for OS and PFS, respectively, unless otherwise specified.

- using ITT population, unstratified Cox proportional hazard model in which the randomization schedule stratification factors and treatment group are included in the model as covariates;
- using ITT population, stratified analysis for both log-rank test and Cox proportional hazard model, but using the stratification factors collected on the case report form (CRF);
- using ITT population, unstratified Cox proportional hazard model in which the stratification factors collected on the CRF and treatment group are included in the model as covariates;
- using ITT population, subjects with primary cause of death attributed to COVID-19 will be censored at one day before the death date (i.e. death date – 1).; and will follow the censoring rule defined in Table 3 for PFS and will use the data prior to the date of death.
- using PP population
- using PP population, unstratified Cox proportional hazard model in which the randomization schedule stratification factors and treatment group are included in the model as covariates;
- using PP population, stratified analysis for both log-rank test and Cox proportional hazard model using the stratification factors collected on the CRF;
- using ITT population, multivariate Cox's proportion hazard model with treatment and randomization schedule stratification factors (i.e. prior therapy, RAS status, and duration of metastatic disease) included in the model as covariate and, adjust for key prognostic factors using stepwise selection process with level of enter alpha= 0.15 and level of remove alpha= 0.15. Key prognostic factors include a set of potential prognostics/predictive factors as described in Section 9.1.5.

An additional sensitivity analyses for OS will be performed

- using ITT population, based on the first exact 480 deaths and the additional subjects who died will be censored at one day before the death date (i.e. death date – 1).
- using ITT population, subjects who take the subsequent anti-cancer therapy and are still alive will be censored at the date of initiating the subsequent anti-cancer therapy for OS.

The following additional sensitivity analyses for PFS will be performed, and all those sensitivity analyses defines the PFS event in an alternative way.

- For Rule 6 of Table 3, subjects who take new anti-cancer therapy are considered as a progression, and the date of progression is on the date of initiating the new anti-cancer therapy. However, if the new anti-cancer therapy is initiated after two or more consecutive missed/non-evaluable tumor assessments, the subjects will still be censored at date of last radiological assessment before the missed assessments. Then, the same analysis methods outlined in Section 9.1.2 will be conducted.

- For Rule 7 of Table 3, ignore the missing tumor assessments, that is, subjects with PD or death after two or more consecutive missed/non-evaluable tumor assessments will be considered as PFS event, and the event date for PD or death will be obtained as usual. Then, the same analysis methods outlined in Section 9.1.2 will be conducted.

9.1.5. Examination of Subgroups

Subgroup analyses will be conducted based on the unstratified Cox proportional hazard model in which the applicable randomization 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 is not sufficient, analysis will not be performed.

The following subgroups will be assessed for OS and PFS:

- Age: < 65 years, >= 65 years
- Sex: Female, Male
- Region: North America, Europe, Asia
- Race: White, Asian, Black or African American, Other (including American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other as recorded on the Demographics eCRF, and subjects with multiple races selected)
- Baseline ECOG Performance Status: 0, 1
- Prior Therapy with Trifluridine/Tipiracil (TAS-102) and/or Regorafenib: Trifluridine/Tipiracil (TAS-102), Regorafenib, Both Trifluridine/Tipiracil (TAS-102) and Regorafenib. This is a stratification factor which will not be included in the model for subgroup analysis.
- RAS Gene Status: Wild Type, Mutant. This is a stratification factor which will not be included in the model for subgroup analysis.
- BRAF Status: Wild Type, V600 E Mutation, Other
- Microsatellite/Mismatch Repair Status: Microsatellite Stable (MSS) and/or proficient mismatch repair (pMMR), Microsatellite Instability-High (MSI-H) and/or deficient mismatch repair (dMMR)
- Duration of metastatic disease (time from 1st Metastatic Diagnosis to Randomization): ≤ 18 months, > 18 months. This is a stratification factor which will not be included in the model for subgroup analysis.
- Number of Prior Chemotherapy Treatment Lines: ≤ 3, > 3
- Number of Prior Chemotherapy Treatment Lines for Metastatic Disease: ≤ 3, > 3
- Prior Treatment with Vascular Endothelial Growth Factor (VEGF) Inhibitors: Yes, No

- Prior Epidermal Growth Factor Receptor (EGFR) Inhibitors: Yes, No
- Prior target treatment
    - No anti-VEGF and no anti-EGFR
    - Anti-VEGF, or anti-EGFR, or both
        - Anti-VEGF and no anti-EGFR
        - Anti-EGFR and no anti-VEGF
        - Both anti-VEGF and anti-EGFR
- Prior Treatment with Immune Checkpoint Inhibitors for MSI-H/dMMR: Yes, No
- Prior Treatment with BRAF Inhibitors for BRAF V600E Mutation: Yes, No
- Primary Tumor Location at First Diagnosis:
    - Colon, Rectum, Colon and Rectum, Unknown
- Primary Tumor Site at First Diagnosis:
    - Colon Left (Splenic flexure, descending colon, transverse colon, sigmoid colon and rectum), Colon Right (Cecum, ascending colon and hepatic flexure), Colon Left and Right, Colon Unknown, Rectum Only, Unknown
- Liver Metastases at Baseline: Yes, No
- Number of Metastatic Tumor Sites Other than Colon or Rectum: Single, Multiple
- Number of Metastatic Tumor Sites: Single, Multiple

The values of stratification factors used for subgroup analysis are actual values of strata collected through eCRF.

All the sensitivity and the subgroup analysis for both OS and PFS will be considered exploratory and may only be supportive of the primary analysis of OS and PFS. Forest plot will also be used to graphically show the results.

9.2. Secondary Efficacy Endpoints and Analyses

Secondary efficacy endpoints include ORR, DCR, and DoR.

9.2.1. Objective Response Rate and Disease Control Rate

The 95% CIs of ORR and $ORR_{UNCONF\ RMED}$ are calculated using the Clopper-Pearson exact binomial method for each treatment group.

The adjusted proportion difference and along with its 95% CI in ORR between treatment groups will be calculated using the Wald method to account for the randomization schedule stratification factors, and p-

value of comparing treatment groups is based on a stratified Cochran-Mantel Hanzel (CMH) test stratified by the randomization schedule stratification factors. If the number of objective responses is not sufficient to utilize the CMH test, a stratified exact CMH test is performed instead. Example SAS code is provided in Appendix 9 and Appendix 10.

Overall objective responses and best overall responses are summarized descriptively for each treatment group and provided in listings by subjects and visit.

The analysis methods outlined for ORR will be similarly applied to DCR.

9.2.2. Duration of Response

The descriptive analysis methods outlined in Section 9.1.1 and Section 9.1.2 for OS and PFS will be similarly applied to DoR. The median, 25% and 75% percentile of time-to-event will be estimated using Kaplan-Meier method with their corresponding 95% CI.

All DoR data is provided in listings by subject.

9.2.3. Best Overall Response

BOR will be determined using time point responses (TPRs) up until the last evaluable TPR prior to or on the date of (i) disease progression as defined by RECIST Version 1.1 (Eisenhauer et al., 2009) or death; or (ii) withdrawal of consent; or (iii) receiving subsequent anti-cancer therapy, whichever is earlier.

The timing of an overall TPR will always be derived based on scan dates not response assessment dates. For a scheduled tumor scan assessment, it is expected that there may be a variation for the actual timing of scans among target, non-target, and new lesions. In assigning a date for the overall response assessment at a visit, the earliest date collected at that visit will be used. Within a grouped timepoint, if there are multiple assessments on different dates for the same target lesions, the last assessment will be used.

A subject's BOR will be determined based on Table 7.

There are two ways of assigning BOR for a subject when the minimum interval for confirmation of CR and PR is not satisfied or if there are no confirmatory scans for CR and PR:

- Adding two more response categories as: unconfirmed CR, unconfirmed PR;
- Assigning BOR as SD, that is, both the unconfirmed CR and unconfirmed PR will be SD.

Both ways of assigning BOR will be implemented.

The number and percentage of subjects in each category of derived BOR (Confirmed CR, Confirmed PR, SD, PD, or not evaluable E]) will be summarized.

Table 7. Best Overall Response When Confirmation of CR and PR are Required

First TPR	Second TPR	Best overall response*^ for ORR	Best Overall Response for $ORR_{UNCONFIRMED}$
CR	CR	CR	CR
CR	PR	SD [b] or PD	Unconfirmed CR
CR	SD	SD [b] or PD	Unconfirmed CR
CR	PD	SD [b] or PD	Unconfirmed CR

First TPR	Second TPR	Best overall response*^ for ORR	Best Overall Response for $ORR_{UNCONFIRMED}$
CR	NE or NA	SD [c] or NE or NA	Unconfirmed CR
PR	CR	PR	Unconfirmed CR
PR	PR	PR	PR
PR	SD	SD [d]	Unconfirmed PR
PR	PD	SD [b] or PD	Unconfirmed PR
PR	NE or NA	SD [c] or NE or NA	Unconfirmed PR
NE	NE	NE	NE
NE	CR	SD	Unconfirmed CR
NE	PR	SD	Unconfirmed PR
NE	SD	SD	SD
NE or NA	PD	PD	PD
SD	PD	SD [b] or PD	SD [b] or PD
SD	CR	SD	SD
SD	PR	SD	SD
SD	SD	SD	SD
SD	NE or NA	SD [c] or NE or NA	SD [c] or NE
PD	No further evaluation	PD	PD

CR = Comp ete Response; NE = Not Eva uab e; NA = Not Ava ab e; ORR = Object ve Response Rate; PD = Progress ve D sease; PR= Part a Response; SD = Stab e D sease.
[a]The m n mum nterva for conf rmat on of CR and PR s 4 weeks.
[b]Best response w be SD f the f rst t me po nt overa response s after 49 days on study. Otherw se, the best response w be PD.
[c]Best response w be SD f the f rst t me po nt overa response s after 49 days on study. Otherw se, the best response w be NE.
[d]Best response w be SD prov ded the cr ter a for PD have not been met from the f rst to second assessment.
* A best overa response of SD can on y be made after the subject s on study for a m n mum of 49 days (counted from Cyc e 1 Day 1). If the subject s on study for ess than 49 days, any tumor assessment nd cat ng stab e d sease before th s t me per od w have a best response of NE un ess PD s dent f ed.
^ Subsequent documentat on of a CR may prov de conf rmat on of a prev ous y dent f ed CR even w th an nterven ng NE (e.g., CR NE CR). Subsequent documentat on of a PR may prov de conf rmat on of a prev ous y dent f ed PR even w th an nterven ng NE or SD (e.g., PR NE PR or PR SD PR). However, on y one (1) nterven ng NE or SD w be a owed between PRs for conf rmat on. Note: n the fo ow ng scenar o, PR SD NE PR, the second PR s not a conf rmat on of the f rst PR.

9.2.4. Tumor Assessment

Tumor assessments of target, non-target, and new lesions are listed by subject and visit.

Quality of life is assessed using EORTC QLQ-C30 (version 3.0) and EQ-5D-5L questionnaires. The assessments are performed at Screening and Day 1 of each cycle until treatment is discontinued. Analyses for quality of life assessment are performed for the ITT population.

9.2.5. EORTC QLQ-C30 Questionnaire

The EORTC QLQ-C30 questionnaire, composed of both multi-item scales and single-item measures, is a 30-item cancer-specific instrument (Aaronson et al, 1993) which are grouped into 15 subscales as detailed below.

1. Global health status/QoL scale
2. Five functional scales: Physical functioning, Role functioning, Emotional functioning, Cognitive functioning, Social functioning
3. Three symptom scales: Fatigue, Nausea and vomiting, Pain
4. Six single items: Dyspnea, Insomnia, Appetite loss, Constipation, Diarrhea, Financial difficulties

Each subscale/single item is scored in accordance to the EORTC QLQ-C30 Scoring Manual (Aaronson et al, 1993). All scales and single-item measures range in score from 0 to 100 after linear transformation. A technical summary of scoring can be found in Appendix 1. Higher score for the Global health status/QoL and functioning scales represent higher functioning (i.e. a better state). However, the direction is opposite in symptom scales and single items. Higher scores on symptom and single-item scales represent higher levels of symptoms (i.e. a worse state).

The number and percent of subjects who completed the questionnaires will be summarized by visit and each treatment group.

9.2.5.1. *Analysis of Change from Baseline in 15 Subscales*

Change from baseline in the scores of each of the 15 subscales will be summarized by visit and each treatment group.

Analysis of change from baseline in the scores of each of the 15 subscales will be performed by visit (i.e. cycle), using a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach. The MMRM model will include treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of scale, and randomization schedule stratification factors as fixed effects. An unstructured variance-covariance structure will be used to model within-subject errors. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. MMRM is based on the assumption of missing at random and the assumption that dropouts would behave similarly to other subjects in the same treatment group, and possibly with similar covariate values, had they not dropped out. Example SAS code is provided in Appendix 10. To ensure the proper amount of data utilized in the model for each visit, the following steps will be implemented to identify data to be included in the model.

(1) Calculate the number of subjects with non-missing assessments for each cycle.

(2) Identify the last cycle with at least 20 subjects in any of the treatment groups and no subsequent cycles having at least 20 subjects in any of the treatment groups.

(3) Assessments after the cycle identified in Step 2 will not be included in the model.

If there is a convergence issue with the unstructured covariance model, Toeplitz, Autoregressive (1) (AR (1)) covariance structure is used, following this sequence until convergence is achieved. If the model still does not converge with AR (1) structure, no results are reported. When the covariance structure is not unstructured, the sandwich estimator for the variance-covariance matrix is derived, using the EMPIRICAL option in the PROC MIXED statement in SAS.

The visit windowing rules defined in Section 7.4 will be applied to identify the record for a cycle of each subject, and hence to be included in the analysis. The comparison are between fruquintinib plus BSC to placebo plus BSC at each scheduled post-baseline visit. The tabulation of MMRM includes estimates of least-square (LS) means, standard errors (SE), and 2-sided 95% CIs for each treatment group. Estimates of the LS mean difference, SE of the difference, 2-sided 95% CI of the difference between treatment groups, and p-value are also presented. As a sensitivity analysis, subjects who have more than one assessment in a cycle (i.e., a quality of life assessment at an unscheduled visit), the worst score for that cycle is used in the analysis of change from baseline in the 15 subscales. The above analysis is replicated using these substituted values.

9.2.5.2. *Analysis of Minimally Important Difference and Time to Deterioration*

Depending on each scale and item, the minimally important difference (MID) cut-off for QoL improvement is defined as a change of at least 6.35 to 14.24 points from baseline, based on a recent validation study on subjects with mCRC (Musoro et al., 2020) and the study (Osoba et al., 1998) cited in the EORTC-QLQ-30 Scoring Manual. The MID cut-off for QoL deterioration, stable, and improvement and in each scale and item are listed in Table 8 based on change scores.

Table 8. Summary of MID for EORTC QLQ-C30 Questionnaire

Scale/item	Deterioration	Stable	Improvement
Global health status/QoL	≤-6.38	-6.38 < and < 8.43	≥8.43
Physical functioning	≤-7.47	-7.47 < and < 7.81	≥7.81
Role functioning	≤-10.66	-10.66 < and < 14.24	≥14.24
Emotional functioning*	≤-10	-10 < and <10	≥10
Cognitive functioning*	≤-10	-10 < and < 10	≥10
Social functioning	≤-6.18	-6.18 < and < 9.23	≥9.23
Fatigue	≥10.79	-7.38 < and < 10.79	≤-7.38
Nausea and vomiting	≥7.75	-6.62 < and < 7.75	≤-6.62
Pain*	≥10	-10 < and < 10	≤-10
Dyspnoea*	≥10	-10 < and < 10	≤-10
Insomnia*	≥10	-10 < and < 10	≤-10
Appetite loss	≥12.28	-9.78 < and < 12.28	≤-9.78
Diarrhea	≥6.35	-7.96 < and 6.35	≤-7.96
Constipation	≥12.75	-10* < and <12.75	≤-10
Financial difficulties*	≥10	-10 < and < 10	≤-10

*The MID of these scale/items were not reported in (Musoro et al., 2020). Instead, the MID for these scale/items were arbitrarily determined at 10 points, following the study (Osoba et al., 1998) cited in EORTC QLQ 30 Scoring Manual. Osoba et al. reported "a little" change as a change of 5 10 points, and "moderate" change as 10 20 points.

The number and percent of subjects achieving MID for each scale (by categories defined in Table 8) are summarized by visit and treatment group.

In addition, for each scale and single item, time to deterioration (TTD) is defined as the time (months) from randomization until the first change of at least -10.66 to 12.75 points (depending on each scale and item) from baseline (Table 8, "Deterioration" column value), or death, whichever comes first. Any subject who does not experience TTD at the time of analysis is censored at the date of the most recent study visit in the database for that subject.

TTD is calculated as (date of the first reduction of at least -10.66 to 12.75 points from baseline, death or most recent visit – date of randomization + 1)/30.4375.
When no post-baseline assessments available, date of randomization will be used for this calculation.

Kaplan-Meier estimates for TTD will be tabulated by treatment group, using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% CIs. In addition, the two-sided p-value will be obtained from the stratified Kaplan-Meier method to account for the stratification factors. The hazard ratio (HR) between the two treatments (fruquintinib vs placebo), together with its 95% CIs will be calculated from a stratified (i.e. accounting for randomization schedule stratification factors) Cox hazard model in which treatment and baseline value of scale will be included as fixed effects.

Data of EORTC QLQ-C30 questionnaire and subscales are listed by subject and visit.

9.2.5.3. *Handling Missing Data for EORTC QLQ-C30 Questionnaire*

The number of and percent subjects of missing data on each of the 15 subscales will be presented by visit and also for the overall trial. Subjects who have died are included in this count.

As a simple sensitivity analysis of the impact of intercurrent events such as death and drop-out, an analysis of covariance (ANCOVA) will be conducted using the change from baseline to the last available assessment for each subject during the period from the date of randomization to the 37 days after the date of last dose. The ANCOVA model, include baseline scale score, randomization schedule stratification factors, treatment, and a baseline score and treatment interaction as fixed-effect variables.

9.2.6. EQ-5D-5L Questionnaire

The EQ-5D is a generic preference-based measure that indirectly measures the utility for health that generates an index-based summary score based upon societal preference weights (Pickard et al 2007).The EQ-5D-5L consists of 5 items that cover 5 main dimensions including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and a general visual analogue scale (VAS) for health status. The range of VAS scoring is from 0 (the worst health imaginable) to 100 (the best health imaginable).

Each of the 5 dimensions comprising the EQ-5D descriptive system is divided into 5 levels of perceived problems as follows.

- Level 1: indicating no problem
- Level 2: indicating slight problems

- Level 3: indicating moderate problems
- Level 4: indicating severe problems
- Level 5: indicating extreme problems

The response levels collected from the EQ-5D-5L five dimensions as a health profile are converted into an EQ-5D-5L index (utility) scores to represent subjects' utility value. The EQ-5D-5L index-based score is typically interpreted along a continuum where a utility value of 1 represents perfect health, 0 represents a state equal to death and a negative value represents a state worse than dead.

The UK value set and scoring algorithm are used to derive the EQ-5D-5L index score for this analysis (Devlin et al., 2018). The detailed scoring algorithm can be found in Appendix 2.

The number and percent of subjects who completed the questionnaires are summarized by visit for each treatment group.

9.2.6.1. *Analysis of Change from Baseline in VAS and Index Scores*

Change from baseline in VAS and index scores are summarized by visit and for each treatment group. The MMRM analysis and the sensitivity analysis described in Section 9.2.5.1 can be similarly applied to the endpoints of

- change from baseline in VAS with the baseline VAS score as covariate;
- change from baseline in EQ-5D-5L index score with the baseline EQ-5D-5L index score as covariate

To ensure the proper amount of data utilized in the model for each visit, the following steps will be implemented to identify data to be included in the model.

(1) Calculate the number of subjects with non-missing assessments for each cycle.

(2) Identify the last cycle with at least 20 subjects in any of the treatment groups and no subsequent cycles having at least 20 subjects in any of the treatment groups.

(3) Assessments after the cycle identified in Step 2 will not be included in the model.

9.2.6.2. *Analysis of Minimally Important Difference and Time to Deterioration*

The appropriate MID cut-off for VAS is defined as a reduction of at least 7 points from baseline, based on a study of 534 cancer subjects evaluated by UK-based scoring algorithm (Pickard et al, 2007).

The appropriate MID cut-off for index score is defined as a reduction of at least 0.063 points from baseline, based on the study on the scoring algorithm from England (McClure et al., 2017). McClure et al. reported the MID in the England population has a mean (standard deviation) of 0.063 (0.013), and a median of 0.064 (interquartile range: 0.055 to 0.073).

The MID cut-off for VAS and index scores for QoL deterioration, stable, and improvement are listed in Table 9.

Table 9. Summary of MID for EQ-5D-5L Questionnaire

Scale/item	Deterioration	Stable	Improvement
VAS	≤-7	-7 < and < 7	≥7
Index Score	≤-0.063	-0.063 < and <0.063	≥0.063

The number and percent of subjects achieving MID are summarized by visit for each treatment group.

In addition, TTD of VAS is defined as the time (month) from randomization until the first reduction of at least 7 points from baseline or death, whichever comes first. TTD of index score is defined as the time (month) from randomization until the first reduction of at least 0.063 points from baseline or death, whichever comes first.

TTD for VAS is calculated as (date of the first reduction of at least 7 points from baseline, death or most recent visit – date of randomization + 1)/30.4375.

TTD for EQ-5D-5L index score is calculated as (date of the first reduction of at least 0.063 points from baseline, death or most recent visit – date of randomization + 1)/30.4375.

Subjects who does not experience TTD at the time of analysis are censored at the last visit. Then, for the two time-to event endpoints

- TTD for VAS
- TTD for EQ-5D-5L index score

When no post-baseline assessments are available, the date of randomization will be used for this calculation, that is, subjects will be censored at the date of randomization.

The Kaplan-Meier method will be used to obtain the descriptive statistics of median, 25% and 75% percentiles along with their 95% CIs by treatment group. In addition, the two-sided p-value will be obtained from the stratified Kaplan-Meier method to account for the randomization stratification factors. The hazard ratio (HR) between the two treatments (fruquintinib vs placebo), together with its 95% CIs will be calculated from a stratified (i.e. accounting for randomization schedule stratification factors) Cox hazard model in which treatment and baseline value of scale will be included as fixed effects.

Results from the descriptive system of 5 dimensions are summarized descriptively by visit for each treatment group. A shift table from baseline for the levels within each of the 5 dimensions is provided by visit and treatment group.

Data of EQ-5D-5L questionnaire are listed by subject and visit.

9.2.6.3. *Handling Missing Data for EQ-5D-5L Questionnaire*

The number of and percent subjects of missing data on the VAS and index score are presented by visit and for the overall trial. Subjects who have died are included in this count.

The sensitivity ANCOVA analysis described in Section 9.2.5.3 will be similarly applied to the endpoints of

- change from baseline in VAS for each subject during the period from the date of randomization to the 37 days after the date of last dose with the baseline VAS score as covariate;
- change from baseline in EQ-5D-5L index score for each subject during the period from the date of randomization to the 37 days after the date of last dose with the baseline EQ-5D-5L index score as covariate

9.2.7. Health Resource Utilization

Data of heath resource utilization including primary reason for visit, type of resource, duration of visit (days) which is calculated as stop date – start date +1, number of visits, concomitant medication prescribed (Yes/No), and special transportation required are summarized descriptively for each treatment group. Each subject may have multiple health care visits during the study period, and the non-missing value from each visit will be utilized in the analysis.

In addition, in the analysis of primary reason for visit, type of resource, concomitant medication prescribed (Yes/No), and special transportation required (Yes/No), only the unique response categories for a subject will be summarized. For example, a subject may have 10 health care visits, the response categories from those 10 visits are just 8 times of “Adverse Event” and 2 times of “Management of mCRC”, hence, this subject will only be counted in those two categories instead of summarizing 10 times in the aforementioned analysis.

Data of heath resource utilization are listed by subject.

9.3. Exploratory Efficacy Endpoints

9.3.1. Circulating Tumor DNA

The analysis of ctDNA will be documented separately, and is not covered in this SAP.

9.3.2. Tumor Marker

Change from baseline in serum CEA will be summarized by visit and for each treatment group.

Data of CEA is listed by subject and visit.

10. Pharmacokinetics

PK population is used for tabulation as specified in this section.

10.1. PK Sampling Schedule

The PK sampling schedule for for the subset of approximately 120 subjects with evaluable ECGs is displayed in Table 2 in the study protocol. Furthermore, the PK sampling schedule for for subjects not included in the approximately 120 subjects with evaluable ECGs in the subset in Table 2 is displayed in Table 3 in the protocol.

10.2. Data Handling

10.2.1. Handling of Missing Data

Missing concentration data for all subjects who are administered scheduled study treatments is considered as non-informative missing and is not imputed. No concentration estimates are provided for missing sample values.

10.2.2. Handling of below the lower limit of quantification (BLQ) Data

For PK concentration summary, the following rules apply:

- PK concentrations below the lower limit of quantification (BLQ) in pre-dose samples and in samples taken before the time of the first quantifiable value are set to zero;
- The PK concentrations BLQ after quantifiable concentration are set to zero

10.2.3. Handling of the Difference between the Scheduled (nominal time) and the Actual Sampling Times (actual time)

For all sampling times, the actual sampling times relative to dosing are calculated as the difference between the actual clock time of sampling and the actual clock time of dosing. The actual post-dose sampling times relative to dosing expressed in hours and rounded off to two decimal digits are used. Actual predose time in sampling times will not be set to 0. Scheduled sampling times are listed but will not be summarized. If the actual time of sampling is missing, it is reported as NR (not recorded) in the listing, the nominal time is used for summary statistics.

10.3. Listing and Presentation of Individual PK Data

PK data are presented by subject, cycle and day (for instance, C1D1, C1D21, C2D1, etc.), and time point.

1. Concentration data for fruquintinib and M11 are presented to the same decimal place and in original units as reported by the bioanalytical lab, e.g., ng/mL;
2. Listing of PK sampling times including nominal and actual time elapsed from dose with the deviation from the nominal time.

10.4. Summary of PK Concentration Data

The observed concentrations for fruquintinib and metabolite M11 are summarized descriptively at each scheduled timepoint and dose level including. Summaries are presented by cycle and day (for instance, C1D1, C1D21, C2D1, etc.) and time point using descriptive statistics.

- If the time deviation is greater than ± 20%, the PK concentration value is excluded from the summary descriptives.
- Predose samples collected after C1D1, will be excluded from summary statistics if the time deviation is greater than ± 20% from 24 hours of the last dose.

PK plasma concentration data at each scheduled timepoint and dose level is presented using the following descriptive statistics.

- n
- arithmetic mean and StdDev
- coefficient of variation (CV)%
- median
- minimum and maximum
- geometric mean and geometric CV%
- number and percent of subject with BLQ

Geometric mean and geometric CV% will not be reportable in the summary statistics if there is a BLQ value at a timepoint. The conventions presented in Table 10 below are used for the presentation of the descriptive statistics of plasma concentrations.

Table 10. PK Reporting Precision

Variable	Summarized with:
Minimum, Maximum	3 significant digits or as needed based on actual measured values
Mean (arithmetic and geometric), Median	3 significant digits
StdDev	3 significant digits
CV% and Geometric CV%	1 decimal point

11. Safety

The Safety population will be used to evaluate the safety endpoints including AEs, clinical laboratory data, vital signs, single 12-lead ECG parameters, ECHO/MUGA parameters, physical examinations, ECOG performance status, extent of exposure and compliance, subsequent anti-cancer medication, procedure or radiotherapy during survival follow-upand death. Unless otherwise specified, the safety data during the treatment period will be evaluated, and the treatment period is defined as the duration from the date of the first study drug administration until 37 days after last dose.

11.1. Adverse Events

AEs are collected throughout the study, commencing from the time the ICF is signed until 37 days after the last dose day of study treatment, or start of a new treatment of anti-tumor therapy, whichever is earlier. AEs related to COVID-19 are determined by sites and recorded in electronic data capture (EDC), as deemed appropriate.

AEs are coded by SOC and PT using MedDRA version 25.0. An AE is considered a TEAE if

1. the onset date is on or after the start of study treatment or if the onset date is missing, or
2. if the AE has an onset date before the start of study treatment but worsened in severity after the study treatment until 37 days after the last dose of study treatment or a new treatment of anti-tumor therapy, whichever is earlier. After this period, treatment-related SAEs will also be considered as TEAEs.

TEAEs related to COVID-19 are also flagged in AE analysis dataset.

An AE is considered treatment-related in the summaries if it is assessed as related to the study treatment by the investigator or if the assessment of relationship to study treatment is missing.

Severity of AEs is graded from Grade 1 to Grade 5 according to the National Cancer Institute Common Terminology Criteria for Adverse Event (CTCAE) version 5.0. Missing severity grade is imputed as Grade 3.

AEs of special interest (AESI) for fruquintinib

According to the IB Version 13.0 (dated 08 November 2021), AESI for fruquintinib are defined to include 10 categories (Table 11). The MedDRA terms used to define AESIs categories are listed in Table **11. MedDRA Terms Used for Adverse Events of Special Interest**

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~~Table~~ 11. For AESI categories (i.e. “haemorrhages”, “hepatic function abnormal”, “hypertension”, “proteinuria”, “thyroid dysfunction”, “embolic and thrombotic events” “gastrointestinal perforation” and “left ventricular ejection fraction decreased”), the PTs to be included in these AESI categories are included in Appendix 3. These terms were selected by subjecting standardized MedDRA queries (SMQ) lists (narrow and/or broad scope depending on the category) for each category and had been used in the fruquintinib clinical development program for

pharmacovigilance. The MedDRA terminology is subject to changes and modifications as medical knowledge develops. Thus, the terms within Table 11. **MedDRA Terms Used for Adverse Events of Special Interest** Formatte Blue

~~Table 11~~ and Appendix 3 could be updated/changed in the future.

Table 11. MedDRA Terms Used for Adverse Events of Special Interest

AESIs Category	Search terms/strategy
Dermatological toxicity	MedDRA SOC "skin and subcutaneous tissue disorders"
Hypertension	MedDRA SMQ "hypertension" (narrow)
Thyroid dysfunction	MedDRA SMQ "thyroid dysfunction" (broad)
Proteinuria	MedDRA SMQ "proteinuria" (narrow)
Hepatic function abnormal	MedDRA SMQ "drug related hepatic disorders-comprehensive search" (narrow)
Hemorrhages	MedDRA SMQ "hemorrhages" (narrow)
Infections	MedDRA SOC "infections and infestations"
Embolic and thrombotic events	MedDRA SMQ "embolic and thrombotic events" (narrow)
Gastrointestinal perforation	MedDRA SMQ "gastrointestinal perforation" (narrow)
Left ventricular ejection fraction decreased	MedDRA SMQ "cardiac failure" (narrow)

11.1.1. Overview of TEAEs

An overall summary of the number and percent of subjects along with the total number of adverse events occurring in each treatment group is provided for the categories listed in Table 12.

Table 12. Overview of TEAEs

Category	Sub-category
All TEAEs	CTCAE Grade ≥3 Treatment-related Treatment-related CTCAE Grade ≥3 Leading to Dose Reduction Leading to Dose Interruption Leading to Treatment Discontinuation Treatment-related Leading to Dose Reduction Treatment-related Leading to Dose Interruption Treatment-related Leading to Treatment Discontinuation Leading to Death
Serious TEAEs	CTCAE Grade ≥ 3 Treatment-related Treatment-related CTCAE Grade ≥3 Leading to Dose Reduction Leading to Dose Interruption Leading to Treatment Discontinuation Treatment-related Leading to Dose Reduction Treatment-related Leading to Dose Interruption Treatment-related Leading to Treatment Discontinuation

Category	Sub-category
	Leading to Death
Treatment-emergent AESIs	CTCAE Grade ≥ 3 Serious Treatment-related Treatment-related CTCAE Grade ≥3 Leading to Dose Reduction Leading to Dose Interruption Leading to Treatment Discontinuation Treatment-related Leading to Dose Reduction Treatment-related Leading to Dose Interruption Treatment-related Leading to Treatment Discontinuation Leading to Death
COVID-19-related TEAEs*	CTCAE Grade ≥ 3 Serious Treatment-related Leading to Dose Reduction Leading to Dose Interruption Leading to Treatment Discontinuation Treatment-related Leading to Dose Reduction Treatment-related Leading to Dose Interruption Treatment-related Leading to Treatment Discontinuation Leading to Death

* COVID-19-related TEAEs will be characterized according to Table 19 Appendix 4

A subject with two or more AEs in a category is counted only once for the subject count.

11.1.2. TEAEs by SOC and PT

The number and percent of subjects experiencing a TEAE within each of the categories and sub-categories listed in Table 12 are also summarized by SOC, PT, and highest CTCAE grade for each treatment group. A subject with two or more adverse events for each combination of SOC and PT is counted only once for the combination.

The summary is sorted in descending order of frequency of SOC according to the sum of Fruquintinib + BSC and Placebo + BSC columns. Within SOC, sort by descending frequency of PT in according to the sum of Fruquintinib + BSC and Placebo + BSC columns.

In addition, the number and percent of subjects are summarized by PT and highest CTCAE grade and by PT and CTCAE grade >=3 for each treatment group.

11.1.3. Treatment-emergent Adverse Events of Special Interest

Treatment-emergent AESI are also summarized by highest CTCAE grade for each treatment group and the subgroups listed below.

Time (days) to onset of first treatment-emergent AESI are descriptively summarized for each AESI and treatment group. Time to first AESI is defined as time interval from date of first administration of study treatment to the earliest onset date among TEAEs within the same AESI categories. That is, if a subject

has multiple AEs occurrences under the same AESI category, the earliest AE onset date will be used as the first onset date to the AESI category.

Adverse events of special interest (AESI) are summarized for the following subgroups.

- Age: < 65 years, >= 65 years
- Sex: Female, Male
- Region: North America (including USA), Europe (including Austria, Belgium, France, Germany, Hungary, Italy, Spain, and United Kingdom); Asia (including Japan)
- Race: White, Asian, Black or African American, Other
- BMI (kg/m^2): < 18.5, >= 18.5 to < 24, >= 24
- Prior Therapy: Trifluridine/Tipiracil (TAS-102), Regorafenib , Both Trifluridine/Tipiracil (TAS-102) and Regorafenib
- RAS Status: Wild Type, Mutant
- Duration of metastatic disease: <= 18 months, > 18 months
- Liver Metastases at Baseline: Yes, No

For AEs falling into the AESI category “Hepatic function abnormal”, a summary table will also be provided by SOC, PT, and highest CTCAE for subjects with the following liver function category at baseline. Each liver function category will be evaluated separately to identify the subjects meeting the criteria. A listing of hepatotoxicity AEs will also be produced for subjects who meet any of the liver function category criteria at baseline (i.e. aspartate aminotransferase [AST] or alanine aminotransferase [ALT] >3x upper limit of normal [ULN] or total bilirubin >2xULN, or alkaline phosphatase [ALP] <2xULN).

- AST or ALT >3xULN & ≤ 5xULN;
- AST or ALT > 5xULN;
- Total bilirubin >2xULN;
- AST or ALT > 3xULN and Total bilirubin >2xULN;
- AST or ALT >3xULN, Total bilirubin >2xULN and ALP <2xULN

11.1.4. Subgroup analysis of AE

Analysis by BMI category (<18.5, ≥18.5 and <24 and ≥24) will be performed for the following AE summary:

- TEAE overview summary

- SAE summary
- Summary of TEAE leading to drug discontinuation
- Summary of TEAE with CTCAE grade ≥3.

11.2. Laboratory Evaluations

Blood and urine samples for the determination of clinical chemistry, hematology, and urinalysis laboratory variables described in Table 13 will be measured.

Clinical laboratory results will be graded according to CTCAE criteria, Version 5.0. Any graded changes that occur following the initiation of study drug and represents at least a 1-grade change from the baseline assessment is defined as treatment emergent. Any assessment, for which CTCAE toxicity grades are not available, will not be included in any analyses for which toxicity grades are required. Grade 0 is assigned to all laboratory values except missing values and not already assigned another grade. Missing values are considered missing.

The non-protocol specified tests and urinalysis results will not be summarized; they will only be included in listings. Data recorded by the laboratory will be converted to the International System of Units (SI) and all presentations will use SI units. Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (LLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings. Quantitative data collected between after date of first dose administration and up to 37 days following the last dose of study medication will be used for analysis.

Table 13. List of Laboratory Parameters

Laboratory Category	Parameters
Hematology	Hemoglobin, Hematocrit, Red Blood Cell Count (RBC), Platelet Count, White Blood Cell Count (WBC), Absolute Neutrophil Count, Neutrophils %, Absolute Lymphocyte Count, Lymphocytes %, Absolute Monocyte Count, Monocytes %, Absolute Eosinophil Count, Eosinophils %, Absolute Basophil Count, Basophils %
Blood Chemistry	Albumin, Blood urea nitrogen (BUN), Creatinine, Aspartate transaminase (AST), Alanine aminotransferase (ALT), Alkaline phosphatase (ALP), Total Bilirubin, Lactate dehydrogenase (LDH), Uric acid, Sodium, Potassium, Chloride, Bicarbonate, Glucose, Calcium, Magnesium, Phosphorus, Total cholesterol, Triglycerides, Total Protein
Blood Chemistry – Thyroid Function	Free triiodothyronine (fT3), Serum free thyroxine (fT4), Thyroid-stimulating hormone (TSH)
Urinalysis	pH, Glucose, Protein, White blood cell, Red blood cell

Laboratory Category	Parameters
Urinalysis Microscopy	Microscopic White Blood cell count, Microscopic Red Blood cell count, Other
Coagulation	Activated Partial thromboplastin time (aPTT), Prothrombin time, International normalized ratio (INR)

All summaries of hematology, blood chemistry (including thyroid function), urinalysis and coagulation parameters are based on the results of SI units, where applicable. Thyroid function parameters are analyzed under blood chemistry category.

Summary tables for hematology, blood chemistry, coagulation, and urinalysis (pH only) laboratory variables include descriptive statistics for result values and change from baseline for all continuous variables by visit and treatment group.

Toxicities for clinical labs will be characterized according to CTCAE, Version 5.0 (Table 20 of Appendix 5 when possible), and the frequency and percentage of subjects with each CTCAE grade for each visit during the treatment period will be described. Moreover, any occurrence of grade 3 or grade 4 during the treatment period will be summarized, and shift in grade from baseline to the worst post-baseline value will be summarized.

Summary tables and listings are also provided for treatment-emergent hepatotoxicity and subjects with or without liver metastasis by each treatment group. Hepatotoxicity is based on the pre-specified thresholds below:

1. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3x upper limit of normal (ULN) and ≤ 5x ULN
2. AST > 3,5,8,10, and 20x ULN, AST > 5x ULN for more than 5 weeks
3. ALT > 3,5,8,10, and 20x ULN, ALT > 5x ULN for more than 5 weeks
4. AST and/or ALT > 3,5,8,10, and 20x ULN, > 5x ULN for more than 5 weeks
5. Total bilirubin elevations > 1.5x, 2x ULN
6. ALP >1.5×, 2 × ULN
7. Potential Drug-Induced Liver Injury (DILI): AST and/or ALT > 3x ULN and (total bilirubin > 1.5×, > 2x ULN)
8. AST and/or ALT >3 × ULN and (TBL >2xULN or international normalized ratio [INR] >1.5)
9. Hy's Law criteria: AST and/or ALT > 3x ULN and total bilirubin ≥ 2x ULN and ALP < 2x ULN

An eDISH plot presenting peak total bilirubin and peak ALT values will also be produced.

Qualitative assessments of urinalysis parameters are summarized for all subjects using the number of subjects with results of negative, trace, or positive.

For the urinalysis parameters, if the test result is "-" or "negative", the investigation interpretation for the lab test will be considered to be "normal". The information of converting urinalysis parameters (i.e. WBC, RBC, and protein) results is provided in Table 21 of Appendix 5.

Summary of clinical significance (Abnormal not clinically significant [NCS] and Abnormal clinically significant [CS]) is also provided by visit and treatment group. Shift from baseline to the worst post-baseline investigators' assessment (i.e. normal, NCS, and CS for quantitative measurements and categorical measurements) will be presented.

All laboratory results (including hematology, blood chemistry, blood chemistry – thyroid function, urinalysis, coagulation, hepatitis, amylase and lipase, and serum/urine pregnancy test data) in SI units are presented in data listings. Tests are listed in alphabetical order within their respective panels (hematology, blood chemistry, urinalysis, and coagulation).

11.3. Vital Signs

Vital signs include systolic blood pressure, diastolic blood pressure, respiratory rate, body temperature, pulse rate, weight, body mass index (BMI) will be computed as weight (kg)/[height (m)]2.

For vital signs, change from baseline to each post-baseline visit and timepoint will be calculated. The potentially clinically significant findings of vital signs will also be defined based on criteria defined in Table 14.

Vital signs are summarized with descriptive statistics for the observed values at each visit and change from baseline to post-baseline visits values by treatment group. The criteria of potentially clinically significant findings are defined in Table 14. The frequency and percentage of subjects with any potentially clinically significant findings during the treatment period will be presented.

Table 14. Potentially Clinically Significant Criteria for Vital Signs

Variable	Criterion value
SBP (mmHg)	Increase from baseline of > 0 - ≤ 20 > 20 - ≤ 40 > 40 Decrease from baseline of > 0 - ≤ 20 > 20 - ≤ 40 > 40
DBP (mmHg)	Increase from baseline of > 0 - ≤ 20 > 20 - ≤ 40 > 40 Decrease from baseline of > 0 - ≤ 20

Variable	Criterion value
	> 20 - ≤ 40 > 40
Heart rate (bpm)	Increase from baseline of > 0 - ≤ 20 > 20 - ≤ 40 > 40 Decrease from baseline of > 0 - ≤ 20 > 20 - ≤ 40 > 40
Weight (kg)	Percentage increase from baseline of < 5% ≥ 5 – < 10% ≥ 10 - < 20% ≥ 20% Percentage decrease from baseline of < 5% ≥ 5 – < 10% ≥ 10 - < 20% ≥ 20%

Vital signs are listed by subject and visit.

11.4. Electrocardiogram

Electrocardiogram (ECG) parameters include heart rate, PR interval, and QT, QT correction Bazett formula (QTcB), QT correction Fridericia formula (QTcF) and a combination of the Q wave, R wave and S wave (QRS) intervals. Potentially clinically significant ECG findings will be identified using the criteria which are included in Table 15.

Table 15. Potentially Clinically Significant Criteria for ECG

Parameter (unit)	Criterion value
Heart Rate (bpm)	> 120
	< 50
PR Interval (msec)	≥ 210
RR Interval (msec)	> 1200
	< 500
QRS Interval (msec)	≥ 120
	≤ 50
QT Interval (msec)	≥ 500
	≤ 300

QTcF, QTcB (msec)	> 450
	> 480
	> 500
	≤ 300
	Increase from baseline > 30
	Increase from baseline > 60
	> 450 and increase from baseline > 30
	> 450 and increase from baseline > 60
	> 480 and increase from baseline > 30
	> 480 and increase from baseline > 60
	> 500 and increase from baseline > 30
	> 500 and increase from baseline > 60

Single 12-lead ECG are collected in all subjects using standardized equipment during cycles 1 to 3. From cycle 4 onward, ECG is only performed as clinically indicated.

For each ECG parameter, the observed values and change from baseline will be summarized. The 12-lead ECG interpretation by investigator are summarized at each visit descriptively, including the number and percent of subjects with normal, abnormal not clinically significant, and abnormal clinically significant results at baseline and each evaluation.

The criteria of potentially clinically significant findings are defined in Table 15. The frequency and percentage of subjects with any potentially clinically significant findings during the treatment period will be presented. Shift table from baseline to worst post-baseline ECG results is provided.

Single 12-lead ECG interpretations by investigator data are listed by subject and visit.

11.5. Echocardiogram

ECHOs are performed at Screening, cycle 2 day 1, and on day 1, every 3 cycles thereafter. Assessment parameters include left ventricular ejection fraction and overall interpretation of cardiac function. MUGAs are permitted if ECHOs cannot be performed.

Categorical summaries of overall interpretation and change from baseline of left ventricular ejection fraction of ECHO/MUGA results at each visit are summarized. A shift from baseline to the worst post-baseline table for overall interpretation is also provided.

ECHO/MUGA data is listed by subject and visit.

11.6. Physical Examination

A comprehensive physical examination at Screening includes subject general appearance, eyes, ears, nose and throat, head and neck, respiratory, cardiovascular, abdomen (gastrointestinal), skin, genitourinary system, lymph nodes, musculoskeletal, neurological assessments.

Limited physical examination at scheduled visits is a subset the comprehensive physical examination as deemed appropriate by the investigator.

Results of physical examination are listed by subject and visit.

11.7. ECOG Performance Status

ECOG performance status will be summarized descriptively using counts and percentages by visit for each treatment group. A shift from baseline to worst post-baseline value table is also provided.

ECOG performance status will be listed by subject and visit.

11.8. Other Safety Endpoints

11.8.1. Anti-cancer Medication during Survival Follow-up

Anti-cancer medication during survival follow-up are classified using the WHODD version March 2022.

The use of anti-cancer medication during survival follow-up will be summarized using discrete summary statistics, each treatment group and overall for the safety population. If a subject took a specific medication multiple times or took multiple medications within a specific ATC or PT, the subject is counted only once for the respective ATC or PT.

Summaries are ordered in alphabetical order of ATC and then, within an ATC, in decreasing frequencies by PT in overall column. If the frequencies tie, an alphabetic order will be applied.

Data of anti-cancer medication during survival follow-up are listed by subject.

11.8.2. Anti-cancer Procedure during Survival Follow-up

The anti-cancer procedures during survival follow-up are coded using MedDRA version 25.0.

The use of anti-cancer procedures during survival follow-up will be summarized using discrete summary statistics in each treatment group and overall for the safety population. If a subject had a specific procedure multiple times or had multiple procedures within a specific SOC or PT, the subject is counted only once for the respective SOC or PT.

Summaries are ordered in alphabetical order of SOC and then, within an SOC, in decreasing frequencies by PT in overall column. If the frequencies tie, an alphabetic order will be applied.

Data of anti-cancer procedure during survival follow-up are listed by subject.

11.8.3. Anti-cancer Radiotherapy during Survival Follow-up

The number and percent of subjects with at least one anti-cancer radiotherapy during survival follow-up are summarized for each treatment group.

Data of anti-cancer radiotherapy during survival follow-up are listed by subject.

11.8.4. Deaths

Primary cause of death and whether autopsy was performed will be summarized descriptively for each treatment group. Similarly, the deaths happening during the treatment period, defined as the period from the date of the first study drug administration until 37 days after last dose, will also be tabulated. Data of deaths are listed by subject. On-treatment death will be flagged.

11.8.5. Impact of COVID-19

The study is conducted during the COVID-19 pandemic, additional data is collected for evaluating the impact of COVID-19.

To eliminate potential hazards to subjects and study staff due to the COVID-19 pandemic while ensuring subjects safety and maintaining data integrity, subjects are allowed remote visits during the pandemic. The planned protocol deviation analyses are described in Section 8.2; planned sensitivity analyses for the PFS and OS are described in Section 9.1.4, and the summary for COVID-19-related TEAEs are included in Section 11.1.1.

Additional summaries related to the COVID-19 pandemic from the following aspects will be produced for ITT population:

- Type of impact on study visit (missing entire visit; Interrupted and/or out of window in-person visit at site; remote visit (virtual or telephone); or other)
- Reason related to COVID-19 (subject diagnosed with COVID-19; quarantined due to COVID-19; site closed or access restricted due to COVID-19; site open but subject unwilling or unable to come to site due to COVID-19; or other)
- Study drug discontinuation due to COVID-19

The number of subjects impacted by COVID-19 during the study investigation period as well as at any time will be summarized by treatment group and overall. The study investigation period is defined as the period from the date of randomization to the 37 days after the date of last study treatment administration.

Supporting listings for the described analyses above will be provided.

11.8.6. Interstitial Lung Disease

Interstitial lung disease data collected, including chest x-ray results and oxygen saturation, are listed by subject.

12. IDMC Review

A subset of TLFs for the study final analysis will be used for IDMC meetings. The specific content of the TLFs submitted to the IDMC are determined by the IDMC members. The results to be reviewed by the IDMC will be primarily based on the safety data. Efficacy data is also provided for the purpose of the planned interim futility analysis after 1/3 of OS events has occurred.

For open sessions, the tables are presented with column Total only and the listings contains no treatment header. For closed sessions, the tables are presented with columns Treatment A + BSC, Treatment B + BSC, and Total, and the listings contain treatment headers. The unblinded statistician to be involved in the closed sessions of the IDMC will share the actual treatment information for Treatment A and Treatment B.

The IDMC may request to be unblinded by treatment group or per-subject basis at any time. The unblinded biostatistician provides the information to unmask. These communications are maintained in the IDMC workspace and submitted to the Trial Master File at the end of the study.

The study is to be terminated in the case of confirmed futility after evaluation of 1/3 of OS events (i.e., 160 OS events).

At any time, the IDMC may request any other safety-related information deemed necessary to contribute to an appropriate review of safety.

Further details of content for open and closed sessions are provided in Section 18, “Content of Open and Closed Sessions”, of the IDMC Charter in order to maintain the blinding of the study.

13. Changes from Analysis Planned in Protocol

- Not applicable.

14. Reference List

Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JCJM, Kaasa S, Klee MC, Osoba D, Razavi D, Rofe PB, Schraub S, Sneeuw KCA, Sullivan M, Takeda F. The European Organisation for Research and Treatment of Cancer A quality-of-life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute* 1993; 85: 365-376.

Brookmeyer R., and Crowley J. (1982). A confidence interval for the median survival time. Biometrics, 29-41.

Devlin et al., Valuing health-related quality of life: An EQ-5D-5L value set for England. Health Economics. 2018;27:7–22. https://doi.org/10.1002/hec.3564

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer. 2009; 45:228-247.

European Organization for Research and Treatment of Cancer. EORTC QLQ-C30 Scoring Manual. https://www.eortc.org/app/uploads/sites/2/2018/02/SCmanual.pdf

EuroQol Research Foundation. EQ-5D-5L User Guide. Version 3.0; September 2019. https://euroqol.org/wp-content/uploads/2019/09/EQ-5D-5L-English-User-Guide_version-3.0-Sept-2019-secured.pdf

Kim, Y., & Won, S. (2013). Adjusted proportion difference and confidence interval in stratified randomized trials. PharmaSUG 2013. https://www.pharmasug.org/proceedings/2013/SP/PharmaSUG-2013-SP04.pdf

McClure et al., Instrument-Defined Estimates of the Minimally Important Difference for EQ-5D-5L Index Scores. Value Health. 2017 Apr;20(4):644-650. doi: 10.1016/j.jval.2016.11.015. Epub 2017 Jan 10. PMID: 28408007.

Musoro et al., Minimally important differences for interpreting European Organisation for Research and Treatment of Cancer (EORTC) Quality of life Questionnaire core 30 scores in subjects with ovarian cancer, Gynecologic Oncology, 10.1016/j.ygyno.2020.09.007, (2020).

Osoba et al., Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol. 1998 Jan;16(1):139-44. doi: 10.1200/JCO.1998.16.1.139. PMID: 9440735.

Pickard et al., Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes. 2007;5:70. doi: 10.1186/1477-7525-5-70.

Pickard AS, Wilke CT, Lin HW, Lloyd A. Health Utilities Using the EQ-5D in Studies of Cancer. *PharmacoEconomics* 2007;25:365–84

15. Programming Considerations

All TLFs and statistical analyses are generated using SAS for Windows, Release 9.4 (SAS Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure outputs adhere to the following specifications.

15.1. General Considerations

- One SAS program can create several outputs
- Each output is stored in a separate file
- Output files are delivered as follows
    - Two compiled pdf files (with bookmark and TOC) – one for tables and figures, and one for listings];
    - Individual rtf file for the TLFs (this is only applicable to the final delivery, e.g. final interim analysis delivery, final database lock delivery for clinical study report);
    - For figures, include the individual .tiff file (this is only applicable to the final delivery, e.g. final IA delivery, final DBL delivery for CSR)
- Numbering of TLFs follows ICH E3 guidance

15.2. Table, Listing, and Figure Format

15.2.1. General

- All TLFs are produced in landscape format on American letter paper size.
- All TLFs are produced using the Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- The data displays for all TLFs have a minimum blank 1-inch margin on all 4 sides.
- Headers and footers for figures are in Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- Legends are used for all figures with more than 1 variable, group, or item displayed.
- Table and listings are in black and white (no color). Figures are in colors, where applicable.
- Only standard keyboard characters are used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, are not used. Hexadecimal-derived characters are used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) are employed on a case-by-case basis.
- Mixed case is used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

15.2.2. Headers

- TLFs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

15.2.2.1. *Headers for Study*

- All output should have the following header at the top of each page:

Hutchison Med Pharma Limited — Page X of Y
Protocol No.: 2019 013 GLOB1 — Data Cut off Date: DDMMMYYYY

15.2.2.2. *Headers for Study – Interim Analysis*

- All output should have the following header at the top of each page:

Hutchison Med Pharma Limited — Page X of Y
Protocol No.: 2019 013 GLOB1 Interim Analysis — Data Cut off Date: DDMMMYYYY

15.2.2.3. *Headers for IDMC Meeting*

- All output should have the following header at the top of each page:

Hutchison Med Pharma Limited — Page X of Y
Protocol No.: 2019 013 GLOB1 IDMC Meeting — Data Cut off Date: DDMMMYYYY

15.2.2.4. *Headers for Japan Safety Lead-in Cohort*

- All output should have the following header at the top of each page:

Hutchison Med Pharma Limited — Page X of Y
Protocol No.: 2019 013 GLOB1 Japan Safety Lead in Cohort — Data Cut off Date: DDMMMYYYY

15.2.2.5. *Headers for Japan Safety Monitoring Committee (JSMC) Meeting*

- All output should have the following header at the top of each page:

Hutchison Med Pharma Limited — Page X of Y
Protocol No.: 2019 013 GLOB1 JSMC Meeting — Data Cut off Date: DDMMMYYYY

15.2.3. Display Titles

- Each TLF are identified by the designation and a numeral. (i.e., Table 14.1.1). A decimal system (x.y and x.y.z) are used to identify TLFs with related contents. The title is centered. The analysis set are identified on the line immediately following the title. The title and table designation are single-spaced. A solid line spanning the margins separate the display titles from the column headers. There is 1 blank line between the last title and the solid line. Parameters or Visits, if applicable, are between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(Intent-to-Treat Population)

15.2.4. Column Headers

- Column headings are displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column is on the far left followed by the treatment group columns. P-values are presented under the 'Fruquintinib + BSC' column.
- For numeric variables, include "unit" in column or row heading when appropriate.
- Analysis set sizes are presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of subjects in the analysis set.
- The order of treatments in the tables and listings is 'Placebo + BSC' first then 'Fruquintinib + BSC', followed by a 'Total' column, where applicable.

15.2.5. Body of the Data Display

15.2.5.1. *General Conventions*

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values are left-justified;
- Whole numbers (e.g., counts) are right-justified; and
- Numbers containing fractional portions are decimal aligned.

15.2.5.2. *Table Conventions*

- Units are included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category are presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages are presented and so counts of 0 are presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups are included.

- An Unknown or Missing category are added to each parameter for which information is not available for 1 or more subjects.

- Unless otherwise specified, the estimated mean, median, Q1, and Q3 for a set of values are printed out to 1 more significant digit than the original values, and standard deviations are printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean (StdDev)	XXX.X (X.XX)
Median	XXX.X
Min, Max	XXX, XXX
Q1, Q3	XXX, XXX
Missing	XXX

- P-values are output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. Every p-value less than 0.001 is presented as <0. If the p-value is returned as >0.999, then present as >0.999.

- Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8), 13 (5.4)). Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation is the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% are presented as 100, without decimal places.

- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of AE data are presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC 2 code), and AEs (by preferred term) are displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically.

- Missing descriptive statistics or p-values which cannot be estimated are reported as “-”.

- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.

- For categorical summaries (number and percent of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject are included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont.)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

15.2.5.3. *Listing Conventions*

- Listings are sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time.

- Missing data are represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.

- Dates are printed in SAS DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates are represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.

- All observed time values are to be presented using a 24-hour clock HH:MM. Time is reported if it was measured as part of the study.

- Units are included where available

15.2.5.4. *Figure Conventions*

- Unless otherwise specified, for all figures, study visits are displayed on the X-axis and endpoint (e.g., treatment mean change from baseline) values are displayed on the Y-axis.

15.2.6. Footnotes

- A solid line spanning the margins separates the body of the data display from the footnotes.

- All footnotes are left justified with single-line spacing immediately below the solid line underneath the data display. Each footnote will end with a period ".".

- Footnotes should always begin with "Note:" if an informational footnote, or a, b, c, etc. if a reference footnote. Each new footnote should start on a new line, where possible.

- Subject specific footnotes are avoided, where possible.

- Footnotes are used sparingly and add value to the table, figure, or listing. If more than six lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data are repeated on each page.

- The order of different types of footnotes need to follow the proper order as shown below

    1. Subject specific footnote, such as [a], [b], *, 1, 2, 3, and etc.;
    2. General footnote starting with “Note: …”, also the text of the footnotes will be properly aligned at the place after the phrase “Note:” if the line of footnote will wrap to the next row.
    3. Abbreviation footnote. The abbreviation of the footnote will be ordered alphabetically, In addition, each word spelling the abbreviation will use uppercase for the first letter unless it is the convention to use lowercase, e.g. “of”, “and”, etc. Each abbreviation will be separated by a “;”
    4. The last line of the footnote section is standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source. For example,

    Source: L st ng 16.2.x.x Tab e Generat on: DDMMMYYYY HH:MM
    Program: xxxx.sas

16. Quality Control

SAS programs are developed to produce outputs such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in Syneos Health SOP Developing Statistical Programs (SOP Number:3907).

Syneos Health SOPs Developing Statistical Programs (3907) and Conducting the Transfer of Biostatistical Deliverables (3908) describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

Syneos Health SOP Pharmacokinetic and Related Data Analyses (3913.01) describes the procedure for the generation and reporting of PK and pharmacodynamics data.

17. Appendix

17.1. Appendix 1. EORTC QLQ-C30 Scoring Algorithm

The principle for scoring these scales is the same in all cases. The steps for scoring are: 1) Estimate the average of the items that contribute to the scale. (i.e. the raw score);
2) Use a linear transformation to standardize the raw score, so that scores range from 0 to 100.

More specifically, if items $I_1, I_2, \ldots, I_n$ are included in a scale, the *RawScore*, *RS*, is the mean of the component items:

$$RawScore \quad RS \quad (I_1 + I_2 + \cdots + I_n)/n$$

Then apply the linear transformation to 0-100 to obtain the desired score for the scale, i.e.

- for **Functional scales**:

$$Score \quad \left\{1 \quad \frac{(RS \quad 1)}{range}\right\} \times 100$$

- for **Symptom scales/items** and **Global health status/QoL**:

$$Score \quad \left\{\frac{(RS \quad 1)}{range}\right\} \times 100$$

where *Range* in the formula is the difference between the maximum possible value of *RS* and the minimum possible value. The QLQ-C30 has been designed so that all items in any scale take the same range of values. Therefore, the range of *RS* equals the range of the item values. Most items are scored 1 to 4, giving *range* = 3. The exceptions are the items contributing to the global health status / QoL, which are 7-point questions with *range* = 6. More detailed information about the items to be included in each scale is summarized in Table 16 below.

To calculate the score for a scale following the aforementioned principles, it is required to at least half of the items have been answered, otherwise, the score will be set as missing. However, for single-item scale, set the score to missing if it is not answered. For example, role functioning and cognitive functioning each contain 2 items, and so these scales can be estimated whenever one of their constituent items is present; physical functioning contains 5 items, and so at least 3 need to have been completed.

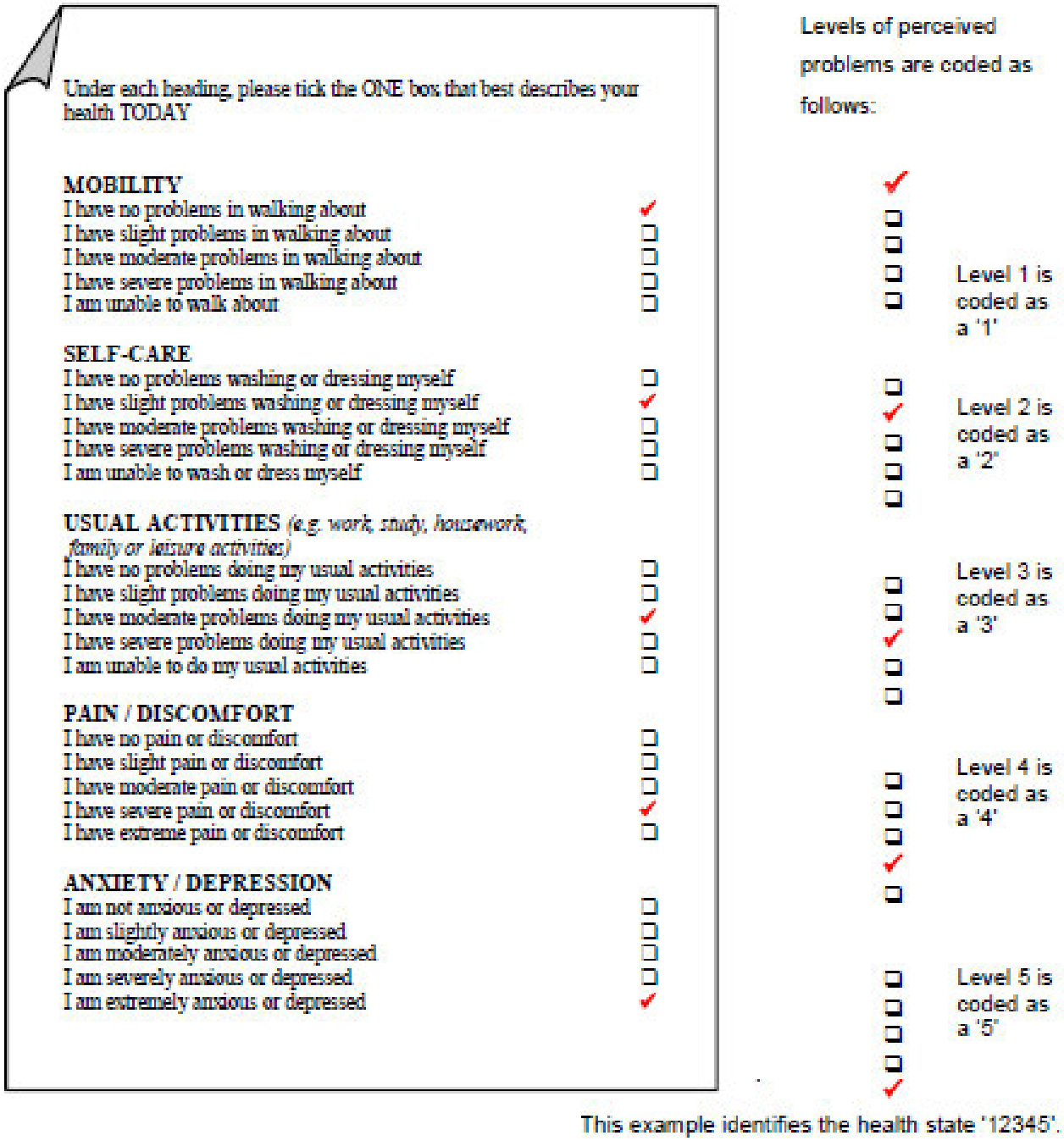
Table 16. Scoring the EORTC QLQ-C30 version 3.0

	Scale	Number of items	Item range	**Version 3.0** Item numbers
Global health status / QoL				
Global health status/QoL (revised)	QL2	2	6	29, 30
Functional scales				
Physical functioning (revised)	PF2	5	3	1 to 5
Role functioning (revised)	RF2	2	3	6, 7
Emotional functioning	EF	4	3	21 to 24
Cognitive functioning	CF	2	3	20, 25
Social functioning	SF	2	3	26, 27
Symptom scales / items				
Fatigue	FA	3	3	10, 12, 18
Nausea and vomiting	NV	2	3	14, 15
Pain	PA	2	3	9, 19
Dyspnoea	DY	1	3	8
Insomnia	SL	1	3	11
Appetite loss	AP	1	3	13
Constipation	CO	1	3	16
Diarrhoea	DI	1	3	17
Financial difficulties	FI	1	3	28

17.2. Appendix 2. Scoring the EQ-5D-5L Descriptive System

The EQ-5D-5L descriptive system can be scored as an example in Figure 2 below. There should be only one response for each dimension.

Figure 2. Example of Scoring the EQ-5D-5L Descriptive System



Then, the EQ-5D-5L index score is a weighted linear combination over 5 dimensions of health status. The coefficient for the weighting for each level of domains are presented in Table 17.

Table 17. EQ-5D-5L weighting coefficient scheme from England for the response of each dimension (Devlin et al., 2018)

Score level of dimension	Coefficient for each level of dimension				
	Mobility	Self-care	Usual activities	Pain/ discomfort	Anxiety/ depression
Level 1: no problem	0	0	0	0	0
Level 2: slight	0.027	0.023	0.023	0.029	0.036
Level 3: moderate	0.035	0.037	0.029	0.039	0.048
Level 4: severe	0.096	0.076	0.075	0.128	0.132
Level 5: unable or extreme [a]	0.127	0.094	0.085	0.155	0.134

[a] For dimensions (Mobility, Self-care, and Usual activities), it takes value “Unable”. For dimensions (Pain/discomfort and Anxiety/depression), it takes value “Extreme”.

The EQ-5D-5L index score is calculated using the equation

$$\text{EQ-5D-5L index score} \quad 1 \quad 2.159 \times \sum \text{coefficient value assigned to the response of each dimention}$$

If any of the 5 dimension scores is missing, the index score will be set to missing.

For example, for a value of health state 23245, the EQ-5D-5L index score is calculated as

$$\text{EQ-5D-5L index score} = 1 - 2.159 \times \sum \text{coefficient value assigned to the response of each dimention} = 1 - 2.159 \times \sum(0.027 + 0.037 + 0.023 + 0.128 + 0.134) = 0.247$$

17.3. Appendix 3. AESI Categories and Preferred Term

Table 18. MedDRA (Version 25.0) Preferred Term List for AESI Categories

AESI Category: Thyroid Dysfunction		
Anti-thyroid antibody	Marine Lenhart syndrome	Thyroid size decreased
Anti-thyroid antibody decreased	Multifocal fibrosclerosis	Thyroid stimulating hormone deficiency
Anti-thyroid antibody increased	Myxoedema	Thyroid stimulating immunoglobulin increased
Anti-thyroid antibody positive	Myxoedema coma	Thyroid therapy
Antithyroid arthritis syndrome	Orbital decompression	Thyroid tuberculosis
Atrophic thyroiditis	Photon radiation therapy to thyroid	Thyroidectomy
Autoimmune hypothyroidism	Polyglandular autoimmune syndrome type II	Thyroiditis
Autoimmune thyroid disorder	Polyglandular autoimmune syndrome type III	Thyroiditis acute
Autoimmune thyroiditis	Post procedural hypothyroidism	Thyroiditis chronic
Basedow's disease	Primary hyperthyroidism	Thyroiditis fibrous chronic
Biopsy thyroid gland abnormal	Primary hypothyroidism	Thyroiditis subacute

Blood thyroid stimulating hormone abnormal	Protein bound iodine decreased	Thyrotoxic cardiomyopathy
Blood thyroid stimulating hormone decreased	Protein bound iodine increased	Thyrotoxic crisis
Blood thyroid stimulating hormone increased	Radioactive iodine therapy	Thyrotoxic myopathy
Butanol-extractable iodine decreased	Radiotherapy to thyroid	Thyrotoxic periodic paralysis
Butanol-extractable iodine increased	Reverse tri-iodothyronine decreased	Thyroxin binding globulin abnormal
Congenital hypothyroidism	Reverse tri-iodothyronine increased	Thyroxin binding globulin decreased
Congenital thyroid disorder	Secondary hyperthyroidism	Thyroxin binding globulin increased
Endocrine ophthalmopathy	Secondary hypothyroidism	Thyroxine abnormal
Euthyroid sick syndrome	Silent thyroiditis	Thyroxine decreased
Exophthalmos	Tertiary hypothyroidism	Thyroxine free abnormal
Free thyroxine index abnormal	Thyreostatic therapy	Thyroxine free decreased
Free thyroxine index decreased	Thyroglobulin absent	Thyroxine free increased
Free thyroxine index increased	Thyroglobulin decreased	Thyroxine increased
Gamma radiation therapy to thyroid	Thyroglobulin increased	Thyroxine therapy

Generalised resistance to thyroid hormone	Thyroglobulin present	Toxic goitre
Goitre	Thyroid atrophy	Toxic nodular goitre
Hashimoto's encephalopathy	Thyroid autotransplantation	Transient hypothyroxinaemia of prematurity
Hashitoxicosis	Thyroid dermatopathy	Tri-iodothyronine abnormal
Hyperthyroidism	Thyroid disorder	Tri-iodothyronine decreased
Hypothyroidic goitre	Thyroid dysfunction in pregnancy	Tri-iodothyronine free abnormal
Hypothyroidism	Thyroid electron radiation therapy	Tri-iodothyronine free decreased
Immune-mediated hyperthyroidism	Thyroid function test abnormal	Tri-iodothyronine free increased
Immune-mediated hypothyroidism	Thyroid gland scan abnormal	Tri-iodothyronine free normal
Immune-mediated thyroiditis	Thyroid hemiagenesis	Tri-iodothyronine increased
Inappropriate thyroid stimulating hormone secretion	Thyroid hormone replacement therapy	Tri-iodothyronine uptake abnormal
Infectious thyroiditis	Thyroid hormones decreased	Tri-iodothyronine uptake decreased
Iodine uptake abnormal	Thyroid hormones increased	Tri-iodothyronine uptake increased
Iodine uptake decreased	Thyroid operation	Ultrasound thyroid abnormal

Iodine uptake increased	Thyroid pain	X-ray therapy to thyroid
Malignant exophthalmos	Thyroid releasing hormone challenge test abnormal	
AESI Category: Proteinuria		
Albumin globulin ratio increased	Beta 2 microglobulin urine increased	Protein urine
Albumin urine present	Globulinuria	Protein urine present
Albuminuria	Microalbuminuria	Proteinuria
Bence Jones protein urine present	Myoglobinuria	Urine albumin/creatinine ratio increased
Bence Jones proteinuria	Orthostatic proteinuria	Urine protein/creatinine ratio abnormal
		Urine protein/creatinine ratio increased
AESI Category: Hypertension		
Accelerated hypertension	Eclampsia	Metabolic syndrome
Aldosterone urine abnormal	Ectopic aldosterone secretion	Metanephrine urine abnormal

Aldosterone urine increased	Ectopic renin secretion	Metanephrine urine increased
Angiotensin converting enzyme increased	Endocrine hypertension	Neurogenic hypertension
Angiotensin I increased	Epinephrine abnormal	Non-dipping
Angiotensin II increased	Epinephrine increased	Norepinephrine abnormal
Angiotensin II receptor type 1 antibody positive	Essential hypertension	Norepinephrine increased
Blood aldosterone abnormal	Gestational hypertension	Normetanephrine urine increased
Blood aldosterone increased	HELLP syndrome	Orthostatic hypertension
Blood catecholamines abnormal	Hyperaldosteronism	Page kidney
Blood catecholamines increased	Hypertension	Postoperative hypertension
Blood pressure abnormal	Hypertension neonatal	Pre-eclampsia
Blood pressure ambulatory abnormal	Hypertensive angiopathy	Prehypertension
Blood pressure ambulatory increased	Hypertensive cardiomegaly	Procedural hypertension
Blood pressure diastolic abnormal	Hypertensive cardiomyopathy	Pseudoaldosteronism
Blood pressure diastolic increased	Hypertensive cerebrovascular disease	Renal hypertension

Blood pressure fluctuation	Hypertensive crisis	Renal sympathetic nerve ablation
Blood pressure inadequately controlled	Hypertensive emergency	Renal vascular resistance increased
Blood pressure increased	Hypertensive encephalopathy	Renin abnormal
Blood pressure management	Hypertensive end-organ damage	Renin increased
Blood pressure orthostatic abnormal	Hypertensive heart disease	Renin-angiotensin system inhibition
Blood pressure orthostatic increased	Hypertensive nephropathy	Renovascular hypertension
Blood pressure systolic abnormal	Hypertensive urgency	Retinopathy hypertensive
Blood pressure systolic increased	Labile blood pressure	Secondary aldosteronism
Catecholamine crisis	Labile hypertension	Secondary hypertension
Catecholamines urine abnormal	Malignant hypertension	Superimposed pre-eclampsia
Catecholamines urine increased	Malignant hypertensive heart disease	Supine hypertension
Dialysis induced hypertension	Malignant renal hypertension	Systolic hypertension
Diastolic hypertension	Maternal hypertension affecting foetus	Tyramine reaction
Diuretic therapy	Mean arterial pressure increased	Withdrawal hypertension

AESI Category: Haemorrhages		
Abdominal wall haematoma	Haemophilic pseudotumour	Petechiae
Abdominal wall haemorrhage	Haemoptysis	Pharyngeal contusion
Abnormal uterine bleeding	Haemorrhage	Pharyngeal haematoma
Abnormal withdrawal bleeding	Haemorrhage coronary artery	Pharyngeal haemorrhage
Achenbach syndrome	Haemorrhage foetal	Pituitary apoplexy
Acute haemorrhagic leukoencephalitis	Haemorrhage in pregnancy	Pituitary haemorrhage
Acute haemorrhagic ulcerative colitis	Haemorrhage intracranial	Placenta praevia haemorrhage
Administration site bruise	Haemorrhage neonatal	Polymenorrhagia
Administration site haematoma	Haemorrhage subcutaneous	Post abortion haemorrhage
Administration site haemorrhage	Haemorrhage subepidermal	Post procedural contusion
Adrenal haematoma	Haemorrhage urinary tract	Post procedural haematoma
Adrenal haemorrhage	Haemorrhagic adrenal infarction	Post procedural haematuria

Anal fissure haemorrhage	Haemorrhagic arteriovenous malformation	Post procedural haemorrhage
Anal haemorrhage	Haemorrhagic ascites	Post transfusion purpura
Anal ulcer haemorrhage	Haemorrhagic breast cyst	Postmenopausal haemorrhage
Anastomotic haemorrhage	Haemorrhagic cerebellar infarction	Postpartum haemorrhage
Anastomotic ulcer haemorrhage	Haemorrhagic cerebral infarction	Post-traumatic punctate intraepidermal haemorrhage
Aneurysm ruptured	Haemorrhagic cyst	Premature separation of placenta
Angina bullosa haemorrhagica	Haemorrhagic diathesis	Procedural haemorrhage
Anorectal varices haemorrhage	Haemorrhagic disease of newborn	Proctitis haemorrhagic
Anticoagulant-related nephropathy	Haemorrhagic disorder	Prostatic haemorrhage
Antiplatelet reversal therapy	Haemorrhagic erosive gastritis	Pulmonary alveolar haemorrhage
Aortic aneurysm rupture	Haemorrhagic gastroenteritis	Pulmonary contusion
Aortic dissection rupture	Haemorrhagic hepatic cyst	Pulmonary haematoma
Aortic intramural haematoma	Haemorrhagic infarction	Pulmonary haemorrhage
Aortic perforation	Haemorrhagic necrotic pancreatitis	Pulmonary haemorrhage neonatal

Aortic rupture	Haemorrhagic occlusive retinal vasculitis	Puncture site bruise
Aponeurosis contusion	Haemorrhagic ovarian cyst	Puncture site haematoma
Application site bruise	Haemorrhagic stroke	Puncture site haemorrhage
Application site haematoma	Haemorrhagic thyroid cyst	Purpura
Application site haemorrhage	Haemorrhagic transformation stroke	Purpura fulminans
Application site purpura	Haemorrhagic tumour necrosis	Purpura neonatal
Arterial haemorrhage	Haemorrhagic urticaria	Purpura non-thrombocytopenic
Arterial intramural haematoma	Haemorrhagic vasculitis	Purpura senile
Arterial perforation	Haemorrhoidal haemorrhage	Putamen haemorrhage
Arterial rupture	Haemostasis	Radiation associated haemorrhage
Arteriovenous fistula site haematoma	Haemothorax	Rectal haemorrhage
Arteriovenous fistula site haemorrhage	Heavy menstrual bleeding	Rectal ulcer haemorrhage
Arteriovenous graft site haematoma	Henoch-Schonlein purpura	Renal artery perforation
Arteriovenous graft site haemorrhage	Hepatic haemangioma rupture	Renal cyst haemorrhage

Astringent therapy	Hepatic haematoma	Renal haematoma
Atrial rupture	Hepatic haemorrhage	Renal haemorrhage
Auricular haematoma	Hereditary haemorrhagic telangiectasia	Respiratory tract haemorrhage
Basal ganglia haematoma	Hyperfibrinolysis	Respiratory tract haemorrhage neonatal
Basal ganglia haemorrhage	Hypergammaglobulinaemic purpura of Waldenstrom	Retinal aneurysm rupture
Basilar artery perforation	Hyphaema	Retinal haemorrhage
Bladder tamponade	Iliac artery perforation	Retinopathy haemorrhagic
Bleeding varicose vein	Iliac artery rupture	Retroperitoneal haematoma
Blood blister	Iliac vein perforation	Retroperitoneal haemorrhage
Blood loss anaemia	Immune thrombocytopenia	Retroplacental haematoma
Blood urine	Implant site bruising	Ruptured cerebral aneurysm
Blood urine present	Implant site haematoma	Scleral haematoma
Bloody discharge	Implant site haemorrhage	Scleral haemorrhage
Bloody peritoneal effluent	Incision site haematoma	Scrotal haematocoele

Bone contusion	Incision site haemorrhage	Scrotal haematoma
Bone marrow haemorrhage	Increased tendency to bruise	Scrotal haemorrhage
Brain contusion	Induced abortion haemorrhage	Shock haemorrhagic
Brain stem haematoma	Inferior vena cava perforation	Skin haemorrhage
Brain stem haemorrhage	Infusion site bruising	Skin neoplasm bleeding
Brain stem microhaemorrhage	Infusion site haematoma	Skin ulcer haemorrhage
Breast haematoma	Infusion site haemorrhage	Small intestinal haemorrhage
Breast haemorrhage	Injection site bruising	Small intestinal ulcer haemorrhage
Broad ligament haematoma	Injection site haematoma	Soft tissue haemorrhage
Bronchial haemorrhage	Injection site haemorrhage	Spermatic cord haemorrhage
Bronchial varices haemorrhage	Instillation site bruise	Spinal cord haematoma
Bullous haemorrhagic dermatosis	Instillation site haematoma	Spinal cord haemorrhage
Bursal haematoma	Instillation site haemorrhage	Spinal epidural haematoma
Cardiac contusion	Intermenstrual bleeding	Spinal epidural haemorrhage

Carotid aneurysm rupture	Internal haemorrhage	Spinal subarachnoid haemorrhage
Carotid artery perforation	Intestinal haematoma	Spinal subdural haematoma
Catheter site bruise	Intestinal haemorrhage	Spinal subdural haemorrhage
Catheter site haematoma	Intestinal varices haemorrhage	Spleen contusion
Catheter site haemorrhage	Intra-abdominal haematoma	Splenic artery perforation
Central nervous system haemorrhage	Intra-abdominal haemorrhage	Splenic haematoma
Cephalhaematoma	Intracerebral haematoma evacuation	Splenic haemorrhage
Cerebellar haematoma	Intracranial haematoma	Splenic varices haemorrhage
Cerebellar haemorrhage	Intracranial tumour haemorrhage	Splinter haemorrhages
Cerebellar microhaemorrhage	Intraocular haematoma	Spontaneous haematoma
Cerebral aneurysm perforation	Intrapartum haemorrhage	Spontaneous haemorrhage
Cerebral aneurysm ruptured syphilitic	Intratumoural haematoma	Stoma site haemorrhage
Cerebral arteriovenous malformation haemorrhagic	Intraventricular haemorrhage	Stomatitis haemorrhagic
Cerebral artery perforation	Intraventricular haemorrhage neonatal	Subarachnoid haematoma

Cerebral cyst haemorrhage	Iris haemorrhage	Subarachnoid haemorrhage
Cerebral haematoma	Joint microhaemorrhage	Subarachnoid haemorrhage neonatal
Cerebral haemorrhage	Jugular vein haemorrhage	Subcapsular hepatic haematoma
Cerebral haemorrhage foetal	Kidney contusion	Subcapsular renal haematoma
Cerebral haemorrhage neonatal	Lacrimal haemorrhage	Subcapsular splenic haematoma
Cerebral microhaemorrhage	Large intestinal haemorrhage	Subchorionic haematoma
Cervix haematoma uterine	Large intestinal ulcer haemorrhage	Subchorionic haemorrhage
Cervix haemorrhage uterine	Laryngeal haematoma	Subclavian artery perforation
Chest wall haematoma	Laryngeal haemorrhage	Subclavian vein perforation
Choroidal haematoma	Lip haematoma	Subcutaneous haematoma
Choroidal haemorrhage	Lip haemorrhage	Subdural haematoma
Chronic gastrointestinal bleeding	Liver contusion	Subdural haematoma evacuation
Chronic pigmented purpura	Lower gastrointestinal haemorrhage	Subdural haemorrhage
Ciliary body haemorrhage	Lower limb artery perforation	Subdural haemorrhage neonatal

Coital bleeding	Lymph node haemorrhage	Subendocardial haemorrhage
Colonic haematoma	Mallory-Weiss syndrome	Subgaleal haematoma
Conjunctival haemorrhage	Mediastinal haematoma	Subgaleal haemorrhage
Contusion	Mediastinal haemorrhage	Subretinal haematoma
Corneal bleeding	Medical device site bruise	Superior vena cava perforation
Cullen's sign	Medical device site haematoma	Testicular haemorrhage
Cystitis haemorrhagic	Medical device site haemorrhage	Thalamus haemorrhage
Deep dissecting haematoma	Melaena	Third stage postpartum haemorrhage
Diarrhoea haemorrhagic	Melaena neonatal	Thoracic haemorrhage
Disseminated intravascular coagulation	Meningorrhagia	Thrombocytopenic purpura
Diverticulitis intestinal haemorrhagic	Menometrorrhagia	Thrombotic thrombocytopenic purpura
Diverticulum intestinal haemorrhagic	Mesenteric haematoma	Thyroid haemorrhage
Duodenal ulcer haemorrhage	Mesenteric haemorrhage	Tongue haematoma
Duodenitis haemorrhagic	Mouth haemorrhage	Tongue haemorrhage

Ear haemorrhage	Mucocutaneous haemorrhage	Tonsillar haemorrhage
Ecchymosis	Mucosal haemorrhage	Tooth pulp haemorrhage
Encephalitis haemorrhagic	Muscle contusion	Tooth socket haemorrhage
Enterocolitis haemorrhagic	Muscle haemorrhage	Tracheal haemorrhage
Epidural haemorrhage	Myocardial haemorrhage	Traumatic haematoma
Epistaxis	Myocardial rupture	Traumatic haemorrhage
Exsanguination	Naevus haemorrhage	Traumatic haemothorax
Extra-axial haemorrhage	Nail bed bleeding	Traumatic intracranial haematoma
Extradural haematoma	Nasal septum haematoma	Traumatic intracranial haemorrhage
Extradural haematoma evacuation	Neonatal gastrointestinal haemorrhage	Tumour haemorrhage
Extravasation blood	Nephritis haemorrhagic	Ulcer haemorrhage
Eye contusion	Nipple exudate bloody	Umbilical cord haemorrhage
Eye haematoma	Occult blood positive	Umbilical haematoma
Eye haemorrhage	Ocular retrobulbar haemorrhage	Umbilical haemorrhage

Eyelid bleeding	Oesophageal haemorrhage	Upper gastrointestinal haemorrhage
Eyelid contusion	Oesophageal intramural haematoma	Ureteric haemorrhage
Eyelid haematoma	Oesophageal ulcer haemorrhage	Urethral haemorrhage
Femoral artery perforation	Oesophageal varices haemorrhage	Urinary bladder haematoma
Femoral vein perforation	Oesophagitis haemorrhagic	Urinary bladder haemorrhage
Foetal-maternal haemorrhage	Omental haemorrhage	Urinary occult blood
Fothergill sign positive	Optic disc haemorrhage	Urinary occult blood positive
Gallbladder haematoma	Optic nerve sheath haemorrhage	Urogenital haemorrhage
Gastric haemorrhage	Oral blood blister	Uterine haematoma
Gastric occult blood positive	Oral contusion	Uterine haemorrhage
Gastric ulcer haemorrhage	Oral mucosa haematoma	Vaccination site bruising
Gastric ulcer haemorrhage, obstructive	Oral purpura	Vaccination site haematoma
Gastric varices haemorrhage	Orbital haematoma	Vaccination site haemorrhage
Gastritis alcoholic haemorrhagic	Orbital haemorrhage	Vaginal haematoma

Gastritis haemorrhagic	Osteorrhagia	Vaginal haemorrhage
Gastroduodenal haemorrhage	Ovarian haematoma	Varicose vein ruptured
Gastrointestinal anastomotic haemorrhage	Ovarian haemorrhage	Vascular access site bruising
Gastrointestinal haemorrhage	Palpable purpura	Vascular access site haematoma
Gastrointestinal polyp haemorrhage	Pancreatic haemorrhage	Vascular access site haemorrhage
Gastrointestinal ulcer haemorrhage	Pancreatic pseudocyst haemorrhage	Vascular access site rupture
Gastrointestinal vascular malformation haemorrhagic	Pancreatitis haemorrhagic	Vascular anastomotic haemorrhage
Genital contusion	Papillary muscle haemorrhage	Vascular graft haemorrhage
Genital haemorrhage	Paranasal sinus haematoma	Vascular pseudoaneurysm ruptured
Gingival bleeding	Paranasal sinus haemorrhage	Vascular purpura
Graft haemorrhage	Parathyroid haemorrhage	Vascular rupture
Grey Turner's sign	Parotid gland haemorrhage	Vein rupture
Haemangioma rupture	Pelvic haematoma	Venous haemorrhage
Haemarthrosis	Pelvic haematoma obstetric	Venous perforation

Haematemesis	Pelvic haemorrhage	Ventricle rupture
Haematochezia	Penile contusion	Vertebral artery perforation
Haematocoele	Penile haematoma	Vessel puncture site bruise
Haematoma	Penile haemorrhage	Vessel puncture site haematoma
Haematoma evacuation	Peptic ulcer haemorrhage	Vessel puncture site haemorrhage
Haematoma infection	Pericardial haemorrhage	Vitreous haematoma
Haematoma muscle	Perineal haematoma	Vitreous haemorrhage
Haematosalpinx	Periorbital haematoma	Vulval haematoma
Haematospermia	Periorbital haemorrhage	Vulval haematoma evacuation
Haematotympanum	Periosteal haematoma	Vulval haemorrhage
Haematuria	Peripartum haemorrhage	Withdrawal bleed
Haematuria traumatic	Peripheral artery aneurysm rupture	Wound haematoma
Haemobilia	Peripheral artery haematoma	Wound haemorrhage
Haemoperitoneum	Peripheral exudative haemorrhagic chorioretinopathy	

Haemophilic arthropathy	Peritoneal haematoma	
	Periventricular haemorrhage neonatal	
AESI Category: Gastrointestinal perforation		
Abdominal abscess	Focal peritonitis	Oesophageal perforation
Abdominal hernia perforation	Gastric fistula	Oesophageal rupture
Abdominal wall abscess	Gastric fistula repair	Oesophageal ulcer perforation
Abscess intestinal	Gastric perforation	Oesophageal-pulmonary fistula
Acquired tracheo-oesophageal fistula	Gastric ulcer perforation	Oesophagobronchial fistula
Anal abscess	Gastric ulcer perforation, obstructive	Oesophagomediastinal fistula
Anal fistula	Gastrointestinal anastomotic leak	Oesophagopleural fistula
Anal fistula infection	Gastrointestinal fistula	Pancreatic fistula
Anal fistula repair	Gastrointestinal fistula repair	Pancreatic fistula repair
Anastomotic ulcer perforation	Gastrointestinal perforation	Peptic ulcer perforation

Anovulvar fistula	Gastrointestinal ulcer perforation	Peptic ulcer perforation, obstructive
Aortoenteric fistula	Gastropleural fistula	Peptic ulcer repair
Aorto-oesophageal fistula	Gastrosplenic fistula	Perforated ulcer
Appendiceal abscess	Ileal perforation	Perineal abscess
Appendicitis perforated	Ileal ulcer perforation	Perirectal abscess
Arterioenteric fistula	Incisional hernia perforation	Peritoneal abscess
Atrio-oesophageal fistula	Inguinal hernia perforation	Peritoneocutaneous fistula
Chemical peritonitis	Intestinal fistula	Peritonitis
Colon fistula repair	Intestinal fistula infection	Peritonitis bacterial
Colonic abscess	Intestinal fistula repair	Pneumoperitoneum
Colonic fistula	Intestinal perforation	Pneumoretroperitoneum
Colo-urethral fistula	Intestinal ulcer perforation	Procedural intestinal perforation
Diverticular fistula	Jejunal perforation	Rectal abscess
Diverticular perforation	Jejunal ulcer perforation	Rectal fistula repair

Diverticulitis intestinal perforated	Large intestinal ulcer perforation	Rectal perforation
Douglas' abscess	Large intestine perforation	Rectoprostatic fistula
Duodenal perforation	Lower gastrointestinal perforation	Rectourethral fistula
Duodenal rupture	Mesenteric abscess	Retroperitoneal abscess
Duodenal ulcer perforation	Neonatal intestinal perforation	Small intestinal perforation
Duodenal ulcer perforation, obstructive	Oesophageal abscess	Small intestinal ulcer perforation
Duodenal ulcer repair	Oesophageal fistula	Spontaneous bacterial peritonitis
Enterocolonic fistula	Oesophageal fistula repair	Umbilical hernia perforation
Enterocutaneous fistula		Upper gastrointestinal perforation
Fistula of small intestine		
AESI Category: Embolic and thrombotic events		
Acute aortic syndrome	Embolism venous	Pseudo-occlusion of internal carotid artery
Acute myocardial infarction	Endarterectomy	Pulmonary artery occlusion

Administration site thrombosis	Eye infarction	Pulmonary artery therapeutic procedure
Adrenal thrombosis	Femoral artery embolism	Pulmonary artery thrombosis
Amaurosis	Fluorescence angiogram abnormal	Pulmonary embolism
Amaurosis fugax	Foetal cerebrovascular disorder	Pulmonary endarterectomy
Angiogram abnormal	Foetal vascular malperfusion	Pulmonary infarction
Angiogram cerebral abnormal	Gastric infarction	Pulmonary microemboli
Angiogram peripheral abnormal	Graft thrombosis	Pulmonary thrombosis
Angioplasty	Haemorrhagic adrenal infarction	Pulmonary tumour thrombotic microangiopathy
Antiphospholipid syndrome	Haemorrhagic cerebral infarction	Pulmonary vein occlusion
Aortic bypass	Haemorrhagic infarction	Pulmonary veno-occlusive disease
Aortic embolus	Haemorrhagic stroke	Pulmonary venous thrombosis
Aortic surgery	Haemorrhagic transformation stroke	Quadriparesis
Aortic thrombosis	Haemorrhoids thrombosed	Quadriplegia
Aortogram abnormal	Hemiparesis	Renal artery angioplasty

Application site thrombosis	Hemiplegia	Renal artery occlusion
Arterectomy	Heparin-induced thrombocytopenia	Renal artery thrombosis
Arterectomy with graft replacement	Hepatic artery embolism	Renal embolism
Arterial angioplasty	Hepatic artery occlusion	Renal infarct
Arterial bypass operation	Hepatic artery thrombosis	Renal vascular thrombosis
Arterial graft	Hepatic infarction	Renal vein embolism
Arterial occlusive disease	Hepatic vascular thrombosis	Renal vein occlusion
Arterial revascularisation	Hepatic vein embolism	Renal vein thrombosis
Arterial stent insertion	Hepatic vein occlusion	Renal-limited thrombotic microangiopathy
Arterial therapeutic procedure	Hepatic vein thrombosis	Retinal artery embolism
Arterial thrombosis	Homans' sign positive	Retinal artery occlusion
Arteriogram abnormal	Hypothenar hammer syndrome	Retinal artery thrombosis
Arteriogram carotid abnormal	Iliac artery embolism	Retinal infarction
Arteriotomy	Iliac artery occlusion	Retinal vascular thrombosis

Arteriovenous fistula occlusion	Iliac vein occlusion	Retinal vein occlusion
Arteriovenous fistula thrombosis	Implant site thrombosis	Retinal vein thrombosis
Arteriovenous graft thrombosis	Incision site vessel occlusion	Revascularisation procedure
Artificial blood vessel occlusion	Infarction	Shunt occlusion
Aseptic cavernous sinus thrombosis	Inferior vena cava syndrome	Shunt thrombosis
Atherectomy	Inferior vena caval occlusion	SI QIII TIII pattern
Atherosclerotic plaque rupture	Infusion site thrombosis	Silent myocardial infarction
Atrial appendage closure	Injection site thrombosis	Spinal artery embolism
Atrial appendage resection	Inner ear infarction	Spinal artery thrombosis
Atrial thrombosis	Instillation site thrombosis	Spinal cord infarction
Autoimmune heparin-induced thrombocytopenia	Internal capsule infarction	Spinal stroke
Axillary vein thrombosis	Intestinal infarction	Splenic artery thrombosis
Basal ganglia infarction	Intra-aortic balloon placement	Splenic embolism
Basal ganglia stroke	Intracardiac mass	Splenic infarction

Basilar artery occlusion	Intracardiac thrombus	Splenic thrombosis
Basilar artery thrombosis	Intraoperative cerebral artery occlusion	Splenic vein occlusion
Blindness transient	Ischaemic cerebral infarction	Splenic vein thrombosis
Bone infarction	Ischaemic stroke	Stoma site thrombosis
Brachiocephalic artery occlusion	Jugular vein embolism	Stress cardiomyopathy
Brachiocephalic vein occlusion	Jugular vein occlusion	Stroke in evolution
Brachiocephalic vein thrombosis	Jugular vein thrombosis	Strokectomy
Brain stem embolism	Lacunar infarction	Subclavian artery embolism
Brain stem infarction	Lambl's excrescences	Subclavian artery occlusion
Brain stem stroke	Left atrial appendage closure implant	Subclavian artery thrombosis
Brain stem thrombosis	Leriche syndrome	Subclavian vein occlusion
Budd-Chiari syndrome	Mahler sign	Subclavian vein thrombosis
Capsular warning syndrome	May-Thurner syndrome	Superficial vein thrombosis
Cardiac ventricular thrombosis	Medical device site thrombosis	Superior sagittal sinus thrombosis

Carotid angioplasty	Mesenteric arterial occlusion	Superior vena cava occlusion
Carotid arterial embolus	Mesenteric arteriosclerosis	Superior vena cava syndrome
Carotid artery bypass	Mesenteric artery embolism	Surgical vascular shunt
Carotid artery occlusion	Mesenteric artery stenosis	Testicular infarction
Carotid artery stent insertion	Mesenteric artery stent insertion	Thalamic infarction
Carotid artery thrombosis	Mesenteric artery thrombosis	Thrombectomy
Carotid endarterectomy	Mesenteric vascular insufficiency	Thromboangiitis obliterans
Catheter directed thrombolysis	Mesenteric vascular occlusion	Thromboembolectomy
Catheter site thrombosis	Mesenteric vein thrombosis	Thrombolysis
Catheterisation venous	Mesenteric venous occlusion	Thrombophlebitis
Cavernous sinus thrombosis	Microembolism	Thrombophlebitis migrans
Central venous catheterisation	Monoparesis	Thrombophlebitis neonatal
Cerebellar artery occlusion	Monoplegia	Thrombosed varicose vein
Cerebellar artery thrombosis	Muscle infarction	Thrombosis

Cerebellar embolism	Myocardial infarction	Thrombosis corpora cavernosa
Cerebellar infarction	Myocardial necrosis	Thrombosis in device
Cerebral artery embolism	Obstetrical pulmonary embolism	Thrombosis mesenteric vessel
Cerebral artery occlusion	Obstructive shock	Thrombosis prophylaxis
Cerebral artery stent insertion	Ophthalmic artery occlusion	Thrombosis with thrombocytopenia syndrome
Cerebral artery thrombosis	Ophthalmic artery thrombosis	Thrombotic cerebral infarction
Cerebral congestion	Ophthalmic vein thrombosis	Thrombotic microangiopathy
Cerebral hypoperfusion	Optic nerve infarction	Thrombotic stroke
Cerebral infarction	Ovarian vein thrombosis	Thrombotic thrombocytopenic purpura
Cerebral infarction foetal	Paget-Schroetter syndrome	Thyroid infarction
Cerebral ischaemia	Pancreatic infarction	Transient ischaemic attack
Cerebral microembolism	Papillary muscle infarction	Transverse sinus thrombosis
Cerebral microinfarction	Paradoxical embolism	Truncus coeliacus thrombosis
Cerebral septic infarct	Paraneoplastic thrombosis	Tumour embolism

Cerebral thrombosis	Paraparesis	Tumour thrombectomy
Cerebral vascular occlusion	Paraplegia	Tumour thrombosis
Cerebral venous sinus thrombosis	Paresis	Ultrasonic angiogram abnormal
Cerebral venous thrombosis	Pelvic venous thrombosis	Ultrasound Doppler abnormal
Cerebrospinal thrombotic tamponade	Penile artery occlusion	Umbilical cord occlusion
Cerebrovascular accident	Penile vein thrombosis	Umbilical cord thrombosis
Cerebrovascular accident prophylaxis	Percutaneous coronary intervention	Vaccination site thrombosis
Cerebrovascular disorder	Peripheral arterial occlusive disease	Vascular access site thrombosis
Cerebrovascular insufficiency	Peripheral arterial reocclusion	Vascular device occlusion
Cerebrovascular operation	Peripheral artery angioplasty	Vascular graft
Cerebrovascular stenosis	Peripheral artery bypass	Vascular graft occlusion
Choroidal infarction	Peripheral artery occlusion	Vascular graft thrombosis
Coeliac artery occlusion	Peripheral artery stent insertion	Vascular operation
Collateral circulation	Peripheral artery surgery	Vascular pseudoaneurysm thrombosis

Compression garment application	Peripheral artery thrombosis	Vascular stent insertion
Coronary angioplasty	Peripheral embolism	Vascular stent occlusion
Coronary arterial stent insertion	Peripheral endarterectomy	Vascular stent thrombosis
Coronary artery bypass	Peripheral revascularisation	Vasodilation procedure
Coronary artery embolism	Peripheral vein occlusion	Vena cava embolism
Coronary artery occlusion	Peripheral vein thrombus extension	Vena cava filter insertion
Coronary artery reocclusion	Phlebectomy	Vena cava filter removal
Coronary artery surgery	Pituitary infarction	Vena cava thrombosis
Coronary artery thrombosis	Placental infarction	Venogram abnormal
Coronary bypass thrombosis	Pneumatic compression therapy	Venoocclusive disease
Coronary endarterectomy	Popliteal artery entrapment syndrome	Venoocclusive liver disease
Coronary revascularisation	Portal shunt procedure	Venous angioplasty
Coronary vascular graft occlusion	Portal vein cavernous transformation	Venous occlusion
Deep vein thrombosis	Portal vein embolism	Venous operation

Deep vein thrombosis postoperative	Portal vein occlusion	Venous recanalisation
Device embolisation	Portal vein thrombosis	Venous repair
Device occlusion	Portosplenomesenteric venous thrombosis	Venous stent insertion
Device related thrombosis	Post procedural myocardial infarction	Venous thrombosis
Diplegia	Post procedural pulmonary embolism	Venous thrombosis in pregnancy
Directional Doppler flow tests abnormal	Post procedural stroke	Venous thrombosis limb
Disseminated intravascular coagulation	Post thrombotic syndrome	Venous thrombosis neonatal
Disseminated intravascular coagulation in newborn	Postinfarction angina	Vertebral artery occlusion
Embolia cutis medicamentosa	Postoperative thrombosis	Vertebral artery thrombosis
Embolic cerebellar infarction	Postpartum thrombosis	Vessel puncture site occlusion
Embolic cerebral infarction	Postpartum venous thrombosis	Vessel puncture site thrombosis
Embolic pneumonia	Precerebral artery embolism	Visceral venous thrombosis
Embolic stroke	Precerebral artery occlusion	Visual acuity reduced transiently
Embolism	Precerebral artery thrombosis	Visual midline shift syndrome

Embolism arterial	Profundaplasty	
	Prosthetic cardiac valve thrombosis	
	Prosthetic vessel implantation	
AESI Category: Hepatic function abnormal		
Acquired antithrombin III deficiency	Gastric variceal ligation	Hypothromboplastinaemia
Acquired factor IX deficiency	Gastric varices	Icterus index increased
Acquired factor V deficiency	Gastric varices haemorrhage	Immune-mediated cholangitis
Acquired factor VIII deficiency	Gastrooesophageal variceal haemorrhage prophylaxis	Immune-mediated hepatic disorder
Acquired factor XI deficiency	Graft versus host disease in liver	Immune-mediated hepatitis
Acquired hepatocerebral degeneration	Guanase increased	International normalised ratio abnormal
Acquired protein S deficiency	Haemangioma of liver	International normalised ratio increased
Acute graft versus host disease in liver	Haemorrhagic hepatic cyst	Intestinal varices
Acute hepatic failure	Hepaplastin abnormal	Intestinal varices haemorrhage

Acute on chronic liver failure	Hepaplastin decreased	Ischaemic hepatitis
Acute yellow liver atrophy	Hepatectomy	Jaundice
Alanine aminotransferase abnormal	Hepatic adenoma	Jaundice cholestatic
Alanine aminotransferase increased	Hepatic angiosarcoma	Jaundice hepatocellular
Allergic hepatitis	Hepatic artery flow decreased	Kayser-Fleischer ring
Alloimmune hepatitis	Hepatic atrophy	Liver carcinoma ruptured
Ammonia abnormal	Hepatic calcification	Liver dialysis
Ammonia increased	Hepatic cancer	Liver disorder
Anti factor X activity abnormal	Hepatic cancer metastatic	Liver function test abnormal
Anti factor X activity decreased	Hepatic cancer recurrent	Liver function test decreased
Anti factor X activity increased	Hepatic cancer stage I	Liver function test increased
Antithrombin III decreased	Hepatic cancer stage II	Liver induration
Ascites	Hepatic cancer stage III	Liver injury
Aspartate aminotransferase abnormal	Hepatic cancer stage IV	Liver operation

Aspartate aminotransferase increased	Hepatic cirrhosis	Liver palpable
AST/ALT ratio abnormal	Hepatic cyst	Liver scan abnormal
Asterixis	Hepatic cyst ruptured	Liver tenderness
Autoimmune hepatitis	Hepatic cytolysis	Liver transplant
Bacterascites	Hepatic encephalopathy	Lupoid hepatic cirrhosis
Benign hepatic neoplasm	Hepatic encephalopathy prophylaxis	Lupus hepatitis
Benign hepatobiliary neoplasm	Hepatic enzyme abnormal	Magnetic resonance imaging hepatobiliary abnormal
Bile output abnormal	Hepatic enzyme decreased	Magnetic resonance proton density fat fraction measurement
Bile output decreased	Hepatic enzyme increased	Mitochondrial aspartate aminotransferase increased
Biliary ascites	Hepatic failure	Mixed hepatocellular cholangiocarcinoma
Biliary cirrhosis	Hepatic fibrosis	Mixed liver injury
Biliary fibrosis	Hepatic function abnormal	Molar ratio of total branched-chain amino acid to tyrosine
Bilirubin conjugated abnormal	Hepatic haemangioma rupture	Nodular regenerative hyperplasia
Bilirubin conjugated increased	Hepatic hamartoma	Nonalcoholic fatty liver disease

Bilirubin excretion disorder	Hepatic hydrothorax	Non-alcoholic steatohepatitis
Bilirubin urine present	Hepatic hypertrophy	Non-cirrhotic portal hypertension
Biopsy liver abnormal	Hepatic hypoperfusion	Ocular icterus
Blood bilirubin abnormal	Hepatic infiltration eosinophilic	Oedema due to hepatic disease
Blood bilirubin increased	Hepatic lesion	Oesophageal varices haemorrhage
Blood bilirubin unconjugated increased	Hepatic lipoma	Parenteral nutrition associated liver disease
Blood fibrinogen abnormal	Hepatic mass	Perihepatic discomfort
Blood fibrinogen decreased	Hepatic necrosis	Peripancreatic varices
Blood thrombin abnormal	Hepatic neoplasm	Portal fibrosis
Blood thrombin decreased	Hepatic neuroendocrine tumour	Portal hypertension
Blood thromboplastin abnormal	Hepatic pain	Portal hypertensive colopathy
Blood thromboplastin decreased	Hepatic sequestration	Portal hypertensive enteropathy
Bromosulphthalein test abnormal	Hepatic steato-fibrosis	Portal hypertensive gastropathy
Cardiohepatic syndrome	Hepatic steatosis	Portal vein cavernous transformation

Child-Pugh-Turcotte score abnormal	Hepatic vascular resistance increased	Portal vein dilatation
Child-Pugh-Turcotte score increased	Hepatic venous pressure gradient abnormal	Portopulmonary hypertension
Cholaemia	Hepatic venous pressure gradient increased	Primary biliary cholangitis
Cholangiosarcoma	Hepatitis	Protein C decreased
Cholestasis	Hepatitis acute	Protein S abnormal
Cholestatic liver injury	Hepatitis cholestatic	Protein S decreased
Cholestatic pruritus	Hepatitis chronic active	Prothrombin level abnormal
Chronic graft versus host disease in liver	Hepatitis chronic persistent	Prothrombin level decreased
Chronic hepatic failure	Hepatitis fulminant	Prothrombin time abnormal
Chronic hepatitis	Hepatitis toxic	Prothrombin time prolonged
Coagulation factor decreased	Hepatobiliary cancer	Prothrombin time ratio abnormal
Coagulation factor IX level abnormal	Hepatobiliary cancer in situ	Prothrombin time ratio increased
Coagulation factor IX level decreased	Hepatobiliary cyst	Radiation hepatitis
Coagulation factor V level abnormal	Hepatobiliary disease	Regenerative siderotic hepatic nodule

Coagulation factor V level decreased	Hepatobiliary neoplasm	Renal and liver transplant
Coagulation factor VII level abnormal	Hepatobiliary scan abnormal	Retrograde portal vein flow
Coagulation factor VII level decreased	Hepatoblastoma	Reye's syndrome
Coagulation factor X level abnormal	Hepatoblastoma recurrent	Reynold's syndrome
Coagulation factor X level decreased	Hepatocellular carcinoma	Splenic varices
Coma hepatic	Hepatocellular foamy cell syndrome	Splenic varices haemorrhage
Computerised tomogram liver abnormal	Hepatocellular injury	Spontaneous bacterial peritonitis
Congestive hepatopathy	Hepatomegaly	Steatohepatitis
Cryptogenic cirrhosis	Hepatopulmonary syndrome	Steatohepatitis
Diabetic hepatopathy	Hepatorenal failure	Subacute hepatic failure
Drug-induced liver injury	Hepatorenal syndrome	Sugiura procedure
Duodenal varices	Hepatosplenomegaly	Thrombin time abnormal
Flood syndrome	Hepatotoxicity	Thrombin time prolonged
Focal nodular hyperplasia	Hyperammonaemia	Total bile acids increased

Foetor hepaticus	Hyperbilirubinaemia	Transaminases abnormal
Galactose elimination capacity test abnormal	Hypercholia	Transaminases increased
Galactose elimination capacity test decreased	Hyperfibrinolysis	Ultrasound liver abnormal
Gallbladder varices	Hypertransaminasaemia	Urine bilirubin increased
Gamma-glutamyltransferase abnormal	Hypocoagulable state	Varices oesophageal
Gamma-glutamyltransferase increased	Hypofibrinogenaemia	Varicose veins of abdominal wall
Gastric variceal injection	Hypothrombinaemia	White nipple sign
		X-ray hepatobiliary abnormal
AESI Category: Left ventricular ejection fraction decreased		
Acute left ventricular failure	Cardiohepatic syndrome	Hepatojugular reflux
Acute pulmonary oedema	Cardiopulmonary failure	Left ventricular failure
Acute right ventricular failure	Cardiorenal syndrome	Low cardiac output syndrome
Cardiac asthma	Chronic left ventricular failure	Neonatal cardiac failure

Cardiac failure	Chronic right ventricular failure	Obstructive shock
Cardiac failure acute	Congestive hepatopathy	Pulmonary oedema
Cardiac failure chronic	Cor pulmonale	Pulmonary oedema neonatal
Cardiac failure congestive	Cor pulmonale acute	Radiation associated cardiac failure
Cardiac failure high output	Cor pulmonale chronic	Right ventricular ejection fraction decreased
Cardiogenic shock	Ejection fraction decreased	Right ventricular failure
		Ventricular failure

17.4. Appendix 4. COVID related AE

Table 19. MedDRA (Version 25.0) Preferred Term List for COVID-19 Related AE

Asymptomatic COVID-19	Occupational exposure to SARS-CoV-2
Breakthrough COVID-19	Post-acute COVID-19 syndrome
Congenital COVID-19	SARS-CoV-2 antibody test positive
Coronavirus infection	SARS-CoV-2 carrier
Coronavirus pneumonia	SARS-CoV-2 RNA decreased
Coronavirus test positive	SARS-CoV-2 RNA fluctuation
COVID-19	SARS-CoV-2 RNA increased
COVID-19 immunisation	SARS-CoV-2 sepsis
COVID-19 pneumonia	SARS-CoV-2 test false negative
COVID-19 prophylaxis	SARS-CoV-2 test positive
COVID-19 treatment	SARS-CoV-2 viraemia
Exposure to SARS-CoV-2	Suspected COVID-19
Multisystem inflammatory syndrome	Thrombosis with thrombocytopenia syndrome
Multisystem inflammatory syndrome in adults	Vaccine derived SARS-CoV-2 infection
Multisystem inflammatory syndrome in children	

17.5. Appendix 5. Clinical Laboratory Parameters CTCAE Criteria

Table 20. Clinical Laboratory Parameters CTCAE Criteria

			ATOXGR			
PARAM (SI Unit)	**Hypo**	**Hyper**	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
Hemoglobin (g/L)		Hemoglobin increased	Increase in >0 - 2 g/dL	Increase in >2 - 4 g/dL	Increase in >4 g/dL	~
	Anemia		Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L	~
Platelets (10^9/L)	Platelet count decreased		<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L
Leukocytes (10^9/L)	White blood cell decreased		<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L
Neutrophils (10^9/L)	Neutrophil count decreased		<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L
Lymphocytes (10^9/L)	Lymphocyte count decreased		<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L
		Lymphocyte count increased	~	>4000/mm3 - 20,000/mm3	>20,000/mm3	~
Eosinophils (10^9/L)		Eosinophilia	>ULN and >Baseline	-	-	-
Activated Partial Thromboplastin Time (s)		Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN	~

			ATOXGR			
PARAM (SI Unit)	**Hypo**	**Hyper**	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
International Normalized Ratio		INR increased	>1.2 - 1.5	>1.5 - 2.5	>2.5	~
Albumin (g/L)	Hypoalbuminemia		<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	~
Glucose (mmol/L)	Hypoglycemia		<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L
Creatinine (umol/L)		Creatinine increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline if baseline was abnormal; >1.5 - 3.0 x ULN if baseline was normal	>3.0 x baseline-6.0xULN if baseline was abnormal; >3.0 - 6.0 x ULN if baseline is normal	>6.0 x ULN
Alkaline Phosphatase (uKat/L)		Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Aspartate Aminotransferase (uKat/L)		Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Alanine Aminotransferase (uKat/L)		Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal

			ATOXGR			
PARAM (SI Unit)	**Hypo**	**Hyper**	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
Serum Calcium (mmol/L)		Hypercalcemia	>ULN - 2.9 mmol/L	>2.9 - 3.1 mmol/L	>3.1 - 3.4 mmol/L	>3.4 mmol/L
	Hypocalcemia		<LLN - 2.0 mmol/L	<2.0 - 1.75 mmol/L	<1.75 - 1.5 mmol/L	<1.5 mmol/L
Magnesium (mmol/L)	Hypomagnesemia	Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	~	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L
			<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L
Potassium (mmol/L)		Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L
	Hypokalemia		<LLN - 3.0 mmol/L	~	<3.0 - 2.5 mmol/L	<2.5 mmol/L
Sodium (mmol/L)		Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
	Hyponatremia		<LLN - 130 mmol/L	125-129 mmol/L	120-124 mmol/L	<120 mmol/L
Total cholesterol (mmol/L)		Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L
Bilirubin (umol/L)		Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
Triglycerides (mmol/L)		Hypertriglyceridemia	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L

			ATOXGR			
PARAM (SI Unit)	**Hypo**	**Hyper**	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
Urinary protein		Proteinuria	1+ proteinuria; urinary protein ≥ULN - <1.0 g/24 hrs	2+ and 3+ proteinuria; urinary protein 1.0-<3.5g/24hrs	4+ proteinuria; urinary protein >= 3.5g/24hrs	~

Table 21. Conversion tables for urinalysis results

Blood/Leucocytes (for parameter Red blood cell and White blood cell)		
Negative	0	0 cells/µL
Trace	1+	1-24 cells/µL
Small	2+	25-79 cells/µL
Medium	3+	80-199 cells/µL
Large	4+	≥ 200 cells/µL

Proteinuria (for parameter protein)				
NCI-CTCAE Grade	Protein by urinalysis	24-hour protein quantitation	Protein by urinalysis	24-hour protein quantitation
0	0		Negative	<10 mg/dL
1	1+	<1.0g	Trace	11-99 mg/dL
2	2+	<2.0g	Small	99-299 mg/dL
2	≥2+	<3.5 g (excluding 3.5 g)	Medium	300-999 mg/dL
3	4+	≥3.5 g	large	>1000 mg/dL

17.6. Appendix 6. Kaplan Meier Estimates and 95% CI from Brookmeyer and Crowley method

17.6.1. SAS Code example for KM estimates and 95% CI from a log-log transformation based on Brookmeyer-Crowley method

Example SAS code for 95% CI calculated from a log-log transformation based on the method by Brookmeyer and Crowley, for median, 25th and 75th percentiles:

```
*** KM Estimates - Quartiles ***;
ods output quartiles=quartiles1;
proc lifetest
        data=ADTTE(where=(PARAMCD="OS"))
        conftype=loglog;
        time AVAL*CNSR(1);
        strata TRTPN;
run;
```

AVAL is the time in months, CNSR is the censoring variable, TRTPN is the treatment group variable.

The output dataset (quartiles1) contains by treatment group, the estimate for median (ESTIMATE, where PERCENT=50), 25% (ESTIMATE, where PERCENT=25), and 75% (ESTIMATE, where PERCENT=75), along with the corresponding 95% CI calculated from a log-log transformation (for each corresponding PERCENT=25, =50 and =75, the CI values are stored in LowerLimit and UpperLimit).

17.6.2. SAS Code example for KM estimates and 95% CI from a linear transformation based on Brookmeyer-Crowley method at selected landmarks

Example SAS code for 95% CI calculated from a linear transformation based on the method by Brookmeyer and Crowley at selected landmarks, for example, at 3, 6, 9, 12, and 18 months:

```
*** KM Estimates - Timelist ***;
proc lifetest
        data=ADTTE(where=(PARAMCD="OS"))
        conftype=linear method=km atrisk timelist=(3, 6, 9, 12, 18) reduceout outsurv=tlist;
        time AVAL*CNSR(1);
        strata TRTPN;
run;
```

AVAL is the time in months, CNSR is the censoring variable, TRTPN is the treatment group variable.

The outsurv dataset (tlist) will provide by treatment group, the estimate (SURVIVAL*100) at specified time points (variable TIMELIST) and the corresponding 95% CIs (SDF_LCL*100, SDF_UCL*100).

17.7. Appendix 7. Stratified Log-Rank Test

Example SAS code for Stratified Log-Rank Test, accounting for randomization schedule stratification factors.

```
*** Stratified Log rank test ***;
ods output LogUniChisq=logunichisq1;
proc lifetest
        data=ADTTE(where=(PARAMCD="OS"))
        method=km;
        time AVAL*CNSR(1);
        strata STRAT1RN STRAT2RN STRAT3RN;
        test TRTPN;
run;
```

AVAL is the time in months, CNSR is the censoring variable, TRTPN is the treatment group variable, and STRAT1RN, STRAT2RN and STRAT3RN are placeholder variables representing the randomization schedule stratification factors.

The output dataset (logunichisq1) contains the p-value for the Log-Rank Test (ProbChiSq) comparing the treatment groups.

17.7.1. Multiplicity Adjustment for Log-Rank Tests for OS and PFS

A fixed-sequence (hierarchical) testing procedure is 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 is ≤ 0.05, then, a superiority test of for PFS will be conducted at the two-sided significance level of 0.05.

The multiplicity adjusted p-value for OS is its raw p-value, and the adjusted p-values for PFS is the maximum value between the p-values produced for the OS and PFS.

```
data pvalue;
  input p @@;
  if (_n_ = 1) then
    pseq = 0;
  pseq = max(pseq, p);
  retain pseq;
  cards;
0.021 0.043
run;
```

The raw p-values used to calculate the adjusted p-value will be obtained from the SAS programming for OS and PFS, then, this sample program will be tailored in the production.

17.8. Appendix 8. Stratified Cox Proportional Hazard Model

Example SAS code for hazard ratio between the 2 treatment groups (fruquintinib vs placebo), and corresponding 95% CIs, calculated from a stratified Cox proportional hazard model (i.e. accounting for randomization schedule stratification factors) in which the treatment group is the only covariate in the model:

```
*** Hazard ratio ***;
ods output hazardratios=hazrat1;
proc phreg
        data=ADTTE(where=(PARAMCD="OS"))
        alpha=0.05;
        model AVAL*CNSR(1)=TRTPN;
        strata STRAT1RN STRAT2RN STRAT3RN;
        hazardratio TRTPN;
run;
```

AVAL is the time in months, CNSR is the censoring variable, TRTPN is the treatment group variable, and STRAT1RN, STRAT2RN and STRAT3RN are placeholder variables representing the randomization schedule stratification factors.

The output dataset (hazrat1) contains the hazard ratio (HazardRatio) and the corresponding 95% CI (WaldLower, WaldUpper). Confirm the order of TRTPN variables is coded so HR < 1 indicates a favorable clinical benefit from fruquintinib over the placebo group.

17.9. Appendix 9. Cochran-Mantel Haenszel test stratified by randomization schedule stratification factors

Example SAS code for p-value of comparing treatment groups based on a Cochran-Mantel Hanzel test stratified by the randomization schedule stratification factors.

```
 *** stratified Cochran-Mantel Haenszel (CMH) test ***;
ods output CMH=cmh1;
proc freq
        data=ADEFF(where=(PARAMCD="ORR"));
        table STRAT1RN*STRAT2RN*STRAT3RN*TRTPN*AVAL/cmh;
run;
```

TRTPN is the treatment group variable and STRAT1RN, STRAT2RN and STRAT3RN are placeholder variables representing the randomization schedule stratification factors.

The output dataset (cmh1) contains the p-value (Prob, corresponding to the Statistic=3, for General Association). If the number of objective responses is not sufficient to utilize the CMH test, a stratified exact CMH test will be performed instead.

17.10. Appendix 10. Adjusted proportion difference between treatment groups with 95% CI using the Wald method to account for randomization schedule stratification factors

Example SAS code for adjusted proportion difference between treatment groups with 95% CI using the Wald method to account for randomization schedule stratification factors:

```
ods output CommonPdiff=pdiff1;
proc freq data = ADEFF(where=(PARAMCD="ORR"));
    tables STRAT1RN*STRAT2RN*STRAT3RN*TRTPN*AVAL/riskdiff(column=2 common
cl=wald);
run;
```

Using ADEFF and variable AVAL, the outcome of interest is ORR (i.e. Objective response rate), TRTPN is the treatment group variable and STRAT1RN, STRAT2RN and STRAT3RN are placeholder variables representing the randomization schedule stratification factors. The above example assumes the response is coded in column 2 (i.e. AVAL is coded as 0, 1, where 1 is response), and that fruquintinib is presented in row 1, and placebo is presented in row 2. The above code will be adjusted for correct presentation based on the actual coding in ADEFF if necessary.

The output (pdiff1) provides an adjusted proportion difference between treatment groups (the variable Value, when Method="Mantel-Haenszel") with a 95% CI (the variables LowerCL, UpperCL, when Method="Mantel-Haenszel") using the Wald method to account for randomization schedule stratification factors.

17.11. Appendix 11. REML-based MMRM

Example SAS code for REML-based MMRM:

```
proc mixed
        data=ADQS(where=(PARAMCD="PHYSF" and ANL20FL="Y"))
        method=reml;
        class USUBJID TRTPN AVISITN STRAT1RN STRAT2RN STRAT3RN;
        model CHG = BASE TRTPN AVISITN TRTPN*AVISITN STRAT1RN STRAT2RN
        STRAT3RN/solution ddfm=kr;
        repeated AVISITN/subject=USUBJID type=UN;
        lsmeans TRTPN*AVISITN/diff cl slice = AVISITN;
run;
```

CHG is the change from baseline in score of the subscale, USUBJID is the subject identification variable, TRTPN is the treatment group variable, AVISITN is a placeholder variable for visit, TRTPN*AVISITN is the treatment group-by-visit interaction, BASE is a placeholder variable for baseline value of scale, and STRAT1RN, STRAT2RN, and STRAT3RN are placeholder variables representing the randomization schedule stratification factors.

Prior to performing this analysis, the visits for each subject are limited within the dataset up to the last cycle with at least 20 subjects in any of the treatment groups (i.e. all subsequent cycles have less than 20 patients in each of the treatment groups). If there is a convergence issue with the unstructured covariance model,

Toeplitz, Autoregressive (1) (AR (1)) covariance structure is used, following this sequence until convergence is achieved. If the model still does not converge with AR (1) structure, no results are reported. When the covariance structure is not unstructured, the sandwich estimator for the variance-covariance matrix is derived, using the EMPIRICAL option in the PROC MIXED statement in SAS.

Statistical Analysis Plan Summary of Changes

Version #	Date (DD-Mmm-YYYY)	Revision Summary
1.0	25-Mar-2021	Original Draft
1.1	15-Nov-2021	Update to address sponsor comments on draft delivery Stable document signed for IA.
1.2	25-Mar-2022	Update to address sponsor comments on v1.0 and v1.1. Some listed below: • Change in visit windows • Clarifications on Exposure duration calculation • Summary of MID for EORTC QLQ-C30 Questionnaire • Table updated • Update on TTD calculation for questionnaires
1.3	09-Jun-2022	Update to address sponsor comments on v1.2.: Some listed below: • Censoring Rules for PFS Table updated • Non COVID population removed • Change in Exposure duration calculation • Change in sensitivity and subgroup analyses for OS and • PFS • Change in AESI definition • AESI Categories and Preferred Term Table updated • MedDRA (Version 25.0) Preferred Term List for COVID-19 • Related AE Table added • PK updates and Change in partial know alive date • imputation rules
1.4	21-Jul-2022	• Section 6.4 and 6.6 about the protocol deviation (just language changes) • Table 4 about the visit window • Section 11.2 some hepatic evaluation criteria added • Table 14.3.4.1.5 to reflect the hepatic criteria changes in the SAP • Listing 16.2.3.3 updates the title; adding a new Listing 16.2.3.4 by site. • Section 7.2.2 last dose date definition • Section 6.5 PK population additional detail • Table 12 additional raw with Treatment-related CTCAE Grade ≥3