TITLE PAGE

Clinical Study Protocol

A Multi-Center, Open-Label, Phase 1/1b Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Anticancer Activity of Fruquintinib in Patients with Advanced Solid Tumors

Protocol Number：	2015-013-00US1
Investigational Product：	Fruquintinib (HMPL-013)
IND:	131038
Sponsor：	Hutchison MediPharma Limited NO. 4, Lane 898, Cailun Road, Zhangjiang Hi-Tech Park, Shanghai, China Post Code: 201203
Protocol Version：	Version 4.0 (Amendment 4)
Protocol Date:	09 Jan 2020
Previous Version:	Version 3.0
Previous Protocol Date:	09 December 2018
Phase:	1

INTRODUCTORY AND CONFIDENTIALITY STATEMENT

This protocol has been prepared according to the International Conference for Harmonisation (ICH) Harmonised Tripartite Guidelines for Good Clinical Practice (issued in June 1996, with an implementation date of January 17, 1997), Food and Drug Administration (FDA) Good Clinical Practice (GCP) guidelines, and Code of Federal Regulations (CFR): 21 CFR 312, 21 CFR 50, 21 CFR 56.

The submission/document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing notice to Hutchison MediPharma Limited and opportunity to object.

EDITION HISTORY

Version 1.0	31 December 2015
Version 1.1 (Amendment 1)	31 July 2017
Version 2 (Amendment 2)	2 July 2018
Version 3 (Amendment 3)	9 December 2018
Version 4 (Amendment 4)	09 January 2020

AMENDMENT SUMMARY

This Protocol 2015-013-00US1 Version 4 (Amendment 4), replaces Protocol 2015-013-2015 Version 3 (Amendment 3; 9 December 2018). A complete amendment history is available in Appendix K.

The primary purpose of Amendment 4 is to add an additional 10 patients to cohort B and to add 3 additional cohorts to the expansion phase of the study. The changes made in this amendment are described in the table below.

Description and Rationale for Change	Sections
Removed references to tumor types in the study title and in the objectives and endpoints of the dose expansion stage to reflect enrollment of patients of different tumor types	Title page Signature Page Synopsis Section 2.2 Dose Expansion Phase (dose expansion)
Added 10 patients to the planned 30 patients with refractory mCRC in Cohort B. This patient population with mCRC reflects the current treatment practice in the US, in which TAS-102 and regorafenib are approved and used in the 3L+ setting. Removed references to assessment times planned for Cohort B to reflect addition of other expansion cohorts that have different assessment times	Section 1.4 Study Rationale Section 2.2.1 Primary Objective Section 2.2.2 Primary Endpoint Section 3.1 Description of the Study Section 3.1.2 Dose Expansion Phase
Added Expansion Cohort C, which consists of approximately 40 patients with mCRC who have progressed on all standard therapies but who *have not* received prior TAS-102 and/or regorafenib (Cohort C). Enrollment of this cohort is based on the positive results of the phase 3 FRESCO trial conducted in China that led to approval of fruquintinib in that indication by the CFDA. Cohort C represents a patient population in the US that is similar to that of the phase 3 FRESCO study.	Section 1.4 Study Rationale Section 2.2.1 Primary Objective Section 3.1 Description of the Study Section 3.1.2 Dose Expansion Phase
Added expansion Cohort D, which consists of approximately 15 patients with advanced, refractory HR+/Her2- metastatic breast cancer (mBC), and expansion Cohort E, which consists of approximately 15 patients with triple-negative breast cancer (TNBC). Cohorts D and E were added based on data from phase 1 studies of fruquintinib conducted in China (2009-013-00CH1) and in the US (Protocol 2015-013-00US1) suggesting clinical activity in populations with mBC.	Section 1.4 Study Rationale Section 2.2.1 Primary Objective Section 3.1 Description of the Study Section 3.1.2 Dose Expansion Phase
Revised total sample size of planned enrollment from approximately 50 patients to 128 patients and total sample size of enrollment in the expansion cohorts from approximately 36 to 116 patients.	Section 3.2 Sample Size Section 8.6 Determination of Sample Size

Description and Rationale for Change	Sections
Added justification of sample sizes for Expansion Cohorts B, C, D, and E.	
Changed the primary endpoint for the dose expansion phase to add progression-free survival (PFS) rate at week 12 for Cohorts B and C, PFS rate at week 16 for Cohort D, and PFS rate at week 24 for Cohort E. Added clarification of definition of PFS rate.	Section 2.2.2 Primary Endpoint (dose expansion stage) Section 8.5 Efficacy Analysis
Revised inclusion criterion 4 to have separate inclusion criteria for dose escalation and for expansion cohorts. Added inclusion criteria for Cohorts C, D, and E.	Section 4.1 Inclusion Criteria
Added Inclusion Criterion 5 to specify that hormone receptor positive mBC patients must have progressed on at least two lines of prior systemic therapy, including hormonal therapy or chemotherapy.	Section 4.1 Inclusion Criteria
Added Inclusion Criterion 6 specify that triple-negative breast cancer patients must have progressed on at least one cytotoxic therapy in the metastatic setting, with exception of subjects who progressed within 12 months of adjuvant therapy.	Section 4.1 Inclusion Criteria
Revised Inclusion Criterion 7 (formerly Inclusion Criterion 5) to add that patients may qualify for enrollment in this study if they have bone lesions in the absence of measurable disease	Section 4.1 Inclusion Criteria
Revised Exclusion Criterion 11 to exclude patients with history of a thromboembolic event within 6 months, rather than 12 months, prior to screening.	Section 4.2 Exclusion Criteria
Added an end-of-study definition per regulatory requirements	Section 3.7 End of Study (new section)
Added survival follow-up of patients	Section 3.1.1 Dose Escalation Phase Section 3.1.2 Dose Expansion Phase Appendix A Schedule of Events
Revised tumor assessment schedule and analysis plan to reflect addition of Cohorts C, D, and E	Section 6.4 Efficacy Assessments Section 8.5 Efficacy Analysis Appendix A Schedule of Events
Added that, for cardiac monitoring, MUGAs are permitted if echocardiograms cannot be performed.	Section 6.3.4 Cardiac Monitoring Appendix A Study Schedule of Events
Revised specifications for recording of deaths	Section 7.1.8.5 Death
Revised sections related to pharmacokinetics to be consistent with the most current version of the Investigator's Brochure (version 11.0).	Section 1.2.2 Nonclinical Pharmacokinetics Section 5.3.3 Drug-Drug Interactions Appendix F Fruquintinib and Concomitant Medication

Description and Rationale for Change	Sections
Revised conditions for termination of the study by the sponsor. Removed provision that the study is considered completed when all patients have continued study drug or the last patient has completed 1 year of treatment.	Section 3.5 Study Early Termination (formerly named Study Completion or Early Discontinuation)
Increased the estimated number of enrollment sites from up to 10 sites to approximately 12 sites.	Section 3.3 Investigational Site
Clarified that dose-limiting toxicity assessment does not apply to the expansion cohorts.	Section 3.1.1a Dose-Limiting Assessment Window Section 6.5.2 Assessments during Treatment Phase Section 7.1.2 Reporting of Dose Limiting Toxicity
Clarified definition of DLT evaluable patients as those who have not received any prior anti-cancer therapy	Section 3.1.1b Definition of DLT Evaluable Patients
Corrected list of laboratory tests. Removed fecal occult blood testing from laboratory tests and added reticulocyte count and cholesterol tests.	Section 6.1.3 Laboratory Tests Appendix A Study Schedule of Events Appendix J Clinical Management of Severe or Serious Hemorrhagic Events
Removed provision that any data analysis carried out independently by the investigator should be submitted to Hutchison MediPharma prior to publication or presentation.	Section 8 Statistical Analysis
Reorganized the Study Assessments and Methods section for improved clarity and flow	Section 6 Study Assessments and Methods
Added study schema for improved clarity	Figure 5 Study Schema
Moved summaries of prior protocol amendments to a new appendix	Appendix K Protocol Amendment History (new appendix)
Non-substantive editorial and formatting changes were made for administrative purposes or improvement in clarity.	Throughout entire document

SIGNATURE PAGE

Declaration of Investigator

Protocol Title： A Multi-Center, Open-Label, Phase 1/1b Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Anticancer Activity of Fruquintinib in Advanced Solid Tumors

I agree to the terms of this CSP. I will conduct the study according to the procedures specified herein and according to the principles of Good Clinical Practice (GCP) and local regulations.

Investigator (name and institutional affiliation)：

Investigator Signature	Date

SIGNATURE PAGE

Declaration of Sponsor

This clinical study protocol and/or its amendment(s) have been subject to critical review and have been approved by the sponsor.

[redacted]
Clinical Development and Regulatory Affairs Department
Hutchison MediPharma (US) Inc.
[redacted]

[redacted]
[redacted], Hutchison MediPharma Limited
[redacted]

SYNOPSIS

Protocol Number	2015-013-00US1
Study Title	A Multi-Center, Open-Label, Phase 1/1b Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Anticancer Activity of Fruquintinib in Patients with Advanced Solid Tumors
Sponsor	Hutchison MediPharma Limited
Investigational Product	Fruquintinib (HMPL-013)
Investigational Centers	Approximately 12 sites in the United States of America
Planned Enrollment	Total of approximately 128 patients. • Approximately 12 patients will be enrolled in the dose escalation phase. • Approximately 116 patients will be enrolled in the dose expansion phase in the following cohorts: o 6 patients in cohort A (solid tumors) o 40 patients in cohort B (mCRC, prior treatment with TAS-102 or regorafenib required) o 40 patients in cohort C (mCRC, no prior treatment with TAS-102 or regorafenib) o 15 patients in cohort D (HR+/Her2- breast cancer) o 15 patients in cohort E (triple negative breast cancer)
Study Duration	Estimated 36 months, including the dose escalation phase and dose expansion phase.
Study Objectives and Endpoints: Dose Escalation Phase	**The primary objective of the dose escalation phase** is to evaluate the safety and tolerability of fruquintinib in patients with advanced solid tumors and to determine the recommended Phase 2 dose (RP2D). **The primary endpoint of the dose escalation phase** is the incidence of DLT in each cohort. DLT is defined as: • Any Grade 4 non-hematologic toxicity; • Any Grade 3 non-hematologic toxicity related to study drug except for nausea/vomiting, diarrhea, constipation, hypertension and electrolyte imbalances downgraded within 3 days with appropriate supportive treatment; • Grade 4 neutropenia lasting >3 days; • Grade 3 febrile neutropenia (absolute neutrophil count [ANC]) $<1.0 \times 10^9$/L with a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than one hour; • Grade 4 thrombocytopenia or Grade 3 thrombocytopenia associated with bleeding;

	• Dose interruption for >14 days due to toxicity. The MTD is the highest dose at which no more than 1 of 6 patients developed a DLT. If 2 or more patients developed DLT at a particular dose level, then that dose has exceeded the MTD. The safety and tolerability of fruquintinib will primarily be evaluated by the frequency and severity of AEs. Other safety parameters include physical examination, vital signs, laboratory test results (ie, hematology, chemistry panel, thyroid function, and urinalysis), 12-lead electrocardiogram, and echocardiogram. **The secondary objectives of the dose escalation phase are:** • To evaluate the PK characteristics of multiple-dose fruquintinib and to investigate the metabolite profile of fruquintinib in the plasma of patients with solid tumors. • To evaluate the anticancer activity of fruquintinib in patients with solid tumors according to RECIST Version 1.1. **The secondary endpoints of the dose escalation phase are:** • The primary PK parameters include: maximum plasma concentration (C_{max}), time to reach maximum concentration (T_{max}), terminal half-life ($t_{1/2}$), area under the concentration-time curve in a selected time interval (AUC_{0-t}), area under the concentration-time curve in the time interval from 0 to infinity ($AUC_{0\infty\infty-\infty}$), apparent clearance (CL/F), apparent volume of distribution (V_z/F) during the terminal phase according to CL/F/Ke, and the accumulation index based on AUC. • The objective response rate (ORR), disease control rate (DCR), duration of response (DoR), progression-free survival (PFS), overall survival (OS) and percentage change in tumor size from baseline according to RECIST v. 1.1.
Study Objectives and Endpoints: Dose Expansion Phase	**The primary objective of the dose expansion phase is**: To evaluate the anticancer activity of fruquintinib at the recommended Phase 2 dose (RP2D) from the dose escalation phase, in patients with advanced solid tumors. **The primary endpoint of the dose expansion phase is**: PFS rate. **The secondary objectives of the dose expansion phase are**: • To evaluate anticancer efficacy of fruquintinib, as assessed by ORR, DCR, DoR, PFS, and OS • To evaluate the pharmacokinetic (PK) characteristics of multiple dose fruquintinib and investigate the metabolite profile of fruquintinib in plasma. • To evaluate the safety of fruquintinib. **The secondary endpoints of the dose expansion phase are:**

	• The objective response rate (ORR), disease control rate (DCR), duration of response (DoR), PFS, overall survival (OS), and percentage change in tumor size from baseline according to RECIST V. 1.1 • The primary PK parameters include: maximum plasma concentration (C_{max}), time to reach maximum concentration (Tmax), terminal half-life (t1/2), area under the concentration-time curve in a selected time interval (AUC_{0-t}), area under the concentration-time curve in the time interval from 0 to infinity ($AUC_{0-\infty}$), apparent clearance (CL/F), apparent volume of distribution (Vz/F) during the terminal phase according to CL/F/Ke, and the accumulation index based on AUC. • Safety, as assessed by the incidence and severity of AEs, physical examinations, vital signs, laboratory test results, 12-lead electrocardiogram, and echocardiogram.
Study Design	This is an open-label study of fruquintinib comprised of a dose escalation phase in patients with advanced solid tumors of any type, and a dose expansion phase in patients with advanced solid tumors of any type (Cohort A), in patients with refractory mCRC (Cohorts B and C), or in patients with mBC (Cohorts D and E). **Dose Escalation/ Phase：** • Approximately 12 evaluable patients will be enrolled. The actual number of patients enrolled will depend on the dose-limiting toxicity (DLT) profile as well as maximum tolerated dose (MTD) level reached in this trial. • The dose levels to be investigated are 3 mg and 5 mg QD, 3 weeks on/1week off. • Six DLT-evaluable patients will be enrolled in the dose escalation phase and will be treated with fruquintinib 3 mg QD (3 weeks on/1week off) orally. If no more than 1 DLT occurs during the DLT observational window (ie, from Days 1-28 in Cycle 1) among the 6 patients, the trial will continue to enroll another 6 patients in the next dose cohort in which fruquintinib 5 mg QD (3 weeks on/1week off) will be tested. • Safety monitoring and evaluation for the dose escalation phase will be carried out by the Safety Review Committee (SRC). • If no more than 1 patient at the dose level of 5 mg QD experiences a DLT, the dose escalation phase is completed and the expansion phase of the study will be conducted. • Upon completion of the dose escalation phase, the SRC will review aggregated safety and PK data and then select a fruquintinib dose as the recommended Phase 2 dose (RP2D) for the expansion phase of the trial.

	• Blood samples for PK assay will be collected in Cycle 1 at the following time points: pre-dose (within 10 minutes), 1, 2, 4, 8, and 24 hours post dose on Days 1, 14 and 21. • Prior to confirmation of a DLT, if a patient received medical intervention or missed 4 or more fruquintinib doses during the DLT observational window, the patient will not be qualified as DLT-evaluable and will therefore be replaced. • If a patient does not meet the definition of DLT-evaluable patient during the DLT observation period, the patient will be replaced. • Patients who have completed the DLT observation period (Days 1-28, Cycle 1) and are deemed to be benefiting from the fruquintinib treatment at the investigator's discretion may continue the fruquintinib treatment until disease progression, death, intolerable toxicity, or at investigator's discretion that the patient can no longer benefit from the study drug. • Tumor evaluations during the dose escalation phase are scheduled at screening and every 8 weeks (± 1 week) thereafter, ie, C3D1, C5D1, C7D1, etc (odd-numbered cycles). Response assessments will be performed by the investigator using according to RECIST Version 1.1. • Patients will be followed until death or study completion. **Dose Expansion Phase:** Once the RP2D is determined, patients may enroll into one of the following cohorts and will receive fruquintinib at the RP2D: • Cohort A: Patients with advanced, refractory solid tumors of any type. • Cohort B: Patients with refractory mCRC who have progressed on all standard chemotherapies and relevant biologics and have also progressed on, or had intolerable toxicity with, at least 1 FDA-approved third-line therapy (TAS-102 or regorafenib). • Cohort C: Patients with refractory mCRC who have progressed on all standard chemotherapies and relevant biologics and *have not* received prior TAS-102 or regorafenib. • Cohort D: Patients with hormone-receptor positive (ER+ and/or PR+)/Her2- metastatic breast cancer who have progressed on at least two line of prior systemic therapy. • Cohort E: Patients with advanced triple negative breast cancer (TNBC) who have progressed on at least one cytotoxic therapy in the metastatic setting. The safety of all enrolled patients in the expansion cohorts will be closely monitored from the first day of fruquintinib dosing until 30 days after the

	last dose. All serious adverse events (SAEs) should be reported from the day the ICF is signed until 30 days after the last dose, regardless of relationship to study drug. All adverse events (AEs) will be graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. Tumor response will be assessed according to RECIST Version 1.1 at screening and at study visits as defined in the Schedule of Events in Appendix A. Confirmation of CR and PR is required at no less than 4-week intervals between the date of initial response and the confirmation assessment date. Patients will be followed until death or study completion
Study Treatment	**Dose Escalation Phase:** Fruquintinib will be administered orally once daily (QD) 3 weeks on/1 week off for every 28-day treatment cycle until disease progression, death, intolerable toxicities, or at investigator's discretion that the patient can no longer benefit from the study drug. **Dose Expansion Phase:** Fruquintinib will be administered orally QD 3 weeks on/1 week off for every 28-day treatment cycle until disease progression, death, intolerable toxicities, or at investigator's discretion that the patient can no longer benefit from the study drug.
End of Treatment (EOT)	The criteria for the end of study treatment are as follows (if any of the following criteria is met): 1. Disease progression (according to RECIST Version 1.1) unless there is reasonable evidence of clinical benefit to justify continuation on the study treatment. The decision to continue treatment should be made by the investigator in consultation with the sponsor. The disease progression date is the date when the radiological disease progression is first reported according to RECIST Version 1.1 criteria; 2. Death; 3. End of this study. Early discontinuation of study treatment will occur if any of the following criteria is met: 1. Patient's withdrawal of consent; 2. Intolerable toxicity; 3. Poor patient compliance; 4. Use of other antitumor treatment during the study; 5. Pregnancy occurred during the study treatment period; 6. Patient is lost to follow-up; 7. Treatment discontinuation is in the best interest of the patient based on the assessment of the investigator and the sponsor.

End of Study	The end of study is defined as the last visit of the last patient.
Inclusion Criteria	To be eligible to participate in the study, patients must meet **all** of the following Inclusion Criteria: 1. Fully understand the study and voluntarily sign the informed consent form; 2. ≥18 years of age; 3. Body weight ≥40 kg; 4. **Dose Escalation Phase:** Histologically or cytologically documented, locally advanced or metastatic solid malignancy of any type (except squamous NSCLC) that has progressed on approved systemic therapy, and for whom no effective therapy or standard of care exists. **Dose Expansion Phase:** **Cohort A:** Histologically or cytologically documented, locally advanced or metastatic solid malignancy of any type (except squamous NSCLC), that has progressed on approved systemic therapy, and for whom no effective therapy or standard of care exists. **Cohort B:** Histologically or cytologically documented adenocarcinoma of the colon or rectum that has progressed on, or had intolerable toxicity to, at least 1 FDA-approved third-line systemic therapy (TAS-102 or regorafenib). Treatment failure is defined as: disease progression during or within 3 months after the last dose of standard therapy, or discontinuation of standard therapy because of unacceptable toxicity. Patients must also have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and, if RAS wild type, an anti-EGFR therapy. Eligibility also requires knowledge of tumor RAS status (wild-type or mutant) as reported by investigators. **Cohort C:** Histologically or cytologically documented adenocarcinoma of the colon or rectum. Patients must have progressed on, or had intolerable toxicity to, at least two prior regimens of standard chemotherapy, but *must not* have received prior TAS-102 or regorafenib. Treatment failure is defined as: disease progression during or within 3 months after the last dose of standard therapy, or discontinuation of standard therapy because of unacceptable toxicity. Prior therapy could have included adjuvant chemotherapy if a tumor had recurred within 6 months after the last administration of treatment. Patients must have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biological therapy and, if RAS wild-type, an anti-EGFR therapy. Eligibility also requires knowledge of tumor RAS status (wild-type or mutant) as reported by investigators. **Cohorts D and E:** Her2-negative metastatic breast cancer, with Her2-negative defined as immunohistochemistry (IHC) 0, 1+, or 2+. If IHC 2+, a negative

	in situ hybridization (FISH, CISH, or SISH) test is required by local laboratory testing a. **Cohort D only:** Histologically- or cytologically-confirmed hormone-receptor positive (ER+ and/or PR+) breast cancer, by local assessment, OR b. **Cohort E only:** Histologically- or cytologically- confirmed triple negative breast cancer with ER-negative, PR-negative tumors as defined by local criteria. 5. Hormone receptor positive mBC patients must have progressed on at least 2 lines of prior systemic therapy, including hormonal therapy or chemotherapy. However, patients may not have received more than 3 prior lines of cytotoxic chemotherapy in the metastatic setting. There is no limit to number of prior lines of hormonal therapy. 6. Triple negative breast cancer patients must have progressed on at least 1 cytotoxic therapy in the metastatic setting, with the exception of subjects who progressed within 12 months of adjuvant therapy. However, patients may not have received more than 5 prior lines of cytotoxic chemotherapy in the metastatic setting. 7. Have measurable disease per RECIST Version 1.1 or bone lesions in the absence of measurable disease (expansion phase only). Lesions that received radiotherapy are not measurable per RECIST Version 1.1. 8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; 9. Expected survival of more than 12 weeks; 10. For female patients of childbearing potential and male patients 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 (on the understanding that this is the only one partner during the whole study duration), 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 rules are valid for male patients involved in this clinical trial if they have a partner of childbirth potential. Male patients must always use a condom. A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (ie, ⩾12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of

	the ovaries and/or uterus).
Exclusion Criteria	Patients will be excluded from the study, if **any** of the following criteria is met: 1. **Cohort C only:** patients who have been previously been treated with TAS-102 or regorafenib 2. Absolute neutrophil count (ANC) <1.5×10^9/L, platelet count <100 × 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; 3. Serum total bilirubin >1.5 × the upper limit of normal (ULN); 4. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 1.5 × ULN in patients without hepatic metastases; ALT or AST > 3 × ULN in patients with hepatic metastases; 5. Serum potassium, calcium, or magnesium levels out of the normal laboratory reference range, and clinically significant in the investigator's judgment; 6. 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 as follows: CrCl (mL/min) = [(140 - age) × (weight in kg) ÷ [72 × (serum creatinine in mg/dL)] (0.85 if female). 7. Urine dipstick protein ≥2+ or 24-hour urine protein ≥1.0 g/24-h. Patients with greater than 1+ proteinuria on urinalysis must undergo a 24-hour urine collection; 8. Uncontrolled hypertension, defined as: systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ⩾90 mm Hg; 9. International Normalized Ratio (INR) >1.5 or activated partial thromboplastin time (aPTT) > 1.5 × ULN, unless the patient is currently receiving or intending to receive anticoagulants for prophylactic purposes. 10. Risk of, or active hemorrhage: history or presence of 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 possibly result in gastrointestinal tract hemorrhage or perforation; within the 6 months prior to screening; 11. History or presence of hemorrhage from any other site (eg, hemoptysis or hematemesis) within 2 months prior to screening; 12. History of a thromboembolic event (including deep vein thrombosis [DVT], pulmonary embolism [PE], stroke and/or transient ischemic attack) within 6 months prior to screening; 13. Patients with squamous NSCLC; 14. 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%; 15. 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. 16. Concomitant medications with a known risk of causing QT prolongation and/or torsade de pointes (See list in Appendix E; source list is continuously updated online at www.qtdrugs.org). 17. Patients who have ever received a VEGFR inhibitor **except** for patients with refractory mCRC enrolled in the dose expansion phase. 18. Systemic anti-neoplastic therapies (except for those described in Exclusion 18) or any investigational therapy within 4 weeks prior to the first dose of study drug, including chemotherapy, radical radiotherapy, hormonotherapy, biotherapy and immunotherapy; 19. 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; 20. Palliative radiotherapy for bone metastasis/lesion within 2 weeks prior to the initiation of study drug; 21. Brachytherapy (ie, implantation of radioactive seeds) within 60 days prior to the first dose of study drug. 22. Use of strong inducers or inhibitors of CYP3A4 within 2 weeks before the first dose of study drug (3 weeks for St John's Wort); P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) substrate within 2 weeks before the first dose of study drug. 23. Surgery or invasive procedure (ie, a procedure that includes a biopsy) within 60 days prior to the first dose of study drug or unhealed surgical incision; 24. Any unresolved toxicities from a previous antitumor treatment greater than CTEAE v. 4.03 Grade 1 (except for alopecia). 25. Known human immunodeficiency virus (HIV) infection; 26. Known clinically significant history of liver disease, including cirrhosis, current alcohol abuse, or active viral hepatitis. For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated. Patients with HCV infection who are currently on treatment are eligible if they have an undetectable ICV viral load. 27. Evidence of ongoing or active infection requiring intravenous antibiotics; 28. Tumor invasion of a large vascular structure (eg, pulmonary artery, superior or inferior vena cava). 29. Women who are pregnant or lactating;

	30. 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; patients requiring steroids within 4 weeks prior to start of study treatment will be excluded; 31. No other malignancy, except for non-melanoma skin cancer, during the 5 years prior to screening; 32. 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; 33. Other disease, metabolic disorder, physical examination anomaly, abnormal laboratory result, or any other condition that investigators suspect may prohibit use of the investigational product, affect interpretation of study results, or put the patient at undue risk of harm based on the investigator's assessment. 34. Known hypersensitivity to fruquintinib or any of its excipients.
Statistical Analysis: By-subject listings will be created for variables from each CRF module, as applicable. Summary tables for continuous variables will contain at least the following statistics: number of patients (n), mean, standard deviation (SD), median, minimum, and maximum. Summary tables for categorical variables will include n, and percentage.	
Safety Assessment	All patients who have received at least one dose of fruquintinib will be included in the safety analysis set (SAS). All DLTs will be listed by dose cohort in DLT-evaluable patients for the dose escalation phase only. Safety will be evaluated based on the frequency and severity of AEs, change of laboratory test results, changes in vital signs, change in ECG, and change in echocardiogram. Safety data will be listed and summarized by dose cohort, for patients overall, and for patients with mCRC (cohorts' B and C) and mBC (cohorts' D and E) who received fruquintinib at the RP2D. The severity of all AEs will be graded by the investigator according to the NCI CTCAE v4.03. All AEs will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Treatment-emergent AEs (TEAEs) will be classified by MedDRA System Organ Class (SOC) and specified by Preferred Term (PT). The incidence of TEAEs, SAEs, adverse events of special interest (AESIs), TEAEs leading to dose interruption, dose reduction, or study drug discontinuation will be summarized. For the laboratory assessments, such as hematology, serum biochemistry, urinalysis, and other urine parameters will be programmatically graded according to CTCAE severity grade. Summary tables will be presented to show the number of patients by CTCAE severity grade with

	corresponding percentages. For parameters for which a CTCAE scale does not exist, the frequency of patients with values below, within, and above the normal ranges will be summarized. Shift tables for selected hematology and serum biochemistry will also be presented showing change in CTCAE severity grade from baseline to worst grade post-baseline.
Pharmacokinetics	All patients who received at least one dose of fruquintinib and have at least one plasma sample obtained and analyzed will be included in the Pharmacokinetic Analysis Set (PKAS). A non-compartmental model analysis will be performed for plasma concentration data by the central laboratory using WinNonlin (enterprise version). The following summary statistics will be presented for concentration data and PK parameters, where appropriate: mean, standard deviation, coefficient of variation (CV%), median, minimum, maximum, geometric mean, and geometric mean CV%.
Efficacy	All patients from the safety analysis set who have at least one post-baseline tumor assessment will be included in the efficacy analysis set (EAS). The ORR and DCR will be summarized by dose cohort with percentages and 95% exact confidence intervals for the EAS. The PFS rate at specific time points (eg, PFS rate at 12 weeks for Cohort C) and its 95% confidence interval will be estimated using the Kaplan-Meier method. PFS, DoR, and OS will be summarized descriptively using Kaplan-Meier medians and quartiles for patients in the SAS. Percentage change in tumor size will be determined for patients with measurable disease at baseline and will be derived at each visit by the percentage change in the sum of the diameters of target lesions (TLs) compared to baseline. The best percentage change in tumor size will be summarized using descriptive statistics and presented using a waterfall plot.

TABLE OF CONTENTS

List of Tables

List of Figures

ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BCRP	Breast cancer resistance protein
BP	Blood pressure
BOR	Best overall response
BUN	Blood urea nitrogen
CBC	Complete blood count
CI	Confidence intervals
CL/F	Apparent clearance
C_{max}	Maximum plasma concentration
CNS	Central nervous system
CR	Complete response
CRC	Colorectal cancer
CRF	Case report form
CRO	Contract Research Organization
C_{ss_av}	Mean concentration at steady state
C_{ss_max}	Maximum concentration at steady state
CT	Computed tomography
CV (%)	Coefficient of variation (percent)
DCR	Disease control rate
DILI	Drug-induced liver injury
DLT	Dose-limiting toxicity
DoR	Duration of response
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EAS	Efficacy Analysis Set
EGFR	Epidermal growth factor receptor
FDG-PET	^{18}F-fluorodeoxyglucose positron emission tomography
FRESCO	Fruquintinib Efficacy and Safety in 3+ Line Colorectal Cancer Patients
GCP	Good Clinical Practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IC_{50}	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Conference for Harmonisation

Abbreviation	Definition
IEC/IRB	Independent Ethics Committee/Institutional Review Board
INR	International normalized ratio
K_e	Elimination rate constant
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events (version [v] 4.03)
NOAEL	No observed adverse effect level
NSCLC	Non−−−small cell lung cancer
ORR	Objective response rate
PD	Progressive disease
PFS	Progression-free survival
P-gp	P-glycoprotein
PI	Principal investigator
PK	Pharmacokinetic(s)
PKAS	Pharmacokinetic Analysis Set
POC	proof-of-concept
PPE	Palmar-plantar erythrodysesthesia
PR	Partial response
PSA	Prostate-specific antigen
PT	Preferred Term MedDRA)
QD	Once daily
QTc	Corrected QT interval
QTcF	Corrected QT interval using the Fridericia method
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors (Version [V] 1.1)
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SD	Stable disease
SDV	Source data verification
SOC	System Organ Class (MedDRA)
SRC	Safety Review Committee
$t_{1/2}$	Half-life
TEAE	Treatment-emergent adverse event
TL	Target lesion
T_{max}	Time to reach maximum plasma concentration
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor

Abbreviation	Definition
VEGFR	Vascular endothelial growth factor receptor
V_z/F	Apparent volume of distribution (determined according to $CL/F/K_e$)
WBC	White blood cell
WHO	World Health Organization

1 BACKGROUND

Angiogenesis is a prominent feature of many physiological and pathological processes, including wound healing, luteinization, and tumor growth [1,2]. It is regulated by a balance between local pro-angiogenic and anti-angiogenic factors. Vascular endothelial growth factor (VEGF) is an important pro-angiogenic factor. It is a key regulator of physiological angiogenesis during embryogenesis, skeletal growth, and reproductive functions. It is also implicated in pathological angiogenesis such as that associated with tumor growth. In the normal state, endothelial cells divide approximately every 7 years, but in the malignant state, this growth rate is accelerated, and endothelial cells can divide as rapidly as every 7 to 10 days. An "angiogenic switch" is necessary for tumors to obtain the necessary nutrients and oxygen to grow larger than a diameter of 1 mm.

The biologic effects of VEGF are mediated through binding to 3 VEGF receptors, VEGFR-1 (Flt-1), VEGFR-2 (KDR or Flk-1), and VEGFR-3. Binding of VEGF to its receptors begins the signaling cascade that regulates cellular events involved in new blood vessel formation that produces a number of biologic effects including endothelial cell mitogenesis and migration, increased vascular permeability, and inhibition of endothelial cell apoptosis. Newly formed tumor vessels are markedly dependent on VEGF, and VEGF mRNA is upregulated in many tumors. Tumor cells represent the major source of VEGF, but tumor-associated stroma is also an important site of VEGF production[2,3].

Overexpression of VEGF has been associated with the promotion of tumor growth, elevation of the vascular permeability of tumor vessels, and poor prognosis in solid tumors, including colorectal carcinoma[4,5], gastric carcinoma[6,7], breast cancer[8,9] and lung cancer[10].

Fruquintinib is a small molecule tyrosine kinase inhibitor (TKI) with a novel chemical structure, which belongs to the quinazoline class. It is a potent and highly selective VEGFR inhibitor discovered by Hutchison MediPharma Limited using rational drug design and high-throughput in vitro and in vivo biological screening of a large number of compounds

1.1 Physical, Chemical and Pharmaceutical Properties of Fruquintinib

1.1.1 Nomenclature

Chinese generic name: 呋喹替尼

English generic name: Fruquintinib

Investigational product ID: HM5006462, HMPL-013 (or 013 as abbreviation)

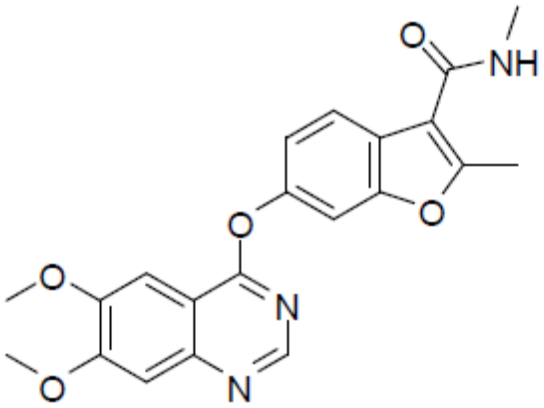
Chinese chemical name:

6-(6,7-二甲氧基喹唑啉-4-氧)-N,2-二甲基-苯并呋喃-3-甲酰胺

English chemical name:

6-(6, 7-dimethoxyquinazolin-4-yloxy)-N,2-dimethylbenzofuran-3-carboxamide

1.1.2 Structure



Molecular formula: $C_{21}H_{19}N_3O_5$

Molecular weight: 393.39

1.1.3 General Properties

White to off-white crystalline powder soluble in glacial acetic acid; very slightly soluble in methanol, acetonitrile, tetrahydrofuran, acetone, 0.1 mol/L hydrochloric acid solution; almost insoluble in water and 0.1 mol/L sodium hydroxide solution.

1.1.4 Presentation

Fruquintinib drug product is presented as 2 capsule strengths with 1 mg and 5 mg drug substance per capsule, respectively, for oral administration.

1.1.5 Composition

The 1 mg capsule is presented as a size 3 hard gelatin capsule containing 52 mg of white to off-white blend powder that is composed of fruquintinib drug substance, microcrystalline cellulose, starch, and talc. The 5 mg capsule is presented as a size 1 hard gelatin capsule containing 260 mg of same blend powder as the 1 mg capsules.

1.1.6 Storage Conditions

Fruquintinib capsules are stored at controlled room temperature with excursions allowed to 30°C and protected from moisture.

1.2 Summary of Nonclinical Studies

[redacted]

[redacted]

1.3 Clinical Experience

The safety and efficacy of fruquintinib (HMPL-013) has been studied in a number of Phase 1, 2, and 3 studies in patients with a variety of solid tumors, including metastatic colorectal cancer (mCRC), and locally advanced, metastatic, or recurrent non-small cell lung cancer (NSCLC) as a single agent or in combination with other anti-cancer therapies. Summary details can be found in the IB (Section 1.2)[11].

1.3.1 Clinical Pharmacokinetics

The PK of fruquintinib was evaluated in patients with advanced malignant solid tumors treated with a single-dose or multiple-dose regimen (Study 2009-013-00CH1). Following administration, a single oral dose of 1, 2, 4, 5 and 6 mg, fruquintinib showed a very low clearance. The selection of the once daily (QD) dose regimen was justified by the terminal elimination $t_{1/2}$ of >35 hours. The AUC and C_{max} generally increased dose-proportionally at the dose levels from 1 mg to 6 mg. Following multiple dosing, fruquintinib exposure reached steady state after QD administration for 14 days. Based on the AUC for the QD dosing interval (24 hours), accumulation of fruquintinib exposure from the first dose to steady state was approximately 3-fold.

The PK of a 4-week continuous dosing regimen of 5 mg QD was compared to a 3-week continuous dosing regimen of 6 mg QD followed by a 1-week break in fruquintinib therapy in patients with solid cancers (Study 2009-013-00CH1). The PK results showed that fruquintinib PK profiles were similar for the 2 dosing regimens on the same dosing days (see Table 2).

Table 2 Pharmacokinetic Parameters of Fruquintinib at Steady State in Patients (Study 2009-013-00CH1)

Steady State	1 mg[a]	2 mg[a]	4 mg[a]	5 mg[a]	6 mg[a]	5 mg 3/1[b]	6 mg 3/1[b]
T_{max} (h)	1	3.0 ± 1.7	5.1 ± 7.9	1.0 ± 0.0	4.0 ± 0.0	3.6 ± 3.8	2.0 ± 1.0
C_{ss_max} (ng/mL)	82.1	109 ± 14.9	290 ± 61.1	398 ± 43.7	508 ± 63.6	383 ± 51.5	457 ± 103
C_{ss_av} (ng/mL)	55.3	--	217 ± 51.1	324 ± 64.1	385 ± 50.6	295 ± 26.7	354 ± 89.2
AUC_{0-12h} (ng•h/mL)	718	1130 ± 92.9	2741 ± 643	4080 ± 678	5135 ± 600	--	--
AUC_{0-24h} (ng•h/mL)	--	--	5212 ± 1227	7784 ± 1539	9230 ± 1215	7070 ± 642	8500 ± 2142
DF (%)	53.0	--	56.3 ± 22.3	33.9 ± 18.1	52.8 ± 10.8	43.8 ± 12.3	42.0 ± 7.0
R-AUC[c]	4.0	3.1 ± 0.7	3.0 ± 0.6	--	2.5 ± 0.7	3.0 ± 0.6	3.2 ± 0.5

a Steady state of Day 14 at once daily continuous regimen.

b Steady state of Day 21 at once daily 3 weeks on/1 week off regimen.

c Accumulation index R-AUC represented the ratio of AUC_{0-24h} at the steady state/AUC_{0-24h} on Day 1. If AUC_{0-24h} unavailable, AUC_{0-12h} was used.

Two additional dosing regimens were compared: a 4-week continuous dosing regimen of 4 mg QD, and a 3-week continuous dosing regimen of 5 mg QD followed by a 1-week break in fruquintinib therapy, were also evaluated in patients with advanced colorectal cancer (Study 2012-013-00CH3). Overall, the PK profiles of fruquintinib obtained in this study were similar to those in the prior trial (Study 2009-013-00CH1).

The effect of food intake on fruquintinib PK was investigated in healthy male adult volunteers at a single oral dose of 4 mg (Study 2012-013-00CH2). The food effect was evaluated by assessment of the bioequivalence between the fasting condition (fasted) and the fed condition (food intake). Fruquintinib exposure was represented by $AUC_{0-\infty}$ and C_{max}. The geometric mean ratios (90% confidence interval [CI]) of fasted/food intake met the bioequivalence criteria of 80%-125% for AUC and 70%-143% for C_{max}. Absorption appeared to occur more slowly in the fed condition than in the fasting condition.

1.3.2 Clinical Safety

Fruquintinib has not been approved in the United States, and clinical development is ongoing. The expected events (identified risks) seen with fruquintinib treatment based on preclinical and clinical data and/or published data on compounds with similar mechanisms of action are summarized in Table 3. The potential risks of fruquintinib are presented in Section 6.5.2 of the IB[11].

Table 3 Identified Risks in Patients Treated with Fruquintinib

System Organ Class	Identified Risks	Frequency[a] Percentage
Endocrine Disorders	Hypothyroidism	Very common (14.2%)
Gastrointestinal Disorders	Abdominal pain/abdominal discomfort	Very common (26.7%)
	Anal pain	Common (3.1%)
	Diarrhea	Very common (25.6%)
	Oral pain	Very common (11.1%)
	Stomatitis	Very common (26.7%)
General Disorders and Administration Site Conditions	Asthenia	Very common (10.4%)
Hepatobiliary Disorders	Hepatic function abnormal (most frequently reported as ALT/AST increased and blood bilirubin increased))	Very common (47.9%)
Infections and Infestations	Infection (most frequently reported as respiratory tract infection and urinary tract infection)	Very common (25.1%)
Investigations	Amylase increased	Common (3.6%)
	Thyroid function test abnormal	Very common (27.7%)
	Platelet decreased	Very common (19.4%)
	Weight decreased	Very common (19.2%)
	WBC decreased	Very common (14.0%)
	Neutrophil decreased	Very common (10.4%)

System Organ Class	Identified Risks	Frequency[a] Percentage
Metabolism and Nutrition Disorder	Decreased appetite	Very common (23.3%)
Musculoskeletal and Connective Tissue Disorders	Arthralgia	Very common (10.1%)
	Back pain	Very common (15.0%)
	Musculoskeletal pain	Very common (11.9%)
Renal and Urinary Disorders	Proteinuria	Very common (52.1%)
Respiratory, Thoracic and Mediastinal Disorders	Dysphonia	Very common (37.6%)
	Pharyngolaryngeal pain/discomfort	Common (8.8%)
Skin and Subcutaneous Tissue	Palmar-plantar erythrodysaesthesia (PPE) syndrome	Very common
	Rash	Very common
	Dermatitis	Common
Vascular Disorders	Hemorrhages (most frequently reported as occult blood positive, haematuria or blood urine present, and epistaxis)	Very common (40.7%)
	Hypertension	Very common (55.4%)

a Frequency ≥1/10: very common; frequency ≥1/100 to <1/10: common. See fruquintinib IB edition 10, Tables 47 and 48.

Table 4 Potential Risks in Patients Treated with Fruquintinib

Preferred Term	n/N	%
Gastrointestinal perforation/fistula	3/386	0.8%
Wound healing delayed	1 (PI assessment: not related)	0.5%
Reversible posterior leukoencephalopathy (RPLS)	0	0

Please refer to the fruquintinib IB[11] for a complete summary of safety information. Mitigation and management of the identified and potential risks for fruquintinib are presented in Section 5.2 of the IB[11].

1.3.3 Clinical Efficacy

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 Table 5). 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 progression free survival (PFS) results established POC in both studies by meeting their respective primary efficacy endpoints.

Table 5 Overall Best Response by Dose Cohort (Study 2009-013-00CH1)

Dose Cohort	Response in Evaluable Patients (N = 34)				Disease Control (%)	Objective Response (%)
	CR	PR	SD	PD	CR+PR+SD	CR+PR
1 mg[a]	0	0	1	0	1 (100)	0
2 mg[a]	0	0	2	0	2 (100)	0
4 mg[a]	0	7	6	2	13 (86.7)	7 (46.7)
5 mg[a]	0	1	2	0	3 (100)	1 (33.3)
6 mg[a]	0	0	0	1	0	0
5 mg[b]	0	5	1	1	6 (85.7)	5 (71.4)
6 mg[b]	0	1	2	2	3 (60.0)	1 (20.0)
Total	0	14	14	6	28 (82.3)	14 (41.1)

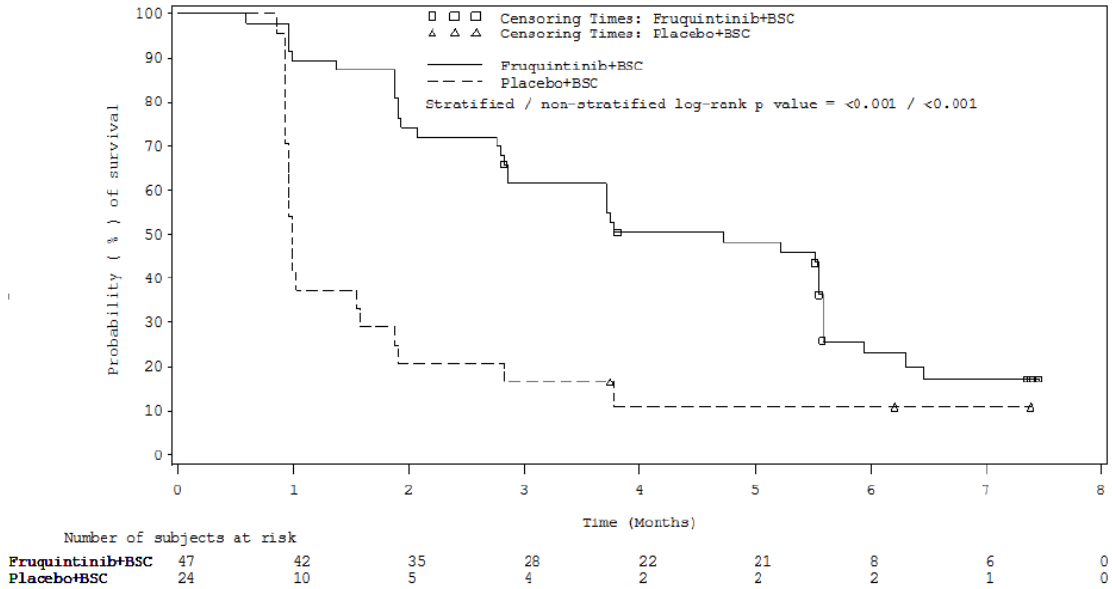
a Continuous regimen.

b 3 weeks on/1 week off regimen.

Study 2012-013-00CH1 was a Phase 2 study investigating the efficacy of fruquintinib in the third-line and later setting in patients with mCRC[12]. A total of 71 patients were included in this study. Compared to the placebo group, the fruquintinib group had a

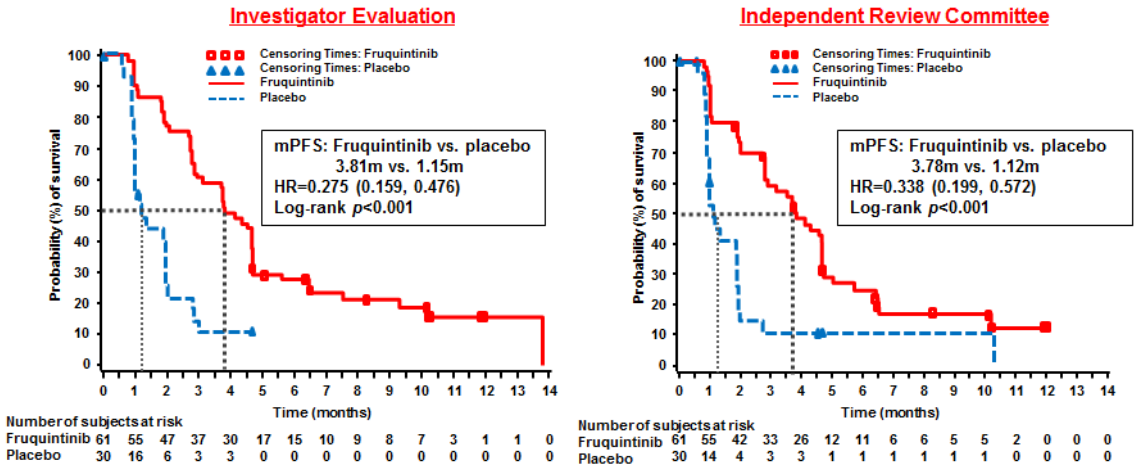
significantly longer PFS: The median (95% CI) PFS of the fruquintinib group was 4.731 (2.858, 5.585) months, while the median (95% CI) PFS of placebo group was 0.986 (0.953, 1.577) months (see Figure 1). The p-value of the stratified log-rank test was <0.001. Stratified HR (95% CI) was 0.302 (0.154, 0.589).

Figure 1 Kaplan-Meier Curve of PFS, by Treatment (Study 2012-013-00CH1)



2014-013-00CH1 study was a Phase 2 study investigating the efficacy of fruquintinib in the third-line setting in advanced NSCLC[13]. A total of 91 patients were included in this study. As shown in Figure 2, fruquintinib significantly improved PFS when patients were treated with fruquintinib monotherapy compared with placebo.

Figure 2 Kaplan-Meier Curve of PFS, by Trial Treatment (Study 2014-013-00CH1)



Study 2013-013-00CH1 (Fruquintinib Efficacy and Safety in 3+ Line Colorectal Cancer patients [FRESCO]) was a Phase 3 study that investigated the efficacy and safety of

fruquintinib in the third-line or later setting in patients with mCRC[14]. A total of 416 patients were included in this study. The primary endpoint was overall survival (OS). Key secondary endpoints were PFS (time from randomization to disease progression of death), ORR (confirmed CR or PR), and disease control rate (CR or PR, or stable disease [SD] recorded ≥ 8 weeks post randomization. Duration of response was also assessed. Safety outcomes included TEAEs.

The fruquintinib group had a significantly longer OS and PFS compared to the placebo group. The median (95% CI) OS of the fruquintinib group was 9.30 (8.18, 1.45) months, while the median (95% CI) OS of the placebo group was 6.57 (5.88, 8.11) months (Figure 3). The p-value of the stratified log-rank test was <0.001. The stratified hazard ratio (HR [95% CI]) was 0.65 (0.51, 0.83). The median PFS (95% CI) of the fruquintinib group was 3.71 (3.65, 4.63) months, while the median (95% CI) PFS of the placebo group was 1.84 (1.81. 1.84) months (Figure 4).

Figure 3 Kaplan-Meier Graph of OS by Trial Treatment (Study 2013-013-00CH1 [FRESCO])

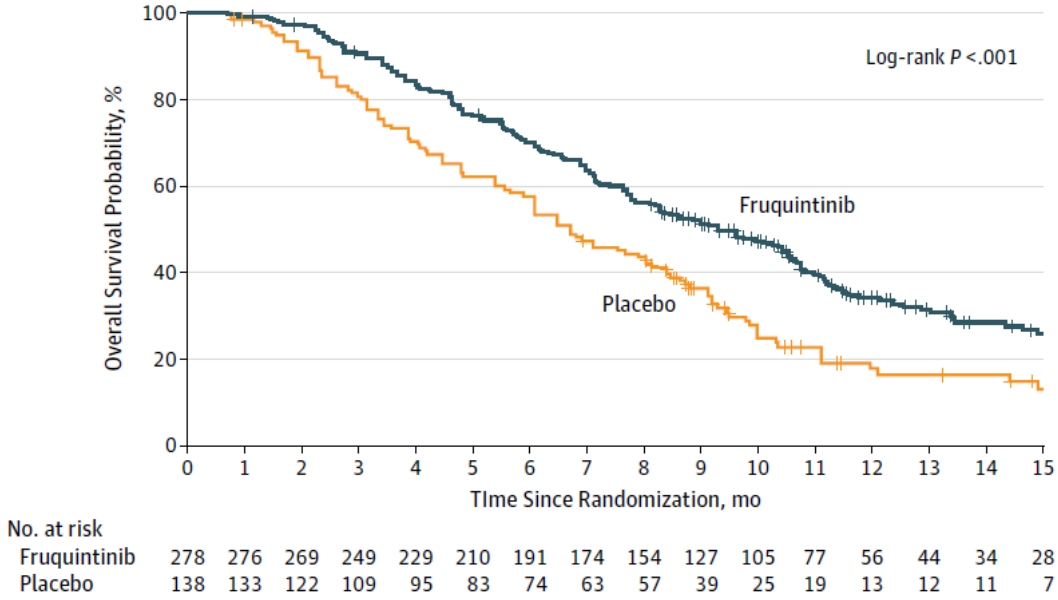
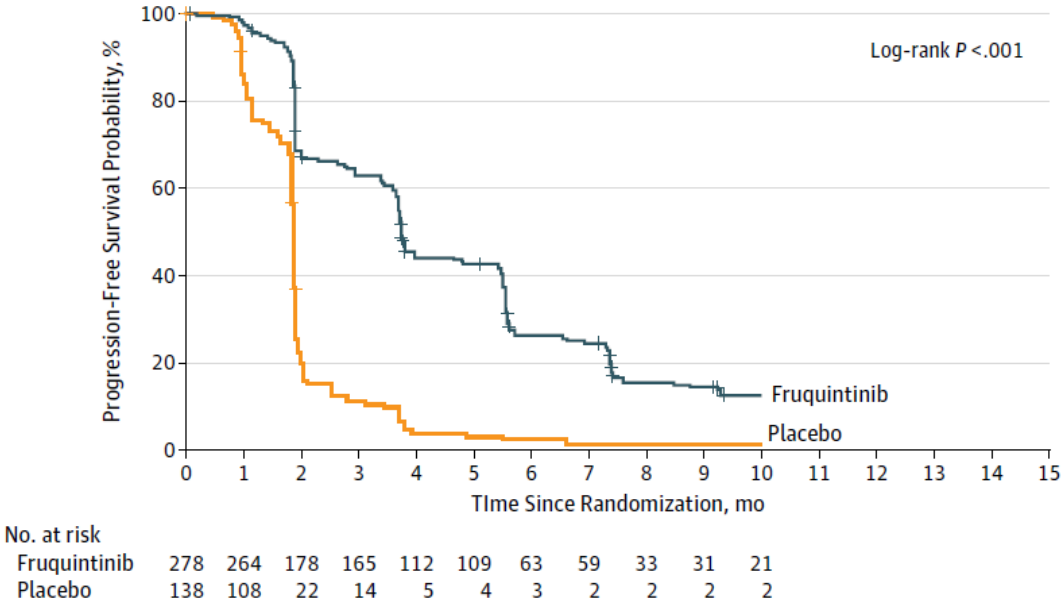


Figure 4 Kaplan-Meier Graph of PFS by treatment arm (Study 2013-013-00CH1)



1.4 Study Rationale

During the pathogenesis of cancer, tumors can secrete a variety of factors to stimulate the formation of tumor vasculature to increase their supply of nutrients and oxygen. Such tumor vasculature is often formed by rapid endothelial cell proliferation and packed coarsely, leading to increased permeability and tumor cell leakage into the circulation.[1] Vascular endothelial cell growth factor (VEGF) and fibroblast cell growth factor (FGF) play key roles in tumor angiogenesis and have become two molecular targets of intense research for anti-angiogenesis therapies[2-3]. Highly selective antibodies against VEGF or its receptor VEGFR have demonstrated significant clinical benefit and have been widely used for the treatment of certain cancers[4]. Small molecule drugs, including sunitinib and sorafenib, targeting the VEGF receptor (VEGFR) tyrosine kinase signaling pathway have also contributed significantly in treating cancer[5,6]. However, most of the early generation small molecule VEGFR tyrosine kinase inhibitors (TKIs) inhibit many kinases other than VEGFR, resulting in "off-target" toxicities[7]. Therefore, improving kinase selectivity has become a key focus for newer generation TKIs.

Fruquintinib, discovered by Hutchison MediPharma, demonstrated much improved kinase selectivity compared to sunitinib and sorafenib in the preclinical setting. Fruquintinib selectively inhibits VEGFR, sparing many other kinases. Preclinical safety evaluation results supported an acceptable safety profile for fruquintinib.

The safety, tolerability, and pharmacokinetic properties of fruquintinib were assessed in a Phase 1 dose escalation study (Study 2009-013-00CH1) that was carried out in patients with advanced solid tumors in China. Results indicated that fruquintinib was well tolerated up to 4 mg QD continuous therapy and 6 mg QD 3 weeks on/1 week off. The maximum tolerated dose (MTD) has been reached in patients treated with the continuous regimen, but not in patients treated with the 3 weeks on/1 week off regimen. The most frequently reported adverse events, including palmar-plantar erythrodysaesthesia (PPE),

proteinuria, and hypertension. The occurrence of aforementioned AEs and laboratory abnormalities are commonly reported in drugs of this class and can be managed effectively. Preliminary clinical efficacy was seen in patients with partial response (PR) and durable stable disease (SD).

Although the MTD was not reached, the experience in China demonstrated that fruquintinib 5 mg (3 weeks on/1 week off) treatment had improved PFS in Chinese patients with metastatic CRC and NSCLC as compared with placebo and was well tolerated. The extensive clinical trial experience in China is the rationale for investigating the 3 mg and 5 mg regimens in the present Phase 1 study. If there are clinically significant differences in the PK of fruquintinib in patients in the United States (US) compared to those of patients in China, the dose escalation sequence may need to be revisited.

The rationale for adding approximately 40 patients with refractory mCRC in dose expansion Cohort B is provided by the results of the phase 3 FRESCO study completed in China (study 2013-013-00CH1 [FRESCO]). FRESCO[14] was a randomized, placebo-controlled, Phase 3 study of fruquintinib that demonstrated a significantly longer OS and PFS for fruquintinib compared to placebo in patients who had progressed on at least 2 lines of chemotherapy and relevant biologics and supported its approval by the CFDA. FRESCO showed an acceptable safety profile for fruquintinib that was consistent with other clinical trials. For additional information about this trial, see Section 1.3.3 above, including Figure 3 and Figure 4. This cohort will evaluate the safety and efficacy of fruquintinib in a patient population of mCRC that is reflective of treatment practice in the US where TAS-102 and regorafenib are approved and used in the third-line or greater setting.

The rationale for adding expansion Cohort C of approximately 40 patients with mCRC who have progressed on all standard chemotherapy and relevant biologics but who *have not* received TAS-102 or regorafenib is also based on the positive results of the Phase 3 FRESCO study completed in China (study 2013-013-00CH1 [FRESCO]). This cohort will evaluate the safety and efficacy of fruquintinib in a patient population in the US that is similar to that of FRESCO.

The rationale for adding Cohorts D (HR+/Her2-) and E (TNBC) of patients each with mBC is to evaluate the safety and efficacy of fruquintinib in patients with mBC based on data from Phase 1 studies of fruquintinib conducted in China (Protocol 2009-013-00CH1) and in the US (Protocol 2015-013-00US1), suggesting clinical activity in the proposed populations of mBC and based on data showing the clinical efficacy of anti-angiogenics in mBC.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Dose Escalation Phase

2.1.1 Primary Objective

The primary objective of the dose escalation phase is to evaluate the safety and tolerability of fruquintinib in patients with advanced solid tumors and to determine the recommended Phase 2 dose (RP2D).

2.1.2 Primary Endpoint

The primary endpoint of the dose escalation phase is the incidence of DLT in each cohort.

DLT is defined as:

- Any Grade 4 non-hematologic toxicity;
- Any Grade 3 non-hematologic toxicity related to study drug except for nausea/vomiting, diarrhea, constipation, hypertension and electrolyte imbalances downgraded within 3 days with appropriate supportive treatment;
- Grade 4 neutropenia lasting >3 days;
- Grade 3 febrile neutropenia (absolute neutrophil count [ANC] $<1.0 \times 10^9$/L with a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than one hour);
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia associated with bleeding;
- Dose interruption for >14 days due to toxicity.

The MTD is the highest dose at which no more than 1 of 6 patients developed DLT. If 2 or more of 6 patients developed DLT at a particular dose level, then that dose has exceeded the MTD.

In general, the safety and tolerability of fruquintinib will be evaluated based on the AE data. Other safety parameters include physical examination, vital signs, laboratory test results (ie, hematology, chemistry panel, thyroid function, and urinalysis), 12-lead electrocardiogram, and echocardiogram.

2.1.3 Secondary Objectives

The secondary objectives of the dose escalation phase include the following:

- To evaluate the PK characteristics of multiple-dose fruquintinib and investigate the metabolite profile of fruquintinib in the plasma of patients with solid tumors.
- To evaluate the anticancer activity of fruquintinib in patients with solid tumors according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.

2.1.4 Secondary Endpoints

- The primary PK parameters include: maximum plasma concentration (C_{max}), time to reach maximum concentration (T_{max}), terminal half-life ($t_{1/2}$), area under the concentration-time curve in a selected time interval (AUC_{0-t}), area under the concentration-time curve in the time interval from 0 to infinity ($AUC_{0\infty-\infty}$), apparent clearance (CL/F), apparent volume of distribution (V_z/F) during the terminal phase according to CL/F/Ke, and the accumulation index based on AUC.

- The objective response rate (ORR), disease control rate (DCR), duration of response (DoR), PFS, overall survival (OS) and percentage change in tumor size from baseline according to RECIST Version 1.1.

2.2 Dose Expansion Phase

2.2.1 Primary Objective

The primary objective in the dose expansion phase is to evaluate the anticancer activity of fruquintinib at the recommended Phase 2 dose (RP2D) from the dose escalation phase, in patients with advanced solid tumors.

2.2.2 Primary Endpoint

The primary endpoint is PFS rate.

2.2.3 Secondary Objectives

- To evaluate anticancer activity of fruquintinib, as assessed by ORR, DCR, DoR, PFS, and OS.
- To evaluate the pharmacokinetic (PK) characteristics of multiple-dose fruquintinib and investigate the metabolite profile of fruquintinib in plasma.
- To evaluate the safety of fruquintinib

2.2.4 Secondary Endpoints

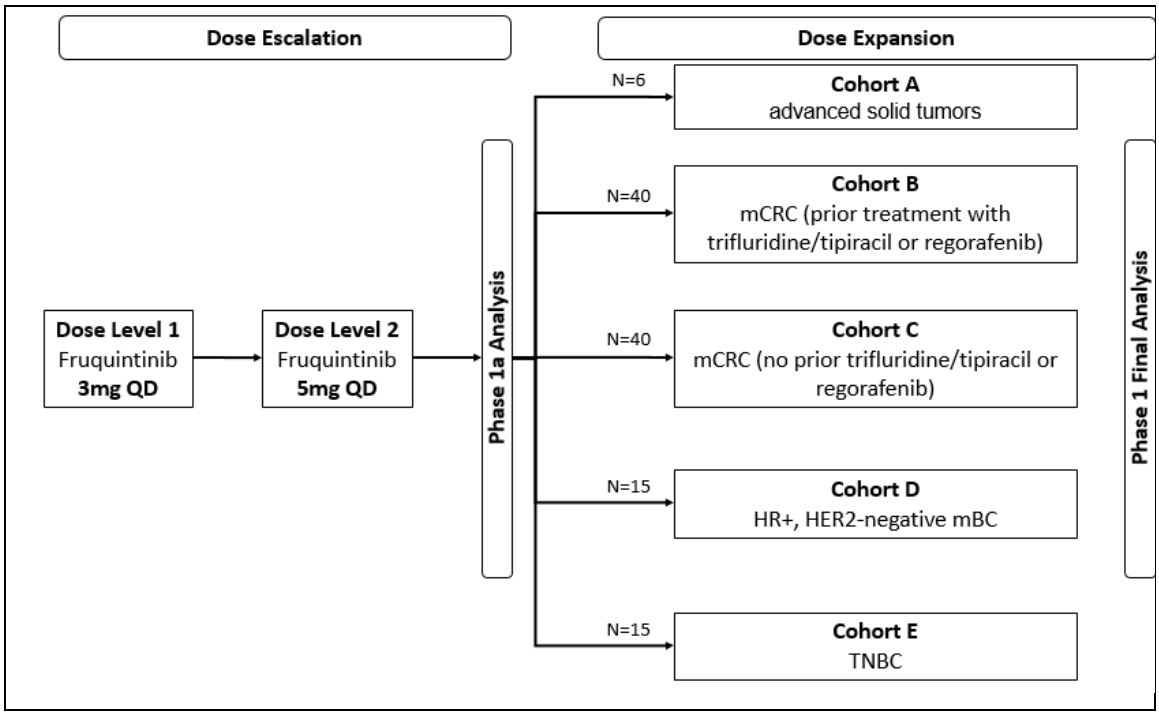
- The objective response rate (ORR), disease control rate (DCR), duration of response (DoR), PFS, overall survival (OS) and percentage change in tumor size from baseline according to RECIST Version 1.1.
- The primary PK parameters include maximum plasma concentration (Cmax), time to reach maximum concentration (Tmax), terminal half-life (t1/2), area under the concentration-time curve in a selected time interval (AUC0-t), area under the concentration-time curve in the time interval from 0 to infinity ($AUC0_{\infty}$-∞), apparent clearance (CL/F), apparent volume of distribution (Vz/F) during the terminal phase according to CL/F/Ke, and the accumulation index based on AUC.
- Safety, as assessed by the incidence and severity of AEs, physical examinations, vital signs, laboratory test results, 12-lead electrocardiogram, and echocardiogram.

3 INVESTIGATIONAL PLAN

3.1 Description of the Study

This is an open-label phase 1/1b study of fruquintinib comprised of a dose escalation phase that will enroll patients with advanced solid tumors of any type, and a dose expansion phase that will enroll patients with advanced solid tumors of any type (Cohort A), refractory mCRC (Cohorts B and C), or mBC (Cohorts D and E) (see study schema in Figure 5.)

Figure 5 Study Schema



3.1.1 Dose Escalation Phase

- Approximately 12 evaluable patients will be enrolled. The actual number of patients will depend on the occurrence of dose-limiting toxicities (DLTs) as well as the MTD level reached in this trial.

- The dose levels to be investigated are 3 mg and 5 mg QD, 3 weeks on/1 week off.

- Six DLT-evaluable patients will be enrolled in the phase and will be treated with fruquintinib 3 mg QD (3 weeks on/1 week off) orally. If no more than 1 DLT occurs during the DLT observational window (ie, from Days 1-28 in Cycle 1) among the 6 patients, the trial will continue to enroll another 6 patients in the next dose cohort in which fruquintinib 5 mg QD (3 weeks on/1 week off) will be tested.

- Safety monitoring and evaluation for the Dose Escalation phase will be carried out by the Safety Review Committee (SRC). Additional information about the SRC is provided in Section 3.4.

- If no more than 1 patient at the dose level of 5 mg QD experiences a DLT, the dose escalation phase is completed and the expansion phase of the study will be conducted.

- Upon completion of the dose escalation/ phase, the SRC will review the aggregated safety and PK data and then select a fruquintinib dose as the RP2D for the expansion phase of the trial.

- Blood samples for PK assay will be collected in Cycle 1 at the following time points: pre-dose (within 10 minutes), 1, 2, 4, 8, and 24 hours post dose on Days 1, 14 and 21.

- Prior to confirmation of a DLT, if a patient has received any prophylactic medical intervention or missed 4 or more fruquintinib doses during the DLT observational window, the patient is not DLT evaluable and will be replaced.

- If a patient does not meet the definition of DLT evaluable patient criterion during the DLT observation period, the patient will be replaced.

- Patients who have completed the DLT observation period (Days 1-28, Cycle 1) and are deemed to be benefiting from the fruquintinib treatment at the investigator's discretion may continue the fruquintinib treatment until disease progression, death, intolerable toxicity, or at investigator's discretion that the patient can no longer benefit from the study drug.

- Please see Appendix A for the Schedule of Events and Section 5.2 for the dose modification instructions.

- Patients will be followed until death or study completion.

a. Dose-Limiting Toxicity Assessment Window

The DLT assessment window will be 28 days in the first cycle (Days 1-28). Any patient who is not considered evaluable for DLT as defined below will be replaced by an additional patient at that same dose level.

NOTE: Dose-limiting toxicity assessment does not apply to the expansion cohorts.

b. Definition of DLT Evaluable Patients:

A DLT evaluable patient has to meet the following criteria:

- Has not received any prior anti-cancer therapy prior to DLT; AND

- Has completed the first 28-day treatment cycle with complete safety evaluations and has received at least 85% of the assigned fruquintinib dose;

  OR

- Has a confirmed DLT during the first 28-day treatment cycle.

c. Definition of a Dose-Limiting Toxicity

- A DLT is defined as one of the toxicities defined for the primary endpoint of the dose escalation phase in Section 2.1.2. These AEs occur during the DLT assessment window (Days 1-28, Cycle 1) and are determined by the investigator to have a reasonable possibility of being related to fruquintinib.
- Any Grade 4 non-hematologic toxicity;
- Any Grade 3 non-hematologic toxicity related to study drug except for nausea/vomiting, diarrhea, constipation, hypertension and electrolyte imbalances downgraded within 3 days with appropriate supportive treatment;
- Grade 4 neutropenia lasting >3 days;
- Grade 3 febrile neutropenia (absolute neutrophil count [ANC] $<1.0 \times 10^9$/L with a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than 1 hour;
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia associated with bleeding;
- Dose interruption for >14 days due to toxicity;

In the absence of clinical abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT.

d. Definition of MTD

The MTD is the highest dose at which no more than 1 of the 6 patients in each cohort of the dose escalation phase develops a DLT. If 2 or more of 6 patients in each cohort of the dose escalation phase develop DLT at a particular dose level, that dose has exceeded the MTD.

3.1.2 Dose Expansion Phase

The objectives of the dose expansion phase are to evaluate the anticancer activity and safety of fruquintinib at the RP2D determined at the end of the dose escalation phase, as described in Section 2.2.

Once the RP2D is determined, patients may enroll into one of the following cohorts and will receive fruquintinib at the RP2D.

- Cohort A: Patients with advanced, refractory solid tumors of any type
- Cohort B: Patients with refractory mCRC who have progressed on all standard chemotherapies and relevant biologics and have also progressed on, or had intolerable toxicity with, at least 1 FDA-approved third-line therapy (TAS-102 or regorafenib).

- Cohort C: Patients with refractory mCRC who have progressed on all standard chemotherapies and relevant biologics and *have not* received prior TAS-102 or regorafenib.
- Cohort D: Patients with hormone-receptor positive (ER+ and/or PR+)/Her2- metastatic breast cancer who have progressed on at least two line of prior systemic therapy.
- Cohort E: Patients with advanced triple negative breast cancer (TNBC) who have progressed on at least one cytotoxic therapy in the metastatic setting.

Detailed patient inclusion and exclusion criteria for each expansion cohort is described in Sections 4.1 and 4.2.

The safety of all enrolled patients will be closely monitored from the first day of fruquintinib dosing until 30 days after the last dose. All SAEs should be reported from the day the informed consent form (ICF) is signed through 30 days after last dose regardless of relationship to study drug. All AEs will be graded in accordance with the NCI CTCAE v4.03.

Tumor response will be assessed according to RECIST Version 1.1 at screening and at study visits according the Schedule of Events (Appendix A). Confirmation of CR and PR is required at no less than 4-week intervals between the date of initial response and the confirmation assessment date.

Patients will be followed until death or study completion (Appendix A).

3.2 Sample Size

Approximately 128 patients will be enrolled in this dose escalation/dose expansion study. Approximately 12 patients will be enrolled in the dose escalation phase, and approximately 116 additional patients (6 with advanced solid tumors of any type, 40 with refractory mCRC who progressed on TAS-102 and/or regorafenib, 40 with mCRC who had not received TAS-102 or regorafenib, 15 with refractory HR+/HER2- mBC, and 15 with advanced, refractory TNBC) will be enrolled in the dose expansion phase.

3.3 Investigational Site

Approximately 12 sites will participate in the study.

3.4 Safety Review Committee

A Safety Review Committee (SRC) will be established under a charter to conduct safety data review and to determine the next step for dose escalation. Safety monitoring and evaluation for dose escalation decisions will be carried out by the SRC upon completion of the of the DLT observation period of the last patient in each cohort. The SRC is chaired by the Sponsor's fruquintinib Clinical Program Leader; members will include the principal investigators (PIs), the Sponsor's PK scientist, medical monitor, and the CRO's medical monitor.

Dose escalation decisions are based on AE and PK data from this ongoing trial, as well as consideration of safety and PK data at comparable drug exposure from patients in

previously conducted clinical trials in China.

Regular safety data review will be conducted at pre-defined intervals and at the end of the DLT observation period (ie, first treatment cycle) of each dose cohort. Safety and PK data from all enrolled patients will include laboratory test results, AEs, electrocardiogram (ECG) results, and PK data.

3.5 Study Early Termination

Hutchison MediPharma has the right to stop the study at any time. The reasons for stopping the study may include, but are not limited to:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

3.6 Patient Discontinuation

All study participants have the right to withdraw from the study at any time. The investigator has the right to discontinue a patient from the study for any medical condition that the investigator determines may jeopardize the patient's safety if he or she continues in the study and for reasons of non-compliance (eg, missed doses, visits) or pregnancy or if the investigator determines it is in the best interest of the patient. Any patient who discontinues treatment should be encouraged to return to the study site for a treatment completion visit. See Appendix A for the assessments that are to be performed for patients who prematurely withdraw from the study during the treatment period. The primary reason for discontinuation must be recorded on the appropriate Case report form (CRF).

Study drug treatment will end if a patient meets any of the following 3 criteria:

1. Disease progression (according to RECIST Version 1.1) unless there is reasonable evidence of clinical benefit to justify continuation on the study treatment. The decision that the patient should continue treatment should be made by the investigator in consultation with the Sponsor. The disease progression date is the date when radiological disease progression is first reported according to RECIST Version 1.1 criteria;
2. Death;
3. End of this study.

Early discontinuation of study treatment will occur if any of the following criteria is met:

1. Patient withdrawal of consent;
2. Intolerable toxicity;
3. Poor patient compliance;
4. Use of other antitumor treatment during the study;
5. Pregnancy occurred during the study treatment period;
6. Patient is lost to follow-up;

7. Treatment discontinuation is in the best interest of the patient based on the assessment of the investigator and the Sponsor.

3.7 End of Study

End of the study is defined as the last visit of the last patient.

4 PATIENT SELECTION

Patients with locally advanced or metastatic solid tumors of any type, and patients with refractory mCRC for whom approved therapy either does not exist or has proven to be ineffective or intolerable are eligible to participate in this study. Patients will undergo a screening period of up to 4 weeks, during which they will be assessed for compliance with the inclusion and exclusion criteria as outlined below.

4.1 Inclusion Criteria

To be eligible to participate in the study, patients must meet **all** of the following Inclusion Criteria:

1. Fully understand the study and voluntarily sign the ICF;

2. ≥18 years of age;

3. Body weight ≥40 kg;

4. **Dose Escalation Phase:**

   Histologically or cytologically documented, locally advanced or metastatic solid malignancy of any type (except squamous NSCLC) that has progressed on approved systemic therapy, and for whom no effective therapy or standard of care exists.

   Dose Expansion Phase:

   Cohort A: Histologically or cytologically documented, locally advanced or metastatic solid malignancy of any type (except squamous NSCLC), that has progressed on approved systemic therapy, and for whom no effective therapy or standard of care exists.

   Cohort B: Histologically or cytologically documented adenocarcinoma of the colon or rectum that has progressed on, or had intolerable toxicity to, at least 1 FDA-approved third-line systemic therapy (TAS-102 or regorafenib). Treatment failure is defined as disease progression during or within 3 months after the last dose of standard therapy, or discontinuation of standard therapy because of unacceptable toxicity. Patients must also have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and, if RAS wild type, an anti-EGFR therapy.

   Eligibility also requires knowledge of tumor RAS status (wild-type or mutant) as reported by investigators.

   Cohort C: Histologically or cytologically documented adenocarcinoma of the colon or rectum. Patients must have progressed on, or had intolerable toxicity to, at least 2 prior regimens of standard chemotherapy, but *must not* have received prior TAS-102 or regorafenib. Treatment failure is defined as disease progression during or within 3 months after the last dose of standard therapy, or discontinuation of standard therapy because of unacceptable toxicity. Prior therapy could have included adjuvant chemotherapy if a tumor had recurred within 6 months after the last administration of

treatment. Patients must have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biological therapy and, if RAS wild-type, an anti-EGFR therapy

Eligibility also requires knowledge of tumor RAS status (wild-type or mutant) as reported by investigators.

Cohorts D and E:

Her2-negative metastatic breast cancer, with Her2-negative defined as immunohistochemistry (IHC) 0, 1+, or 2+. If IHC 2+, a negative in situ hybridization (FISH, CISH, or SISH) test is required by local laboratory testing.

a. **Cohort D only:** Histologically- or cytologically-confirmed hormone-receptor positive (ER+ and/or PR+) breast cancer, by local assessment.
OR
b. **Cohort E only:** Histologically- or cytologically- confirmed triple negative breast cancer with ER-negative, PR-negative tumors as defined by local criteria.

5. Hormone receptor positive mBC patients must have progressed on at least 2 lines of prior systemic therapy, including hormonal therapy or chemotherapy. However, patients may not have received more than 3 prior lines of cytotoxic chemotherapy in the metastatic setting. There is no limit to number of prior lines of hormonal therapy.

6. Triple negative breast cancer patients must have progressed on at least 1 cytotoxic therapy in the metastatic setting, with the exception of subjects who progressed within 12 months of adjuvant therapy. However, patients may not have received more than 5 prior lines of cytotoxic chemotherapy in the metastatic setting.

7. Have measurable disease per RECIST Version 1.1, or bone lesions in the absence of measurable disease (Dose Expansion phase only). Lesions that received radiotherapy are not measurable per RECIST Version 1.1.

8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1;

9. Expected survival of more than 12 weeks;

10. For female patients of childbearing potential and male patients 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 (on the understanding that this is the only one partner during the whole study duration), 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 rules are valid for male patients involved in this clinical trial

if they have a partner of childbirth potential. Male patients must always use a condom.

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (ie, ≥12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of the ovaries and/or uterus).

1.1 Exclusion Criteria

Patients will be excluded from the study if **any** of the following criteria is met:

1. **Cohort C only:** patients who have been previously been treated with TAS-102 or regorafenib

2. Absolute neutrophil count (ANC) $<1.5 \times 10^9$/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;

3. Serum total bilirubin >1.5 × upper limit of normal (ULN);

4. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >1.5 × ULN in patients without hepatic metastases; ALT or AST > 3 × ULN in patients with hepatic metastases;

5. Serum potassium, calcium, or magnesium levels out of the normal laboratory reference range, and clinically significant in the investigator's judgment;

6. 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 as follows: CrCl (mL/min) = [(140 - age) × (weight in kg) ÷ [72 × (serum creatinine in mg/dL)] (0.85 if female).

7. Urine dipstick protein ≥2+ or 24-hour urine protein ≥1.0 g/24-h. Patients with greater than 1+ proteinuria on urinalysis must undergo a 24-hour urine collection;

8. Uncontrolled hypertension, defined as: systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg;

9. International Normalized Ratio (INR) >1.5 or activated partial thromboplastin time (aPTT) > 1.5 × ULN, unless the patient is currently receiving or intending to receive anticoagulants for prophylactic purposes.

10. Risk of, or active hemorrhage: history or presence of active gastric/duodenal ulcer or ulcerative colitis, active hemorrhage of an unresected gastrointestinal tumor, history of perforation of fistulas; or any other condition that could possibly result in gastrointestinal tract hemorrhage or perforation within 6 months prior to screening

11. History or presence of hemorrhage from any other site (eg, hemoptysis or hematemesis)

within 2 months prior to screening;

12. History of a thromboembolic event (including deep vein thrombosis [DVT], pulmonary embolism, stroke and/or transient ischemic attack) within 6 months prior to screening;

13. Patients with squamous NSCLC;

14. 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%;

15. Mean corrected QT interval (QTc) 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.

16. Concomitant medications with a known risk of causing QT prolongation and/or torsade de pointes (see list in Appendix E; source list is continuously updated online at www.qtdrugs.org);

17. Patients who have ever received a VEGFR inhibitor, **except** for patients with mCRC enrolled in the dose expansion phase;

18. Systemic anti-neoplastic therapies (except for those described in Exclusion 18) or any investigational therapy within 4 weeks prior to the first dose of study drug, including chemotherapy, radical radiotherapy, hormonotherapy, biotherapy and immunotherapy;

19. 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;

20. Palliative radiotherapy for bone metastasis/lesion within 2 weeks prior to the initiation of study drug;

21. Brachytherapy (ie, implantation of radioactive seeds) within 60 days prior to the first dose of study drug;

22. Use of strong inducers or inhibitors of CYP3A4 within 2 weeks before the first dose of study drug (3 weeks for St John's Wort); P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) substrate within 2 weeks before the first dose of study drug (see Appendix F for a list of such medications);

23. Surgery or invasive procedure (ie, procedure that includes a biopsy) within 60 days prior to the first dose of study drug or unhealed surgical incision;

24. Any unresolved toxicities from a previous antitumor treatment greater than

CTCAE v 4.03 Grade 1 (except for alopecia);

25. Known human immunodeficiency virus (HIV) infection;

26. Known clinically significant history of liver disease, including cirrhosis, current alcohol abuse, or active viral hepatitis. For patients with evidence of chronic hepatitis B (HBV), the HBV viral load must be undetectable on suppressive therapy, if indicated. Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

27. Evidence of ongoing or active infection requiring intravenous antibiotics;

28. Tumor invasion of a large vascular structure (eg, pulmonary artery, superior or inferior vena cava).

29. Women who are pregnant or lactating;

30. 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; patients requiring steroids within 4 weeks prior to start of study treatment will be excluded;

31. No other malignancy, except for non-melanoma skin cancer, during the 5 years prior to screening;

32. 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;

33. Other disease, metabolic disorder, physical examination anomaly, abnormal laboratory result, or any other condition that investigators suspect may prohibit use of the investigational product, affect interpretation of study results, or put the patient at undue risk of harm based on the investigator's assessment;

34. Known hypersensitivity to fruquintinib or any of its excipients.

5 STUDY TREATMENT

5.1 Investigational Product

5.1.1 Investigational Product Supply

Fruquintinib will be supplied by Hutchison MediPharma Limited.

5.1.2 Drug Formulation and Specification

Hutchison MediPharma Limited authorizes WuXi AppTec (Shanghai) Co. Ltd to manufacture and package fruquintinib capsules. The technical guidance and quality assurance will be conducted by Hutchison MediPharma Limited.

Table 6 Drug Formulation and Strength

Formulation	Strength	Route of Administration
Capsule	1 mg	Oral
Capsule	5 mg	Oral

5.1.3 Packaging and Drug Labeling

The investigational drug is packaged in white high-density polyethylene bottle with 30 capsules of 1 mg per bottle and 25 capsules of 5 mg per bottle.

The following information will appear on the label affixed to either the bottle or carton; additional information will be added as required:

- Sponsor identification
- Protocol number
- Drug identification
- Quantity of contents
- Storage conditions
- Dosing instructions
- Route of administration
- Blank spaces to write the patient's identification number
- Lot number

5.1.4 Drug Storage

All study drugs should be kept in a secure place under appropriate storage conditions (10ºC to 30ºC). The investigational product label on the pack specifies the appropriate storage. Fruquintinib capsule should not be used beyond expiration date provided by the manufacturer. The intended shelf life of fruquintinib capsules is 2 years.

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

5.1.5 Drug Accountability

All study drug required for this study will be provided by Hutchison MediPharma. 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 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.

5.1.6 Dose and Administration

After the SRC review of Cohort 2, the RP2D was declared as 5 mg QD, 3 weeks on/1 weeks off each 28-day cycle. Patients from Cohort 1 who remain in the study may have their fruquintinib dose escalated to 5 mg QD at the discretion of the investigator and with the agreement of the Sponsor.

If baseline (pre-dose) PK blood samples need to be collected on the days of PK sample collection, patients must take the investigational product after sampling at site.

It is recommended that fruquintinib be taken with water (approximately 200 mL or 1 cup), 1 hour before breakfast. The administration time should be accurately recorded on the days of PK sampling.

On the days of PK sampling, patients should avoid high-fat meals for the entire day and avoid consumption of any liquids other than water (up to 200 mL) within 1 hour before or after drug administration. The patient is encouraged to avoid, or minimize the use of caffeine-containing foods or drinks, tobacco, tobacco products, and alcohol during the entire study. If the patient cannot avoid taking any of the above listed substances during the study, it should be regarded as a habit and documented as demographic data.

The following substances are **prohibited** during the study: grapefruit or grapefruit juice, illegal drug use, or excessive (> 1 drink/day) alcohol use.

If patients miss a dose in the morning, a replacement dose can be taken before 6 pm on the same day. Otherwise, the patient should not make up the missed dose, but should resume scheduled doses the next day per protocol. The missed dose should be reported to the investigators and recorded in the CRF.

5.2 Dose Modification

5.2.1 General Dose Adjustment Note

The severity of AEs will be graded according to the NCI CTCAE v4.03. Reasons for dose modifications or delays, the supportive measures taken, and the outcome will be documented in the patient's chart and recorded in the CRF.

- Any toxicity that meets the definition of DLT during the DLT observation period will be considered as DLT for purposes of dose escalation and MTD determination.

- 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 patient 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 will be continued at the same dose. In addition, no dose reductions or interruptions will be required for anemia (non-hemolytic) because it can be satisfactorily managed, unless serious (Grade ≥3) hemorrhage is present.

- To recover from acute toxicity, unless otherwise indicated, the treatment can be interrupted for up to 14 days. If a treatment delay longer than 14 days is required, the patient should be discontinued from the study drug. 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.

5.2.2 Dose Modification Guidance

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

Dose reduction guidelines by starting dose and for haematologic and non-haematologic toxicities other than PPE, proteinuria, hypertension, decreased platelet count, hemorrhage, and liver function impairment are shown in Table 7 and Table 8. In principle, treatment should be held until AE/toxicity resolves or improves to ≤Grade 1. If a Grade 3 toxicity is expected to be manageable and reversible with a dose reduction, treatment should be held until toxicity resolves to ≤Grade 1. Patients with Grade 3 non-haematologic toxicity that does not resolve to ≤Grade 1 within 2 weeks should permanently discontinue the study drug.

Patients starting at 5 mg QD are allowed to have two 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. Patients starting at 3 mg QD are allowed to have 1 dose reduction (ie, from 3 mg QD to 2 mg QD). The lowest dose level permitted in the study is 2 mg (see Table 7).

Table 7 Dose Modification Sequence by Starting Dose

Starting Dose*	3 mg	5 mg
-1 Dose	2 mg	4 mg
-2 Dose	Off study drug	3 mg
	Only 1 dose reduction is allowed for patients starting at 3 mg QD dose.	A maximum of 2 dose reductions is allowed for patients starting at the 5 mg dose.

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

Table 8 Dose Modification for Hematologic and Non-Hematologic Toxicity

NCI CTCAE v4.03 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.

5.2.2.2 Dose Modification and Treatment Suggestions for Selected Identified Risks

The dose modification and treatment suggestions for specific identified risks are provided in Table 9 (PPE), Table 10 (proteinuria), Table 11 (hypertension), Table 12 (decreased platelet count), Table 13 (hemorrhage at any site), and Table 14 (abnormal liver function).

Table 9 Dose Modification for PPE

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	The drug could be interrupted; and no dose reduction 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.	The drug can be interrupted; the drug should be reduced to a lower 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 10 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)	The drug can be interrupted and then reduced to lower 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	The drug can be interrupted and then reduced to lower dose level if 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 11 Dose Modification for Hypertension

AE Grading and Definitions	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 mmHg (or <130/80 mmHg in patients with chronic renal disease and/or diabetes). Refer to Appendix I.
Grade 3: SBP ≥ 160 mmHg or DBP ≥100mmHg; or more than one drug or more intensive therapy are used	Interrupted once Grade3 hypertension lasting more than 7 days after using or adjusting antihypertensive drug; Should the BP of the patient recover to Grade 1 or the baseline level, one time of dose reduction shall be made.	Treatment objective: lower the blood pressure to <140/90 mmHg (or <130/80 mmHg in patients with chronic renal disease and/or diabetes). Refer to Appendix I.
Grade 4: Life threatening (eg, malignant hypertension, temporary or permanent neurological deficits and hypertensive crisis)	The drug should be terminated.	Emergent medical treatment.

Table 12 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	Be interrupted and continue the drug treatment with the same dose should 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.
	Be interrupted and then reduced to the lower dose level should 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	Be interrupted and reduced to the lower dose level should the AE recovered 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	The study drug should be terminated permanently.	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 13 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]	The study drug should be terminated permanently.	Emergent medical intervention[b]

a Refer to Appendix J for clinical management of severe or serious hemorrhage.

b 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 (See Section 5.3.1 Concomitant therapies).

Table 14 Dose Adjustment for Abnormal Liver Function

AE Grading[a]	Dose Adjustment	Treatment Suggestions
Grade 1	None.	Perform follow-up visit as scheduled.
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 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 Section 7.1.2 for special reporting requirements and Appendix H for additional information regarding Hy's Law.

5.3 Concomitant and Excluded Therapies

5.3.1 Concomitant Therapies

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient between the 7 days preceding the screening evaluation and the termination visit. All concomitant medications should be reported to the investigator and recorded on the appropriate CRF.

Patients who use hormonal therapy with GnRH agonists for prostate cancer, oral contraceptives, hormone-replacement therapy, or other allowed maintenance therapy should continue their use.

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

- Patients who are receiving warfarin or Coumadin-like products should have their INR monitored and maintained at the lower third of the therapeutic range (ie, 2.0-2.3), unless a higher INR is required for anti-thrombotic efficacy.

- Patients who require low-molecular-weight heparin should receive the prophylactic dose and monitoring as specified by the appropriate product information label.

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

Patients that develop arterial thromboembolic events should discontinue the study drug. If a patient 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.

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

5.3.2 Excluded Therapies

Any therapy intended for the treatment of cancer (with the exceptions as noted above), 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.

Prophylactic antiemetic, granulocyte colony stimulating factors, granulocyte macrophage colony-stimulating factors, platelet simulating factors or erythropoietin are not allowed during the DLT observation period in the dose escalation phase.

Concomitant use of acid-reducing agents (eg, proton pump inhibitors, histamine receptor antagonists, antacids) during the dose escalation phase should be avoided as those agents may interfere with identifying reliable MTD and/or RP2D.

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

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.

5.3.3 Drug-Drug Interactions

The potential of pharmacokinetic drug-drug interaction was tested *in vitro*. Fruquintinib was not a substrate of efflux transporters. Fruquintinib showed dose-dependent inhibition on P-gp and BCRP. Based on the data for digoxin transport (mediated by P-gp) and estrone-3-sulfate transport (mediated by BCRP), the IC_{50} on P-gp and BCRP was estimated to be 4.60 and 1.29 μM, respectively.

According to the present metabolism data, enzymes CYP3A4/5 play an important role in the metabolism of fruquintinib. Fruquintinib had no marked inhibitory effects on CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5 (IC_{50} >10 μM) and no induction of CYP1A2, [redacted] and CYP3A4 at the tested concentration of 10 μM. No marked time-dependent inhibition was observed for CYPS 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5.

Substrates of P-gp and BCRP, and inducers and inhibitors of CYP3A4/5 should not be administered concomitantly with fruquintinib, unless investigators consider it necessary. In this case, efficacy reduction and toxicity increases resulting from the interaction should be closely monitored. Examples of the medicines to avoid are listed in Appendix F.

6 STUDY VISITS, ASSESSMENTS, AND METHODS

6.1 Screening and Pre-treatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or procedures. Medical history and demographic information, including clinically significant diseases within the previous 5 years, oncology history (including cancer name, primary diagnosis date, stage of diagnosis, prior anti-cancer therapies, and procedures) should be recorded in CRF. Informed consent forms for patients who are not subsequently enrolled will be maintained at the study site. All screening evaluations must be completed and reviewed by the investigator and the clinical monitor to confirm that patients meet all eligibility criteria before the first administration of fruquintinib.

Please see the Study Flowchart provided in Appendix A for the schedule of screening and pre-treatment assessments. Screening and pre-treatment tests will be performed within 28 days of the first dose of study drug, unless otherwise specified. Results of standard of care tests performed prior to obtaining informed consent and within 28 days prior to study entry may be used (except hematology, coagulation tests, clinical chemistry, or urinalysis results).

6.2 Assessments During Treatment Phase

All visits must occur within ± 3 days (± 1 day during cycle 1) from the scheduled date, unless otherwise noted (see Appendix A). All assessments will be performed on the day of the specified visit unless a time window is specified. Please see the Study Flowchart provided in Appendix A for the schedule of treatment period assessments.

If scheduled study assessments cannot be obtained because of a holiday, assessments during Cycle 1 should be done either prior to or immediately after the schedule interruption, regardless of the proximity to the next scheduled visits. If assessments cannot be obtained due to a holiday for any other cycle, these assessments should be obtained at the soonest following date, unless the soonest following date is within 7 days of other, regularly scheduled study assessments.

If during the DLT assessment window, 2 or more patients in a single cohort experience the same study drug-related Grade 3 toxicity that does not otherwise qualify as a DLT, the patients subsequently enrolled to this dose level and to the subsequent dose level will undergo increased monitoring during Cycle 1, as clinically indicated. Note: DLTs will not be collected during the Dose Expansion Phase.

6.3 Safety Assessments

6.3.1 Vital Signs Assessment

Vital signs will include measurements of body temperature, heart rate, respiratory rate, and systolic and diastolic blood pressure while the patient is in a seated position. The patient should be seated for approximately 5 minutes before the measurement of the blood pressure. For patients with a baseline history of hypertension, or those who develop hypertension during the study, blood pressure should be monitored daily by the patient at home, at

3 hours (±2 hours) after the daily doses of anti-hypertensive medication, and the results recorded in a blood pressure diary. Patients monitoring their blood pressure should bring their diary to each study visit.

6.3.2 Physical Examination

A complete physical examination at screening should include the evaluation of head, eye, ear, nose, and throat; and cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems.

At subsequent visits, a limited physical examination will be performed to assess changes from baseline abnormalities, any new abnormalities, and to evaluate patient-reported symptoms. New or worsened abnormalities should be recorded as AEs if appropriate. In order to assess changes from baseline and screen for new abnormalities, the limited physical examination should assess for new or changed skin lesions, enlarged lymph nodes, and palpable masses. Patient-reported symptoms should be directed to address the symptoms.

Body height will be measured only at screening.

6.3.3 Laboratory Tests

Samples for hematology, serum chemistry, urinalysis pregnancy, thyroid function, and specific tumor marker testing will be analyzed at the study site's local laboratory. Laboratory assessments will include the following:

Hematology (complete blood count [CBC], including red blood cell [RBC] count, hemoglobin, hematocrit, reticulocyte count, white blood cell [WBC] count with differential [neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells], and platelet count; INR and aPTT);

Serum chemistry (blood urea nitrogen [BUN], creatinine and creatinine clearance, sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorus, glucose, triglycerides, total bilirubin, total cholesterol, ALT, AST, alkaline phosphatase (ALP), lactate dehydrogenase [LDH], uric acid, total protein and albumin);

Serum pregnancy test at screening and at the Treatment Completion Visit for all women of childbearing potential, including those who have had a tubal ligation;

Urine pregnancy test at each day 1 visit, starting at Cycle 2 Day 1, for all women of childbearing potential, including those who have had tubal ligation;

Urinalysis (pH, glucose, protein, and blood);

Thyroid function (thyroid stimulating hormone [TSH], free T3, and free T4); and

Specific tumor markers (tumor markers to be collected will be addressed in Section 6.4)

The normal value range of laboratory examination indicators at the study site's local laboratory will be collected prior to the study.

6.3.4 Cardiac Monitoring

Left ventricular ejection fraction (LVEF) assessed via echocardiogram and 12-lead ECGs

are required to be performed as scheduled; ECG shall be performed pre-dose and at 3 hours (± 15 minutes) post fruquintinib dose on Days 1 and 15 in Cycle 1. ECG will be conducted on Day 1 of each cycle from Cycle 2 and onward. QTcF interval should be calculated and be closely monitored. See Appendix A. MUGAs are permitted if echocardiograms cannot be performed.

Test results will be reviewed by the investigator to determine patient eligibility at screening. Additional tests and other cardiac monitoring should be performed as clinically indicated during the study.

6.4 Efficacy Assessments

Tumor Assessment

All measurable and evaluable lesions should be assessed and documented at screening and re-assessed at each subsequent tumor evaluation (see Appendix A). Assessments should include computed tomography (CT) scans with oral or IV contrast (unless contraindicated) of the chest, abdomen, and pelvis. MRI scans are allowed if CT contrast is contraindicated. Other methods of assessment should be utilized as clinically indicated.

Tumor assessments for dose escalation cohorts, Dose Expansion Cohort C, Dose Expansion Cohort D, and Dose Expansion Cohort E are scheduled at Screening and every 8 weeks (±1 week) thereafter, ie, C3D1, C5D1, C7D1, etc. (odd-numbered cycles).

Tumor assessments for Dose Expansion Cohort A and Dose Expansion Cohort B are scheduled at Screening, C2D1, C3D1, C4D1, and every 8 weeks (±1 week) thereafter, ie, C6D1, C8D1, C10D1, etc. (even-numbered cycles).

Subjects who permanently discontinue study drug for reasons other than progression of disease should continue to be followed for efficacy according to the schedule in Appendix A.

All subjects are to have tumor assessments performed at the Treatment Completion visit, unless the subject was discontinued from treatment because of disease progression or the subject had tumor assessments performed within 14 days of the last dose of study drug.

At the investigator's discretion, CT scans may be repeated at any time if progressive disease is suspected.

Disease status will be assessed using RECIST Version 1.1 (see Appendix C). The same imaging procedure used to define measurable lesions at baseline must be used throughout the study for each patient.

At the investigator's discretion, other methods of assessment of measurable disease as per RECIST may be used. Examples of other assessment methods include tumor markers, such as prostate-specific antigen (PSA) and cancer antigen 125 (CA-125) levels for patients with prostate and ovarian cancer, respectively. However, tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete response.

6.5 Study Completion/Early Termination Visit

Patients who complete the study or discontinue study drug will be asked to return to the

clinic at 30 (± 7) days after the decision to permanently discontinue treatment with fruquintinib. Ongoing AEs will be followed until the event has resolved to baseline grade, the event is assessed as stable by the investigator, new anti-tumor treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or when it has been determined that the study treatment or participation is not the cause of the AE.

Please see the Study Flowchart provided in Appendix A for assessments to be performed at the study completion or early termination visit.

7 SAFETY PLAN

Patients will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of AEs, physical examinations, and laboratory measurements.

Except as noted in the current edition of the Investigator's Brochure, no other special warnings or precautions are appropriate.

7.1 Adverse Events

7.1.1 Adverse Events

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 v4.03.

7.1.2 Reporting of Dose Limiting Toxicity

Investigators are required to report DLT events to the Sponsor within **48** hours of first awareness, during the dose escalation stage. The communication must include an email that describes the event and indicates which DLT criterion was met (see Section 3.1.1 c, Definition of a Dose-Limiting Toxicity). The Sponsor's medical monitor must confirm that the event meets the DLT definition and communicate this back to the investigator by email. A notification of each DLT event will be distributed by email to all investigators shortly after confirmation. DLT events are again reviewed together with other safety data and PK data, at the SRC meeting upon completion of the DLT window of each dose cohort.

NOTE: Reporting of DLTs is not required during the dose expansion phase.

7.1.3 Serious Adverse Events and other AEs that require Expedited Reporting

7.1.3.1 Serious Adverse Event Definition

A serious adverse event (SAE) is any AE that has any of the following characteristics:

- Fatal (ie, the AE actually causes or leads to death, except for deaths caused by the progress of disease)
- Life threatening (ie, the AE, in the view of the investigator, places the patient at immediate risk of death)
- Requires or prolongs inpatient hospitalization (excluding emergency or outpatient treatment)
- Results in persistent or significant disability/incapacity (ie, the AE results in substantial disruption of the patient's ability to conduct normal life functions)

- A congenital anomaly/birth defect in a neonate/infant born to a female patient or female partner of a male patient exposed to the investigational product(s)

- Considered as a significant medical event by the investigator (eg, may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

- If an AE meets any of the above serious criteria, the AE should be reported to the sponsor as an SAE no more than 24 hours after awareness of the SAE.

7.1.3.2 Potential Drug-Induced Liver Injury

The investigator is required to discontinue study drug immediately and report all potential events of drug-induced liver injury (DILI), as defined below, regardless of whether it is a non-serious or serious AE to the sponsor no more than 24 hours after learning of the event.

- Serum AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN.

This combination of lab abnormalities meets the biochemical criteria for Hy's law, which is associated with a markedly increased possibility of severe DILI, and may progress to liver transplantation or death. Some patients may present with symptoms such as: fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%). If Hy's law is met, fruquintinib should be immediately discontinued, and patients need to be very closely monitored (bilirubin, ALP, AST, 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.

The findings described above must be reported to the sponsor no more than 24 hours after awareness of the event.

7.1.3.3 Severe Hemorrhagic Events

When a hemorrhagic event meets NCI CTCAE ≥ Grade 3 severity (regardless of whether it is serious or non-serious), the event should be reported to the sponsor no more than 24 hours after first awareness of the event.

The management of severe or serious hemorrhagic events will be conducted according to Appendix J.

7.1.4 Adverse Events Reporting Period

After informed consent, but prior to initiation of study drug, all SAEs regardless of attribution will be collected.

After initiation of study drug, all AEs and SAEs, regardless of attribution will be collected until 30 days following 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.

7.1.5 Eliciting Adverse Events

A consistent methodology of non-directive questioning for eliciting AEs at all patient 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?"

7.1.6 Assessment of Severity

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

For each AE and SAE recorded on the applicable CRF, the investigator will make an assessment of severity through clinical description by referring to the five-grade determination standard in the NCI CTCAE v4.03. Please use the guideline below for the assessment of severity when the observed or reported AE is not listed in the NCI CTCAE v4.03:

- 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.

Activities of Daily Living

*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.

7.1.7 Causality of Adverse Events

The investigator will assess causal relationship between study drug and each AE.

For SAEs, a causal relationship will also be assessed for concomitant medications, study procedures and additional study drug, etc. A guideline to the interpretation of causality is provided in Appendix G.

7.1.8 Recording 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 in the CRF on the AE page.

All AEs (including SAEs) would be recorded on the AE CRF, and the check box for "Serious" would be ticked for entries that fit the criteria for SAEs. The investigator would 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 CRF.

7.1.8.1 Diagnosis vs Symptoms and Signs

If known, a diagnosis should be recorded on the CRF rather than individual signs and symptoms (eg, record only liver failure or hepatitis rather than 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 CRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

7.1.8.2 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 CRF 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 CRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the CRF.

7.1.8.3 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution between patient evaluation time points. Such events should only be recorded once in the CRF. 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, resolves between patient evaluation time points, and subsequently recurs. All recurrent AEs should be recorded on the CRF respectively.

7.1.8.4 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

It is the investigator's responsibility to review all laboratory findings and abnormal vital signs. Medical and scientific judgment should be exercised in deciding if an isolated laboratory abnormality should be classified as an adverse event.

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 CRF.

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 CRF. 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 CRF, unless their severity, seriousness, or etiology changes.

7.1.8.5 Death

Deaths that occur during the protocol-specified AE reporting period that are attributed by the investigator solely to progression of disease should not be reported as AE/SAE. All other on-study deaths, regardless of relationship to study drug, must be recorded on the AE CRF and immediately reported to the sponsor. When a death is recorded, the underlying condition that caused or primarily contributed to the fatal outcome should be reported expeditiously as an SAE and death listed as the outcome of the event on the CRF. If the primary cause of death is unknown and cannot be ascertained at the time of reporting,

please record "Unknown cause of death" on the AE CRF, and "unexplained/unknown death" should be expeditiously reported as a SAE before further investigations into the specific cause of death. If the death is attributed to progression of disease, it should not be recorded or reported as an AE/SAE but the investigator will record the death on the End of Treatment and End of Study CRFs as appropriate.

7.1.8.6 Preexisting Medical Condition

A preexisting medical condition is one that is present at screening. Such conditions should be recorded on the CRF 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 CRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (eg, "more frequent headaches").

7.1.8.7 Hospitalization, Prolonged Hospitalization, or Surgery

The investigator must document any AE that results in hospitalization or prolonged hospitalization unless the patient is hospitalized for 1 or more of the following reasons:

- To undergo an efficacy measurement for the study
- To undergo a diagnostic or elective surgical procedure for a preexisting medical condition that has not changed
- To receive scheduled therapy for the target disease of the study

In addition, hospitalization due solely to the progression of underlying advanced solid tumors should not be reported as a SAE.

7.1.8.8 Pregnancy

A female patient 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 to the sponsor (the reporting period for pregnancy continues up to 30 days after completion of the study drug). The investigator should counsel the patient and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Pregnancies occurring up to 30 days after the completion of the study drug must also be reported to the investigator.

Male patients 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.

Spontaneous abortion should always be classified as serious (as the sponsor considers these medically significant), recorded on the CRF, and expeditiously reported to sponsor.

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

7.1.8.9 Worsening of Solid Tumor

Worsening and/or progression of the patient'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.

7.2 Expedited Reporting Requirements

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:

- Serious adverse events (from informed consent to 30 days following the last dose of study drug or a new treatment of anti-tumor therapy)
- Potential DILI events, regardless of seriousness
- Severe hemorrhagic events (NCI CTCAE Grade ≥3), regardless of seriousness
- Pregnancies
- SAEs occurring beyond the above-mentioned time limit (30 days after the discontinuation of the study drug), if considered related to the study investigational drug, should also be reported to the sponsor.

7.3 Duration of Follow-Up for Adverse Events

The investigator will follow all unresolved AEs and SAEs until the events are resolved or stabilized, the patient is lost to follow-up, or it has been determined that the study treatment or participation is not the cause of the AE/SAE. Resolution of AEs and SAEs (with dates) should be documented on the appropriate CRF and in the patient'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 CRF.

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

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

8 STATISTICAL ANALYSIS

All statistical analysis will be performed under the direction of Hutchison MediPharma personnel.

The final analysis of study data will be based on all patient data up to the time when either all patients have discontinued the study or the study has been terminated. Details of the statistical analysis and data reporting will be provided in the Statistical Analysis Plan (SAP) document finalized prior to database lock.

Data will be summarized using descriptive statistics (continuous data) and/or contingency tables (categorical data) for demographic and baseline characteristics, efficacy measurements, safety measurements, and PK measurements. Information regarding compliance with disease assessments and availability of data will be documented. Graphical techniques (eg, waterfall plots, Kaplan-Meier curves) will be used when such methods are appropriate and informative. The baseline value used in each analysis will be the last (most recent) pre-treatment value. Analyses will be based upon the observed data unless methods for handling missing data are specified. Analyses will be performed using SAS® (Version 9.1 or higher).

8.1 Analysis Populations

The following analysis populations are defined for the study:

- Safety Analysis Set (SAS): This population includes all patients who have received at least one dose of fruquintinib. Safety data will be evaluated based on this population's outcome. Patients in the SAS will be analyzed by their actual dose initially received. If patients have dose reduction during the study, all data will be summarized/analyzed based on the initial dose of study drug received.

- Pharmacokinetic Analysis Set (PKAS): This population will include all patients who received at least one dose of fruquintinib and have at least 1 PK sample obtained and analyzed.

- Efficacy Analysis Set (EAS): This population includes all patients who have received at least 1 dose of fruquintinib and have at least 1 post-baseline tumor assessment. All efficacy endpoints will be analyzed based on this analysis set.

8.2 Analysis of the Conduct of the Study

A patient listing of all treated patients will be generated to describe site, patient number, screening date, first dosing date, duration of study treatment, analysis set in which the patient is included and disposition. In the patient disposition listing, reason for study drug discontinuation will be included. A table will be created to summarize these categories in terms of number and percent for each of the analysis set defined above.

Patient demographics and baseline characteristics, such as age, sex, race/ethnicity, weight, type of malignancy, duration of malignancy, site of metastatic disease, and baseline ECOG performance status, will be listed and summarized. All summaries will be presented overall, by dose level, and by tumor specific cohorts.

Major protocol deviations related to study inclusion or exclusion criteria, conduct of the trial, patient management, or patient assessment will be listed.

Study drug administration data will be listed by dose level, and any dose modifications will be flagged. Descriptive information will be provided regarding number of cycles, total duration of study drug exposure, actual duration of study drug taken, cumulative dose of study drug, dose intensity and relative dose intensity and the number and timing of prescribed dose reductions and interruptions.

8.3 Safety Analysis

Safety will be assessed through AEs, laboratory assessments, vital signs, and ECG results. Safety data will be listed and summarized by dose cohort across the 2 phases. All DLT events will be listed by dose cohort for the dose escalation phase only.

Severity of AEs will be graded by the investigator according to NCI CTCAE v4.03. If a CTCAE criterion does not exist, the grade corresponding to the appropriate adjective will be used by the investigator to describe the maximum intensity of the adverse event: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life threatening), or Grade 5 (fatal) (see Section 7.1.6). All AEs will be coded with Medical Dictionary for Drug Regulatory Activities (MedDRA).

All AEs will be listed. The focus of safety data summarization will be on treatment-emergent adverse events (TEAEs), which are defined as AEs that occur or worsen in the period extending from the first dose of study drug to 30 days after the last dose of study drug in this study.

TEAEs will be summarized as the number of patients and corresponding percentage by MedDRA System Organ Class (SOC) as well as Preferred Term (PT). The incidence of TEAEs, SAEs, adverse events of special interest (AESIs), AEs leading to dose interruption, reduction, or treatment discontinuation will be presented by SOC and PT; by relationship to the investigational product and by toxicity grade for each dose level. Changes in laboratory data will be summarized by severity grade using the NCI CTCAE v4.03. When abnormal laboratory results at the patient level are counted, the worst value during study treatment will be chosen.

8.4 Pharmacokinetic Analysis

Data of plasma concentration versus time are analyzed for PK parameters using the non-compartmental model by WinNonlin enterprise version software. The mean value, standard deviation, coefficient of variation (CV%), median value, minimum value, maximum value, geometric mean value and geometric mean CV% will be reported.

Individual and mean plasma fruquintinib concentration versus time data will be tabulated and presented. The individual and mean PK parameters based on the fruquintinib concentration versus time data, will include, but not be limited to total plasma exposure ($AUC_{0\text{-}t}$ and $AUC_{0\infty\infty\text{-}\infty}$), maximum plasma concentration (C_{max}), apparent clearance (CL/F), and apparent volume of distribution (V_z/F). The terminal half-life ($t_{1/2}$) will also be estimated. The actual times of plasma sample collection will be used for the PK analysis.

The methods for calculating pharmacokinetic parameters of fruquintinib:

- C_{max}: the maximum observed plasma concentration over the sampling period, taken directly from the data.
- T_{max}: time to reach C_{max}, taken directly from the data.
- The first-order rate constant associated with the negative slope of the terminal portion of the log-linear concentration-time curve. A minimum of three points will be used.
- Area under the plasma concentration versus time curve (AUC) to be determined by the trapezoidal rule (linear up/log down), where AUC_{0-t} is the AUC from time zero until the last concentration point and $AUC_{0\infty\infty-\infty}$ is the AUC_{0-t} + last concentration point divided by elimination rate constant (K_e).
- Half-life ($t_{1/2}$) to be determined according to $t_{1/2} = 0.693/K_e$ where possible.
- CL/F: apparent systemic clearance to be determined according to dose/$AUC_{0\infty\infty-\infty}$
- V_z/F: apparent volume of distribution, determined according to CL/F/K_e
- Accumulation ratio: AUC_{Day14}/AUC_{Day1} or AUC_{Day21}/AUC_{Day1}

Where the concentration data are missing or listed as less than the lower limit of quantification, they will be regarded as zero (0) if occurring before C_{max}. After C_{max}, zero points will not be included in calculations.

Individual and mean fruquintinib concentrations will be plotted by dose level.

Pharmacokinetic analysis of fruquintinib and its metabolites will be performed using the same technology.

Venous blood samples for determination of concentrations of fruquintinib in plasma will be taken at the times presented in Appendix D. If dose interruption occurs more than 5 days (including 5 days) of PK sampling, the blood taking should be cancelled or at investigator's discretion. The date and time of collection of each sample and the date and time of dose will be recorded.

8.5 Efficacy Analysis

The efficacy endpoints include PFS, ORR, DCR, and OS. Efficacy data will be listed and summarized by dose cohort and disease type.

The ORR and DCR will be summarized with percentages and 95% exact confidence intervals. The PFS rate at week 12 (Cohorts B and C) and week16 (Cohorts D and E) and its 95% confidence intervals will be estimated by the Kaplan-Meier method. PFS, DoR, and OS will be summarized descriptively using Kaplan-Meier medians and quartiles. Percentage change in tumor size from baseline will be determined for patients with measurable disease at baseline and derived at each visit by the percentage change in the

sum of the diameters of target lesions (TLs) compared to baseline. Best percentage change in tumor size will be summarized using descriptive statistics and presented using a waterfall plot.

Objective Response Rate (ORR)

The ORR is defined as the percentage of patients with at least one best overall response (BOR) of CR or PR according to RECIST Version 1.1. To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met.

The BOR in an individual patient according to the RECIST criteria is the best response recorded from the start of treatment until documented RECIST progression or the date of any further anticancer therapy, whichever comes first. In the case of a patients without documented progression or additional anticancer therapy, BOR is determined using all available visit up until the last evaluable visit response.

Disease Control Rate (DCR)

Disease control rate is defined as the percentage of patients with a best overall response of CR, PR, or SD.

Progression Free Survival (PFS)

Progression free survival is defined as the time from date of first dose of study drug until the date of an objective disease progression as defined by RECIST v1.1 or death due to any cause.

Patients who have not objectively progressed or died by the date of the analysis cut-off or received any further antitumor therapy will be censored at the time of the last evaluable objective tumor assessment before the cut-off date or the antitumor therapy start date.

Progression-free survival rate is defined as the percentage of patients without evidence of progression or death at specific time points, such as week 12 (cohorts B and C), week 16 (cohort D and E) on study.

Duration of Response (DoR)

Duration of response is defined as the time from date of the first objective response, CR or PR, whichever comes first, until the occurrence of documented disease progression or death in the absence of disease progression. If a patient does not progress following a response, then the DoR will be censored at the same time of PFS.

Percentage Change in Tumor Size from Baseline

Percentage change in tumor size will be determined for patients with measurable disease at baseline and is derived at each visit by the percentage change in the sum of the diameters of target lesions compared to baseline.

Overall Survival (OS)

Overall survival is defined as the time from the date of the first dose of study drug until the date of death (any cause). Patients who did not die at the time of the statistical analysis will be censored at the time at which they were last known to be alive.

8.6 Determination of Sample Size

The total number of patients enrolled will depend on the number of dose escalations and the need to further characterize individual cohorts of single-agent fruquintinib administered at the RP2D.

Dose Escalation Phase

The sample size may vary depending on the number of dose levels evaluated and the number of DLTs observed in each cohort. Patients who are considered not evaluable for DLT or PK will be replaced. The sample size may increase when these patients are replaced.

Dose Expansion Phase

The primary objective of the dose expansion phase is to evaluate the anticancer activity of fruquintinib in patients with advanced solid tumors, treated at the RP2D from the dose escalation phase.

Approximately 6 patients with advanced, refractory solid tumors of any type will be enrolled in Cohort A. This sample size is not based on a formal statistical assumption.

Additionally, enrollment in disease specific cohorts is planned as follows:

- 40 patients in Cohort B (refractory mCRC with progression on TAS-102 and/or regorafenib)
- 40 patients in Cohort C (refractory mCRC that has progressed on standard chemotherapies and relevant biologics but has NOT received TAS-102 or regorafenib)
- 15 patients in Cohort D (HR+/Her2- mBC)
- 15 patients in Cohort E [triple negative breast cancer (TNBC)]

The number of patients in each cohort can provide adequate precision for the estimated incidence rates of patients having a specific AE, patients with CR/PR (ORR), patients with

CR/PR/SD (DCR), or PFS rate at a specific time point.

Shown below in Table 15 and Table 16 are the range of incidence rates and the corresponding 95% Confidence Intervals (CI) for a sample size of 15 and 40 patients, respectively. As shown in the table, the 95% CI is approximately equal to an estimated incidence rate of ±16% to 28% for a sample size of 15 patients and estimated incidence rate of ±7% to 16% for a sample size of 40 patients.

Table 15 Estimated Incidence Rates and 2-Sided 95% Confidence Intervals for N=15 Patients

Number of Cases	Observed Incidence Rate	95% CI Lower Limit	95% CI Upper Limit
0	0	0.00	0.22
3	0.2	0.04	0.48
6	0.4	0.16	0.68
9	0.6	0.32	0.84
12	0.8	0.52	0.96
15	1	0.78	1.00

95% Clopper-Pearson Interval for binomial distribution

Table 16 Estimated Incidence Rates and 2-Sided 95% Confidence Intervals for N=40 Patients

Number of Cases	Observed Incidence Rate	95% CI Lower Limit	95% CI Upper Limit
0	0	0.00	0.09
4	0.1	0.03	0.24
10	0.25	0.13	0.41
20	0.5	0.34	0.66
30	0.75	0.59	0.87
40	1	0.91	1.00

95% Clopper-Pearson Interval for binomial distribution

9 ETHICS

9.1 Independent Ethics Committee/Institutional Review Board (IEC/IRB)

This protocol, protocol amendment(s), the ICFs, any information to be given to the patient, and relevant supporting information must be submitted by the PI to the IEC/IRB for review and approval before the study is initiated. In addition, any patient recruitment materials must be approved by the IEC/IRB.

The PI is responsible for providing written summaries of the status of the study to the Independent Ethics Committee/Institutional Review Board (IEC/IRB) annually or more frequently in accordance with the regulatory requirements and policies and procedures established by the IEC/IRB. Investigators are also responsible for promptly informing the IEC/IRB of any protocol changes or amendments and of any unanticipated problems involving risk to human patients or others.

In addition to the requirements to report protocol-defined AEs to the sponsor or its designee, investigators are required to report promptly to their respective IEC/IRB all unanticipated problems involving risk to human patients. Some IECs/IRBs may want prompt notification of all SAEs, whereas others require notification only about events that are serious, considered related to study drug, and unexpected.

9.2 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.

9.3 Patient Informed Consent

The investigator or his/her representative will explain the nature of the study to the patient and answer all questions regarding this study. Before any study-related screening procedures are performed on the patient, the ICF will be reviewed, signed, and dated by the patient and the person who administered the informed consent. A copy of the signed informed consent document will be given to the patient and the original will be placed in the patient's medical record and must be available for verification by study monitors at any time. If applicable, the ICF will be provided in a certified translation of the local language.

The ICF should be revised whenever there are changes to procedures outlined in the document or when new information becomes available that may affect the willingness of the patient to participate.

For any updated or revised ICFs, the case history for each patient shall document the informed consent process and that written informed consent was obtained from the patient for the updated/revised ICF for his/her continued participation in the study. The final revised IEC/IRB-approved ICF must be provided to Hutchison MediPharma for regulatory purposes.

Signed and dated ICFs must remain in each patient’s study file and must be available for verification by study monitors at any time.

10 STUDY DOCUMENTATION, CASE REPORT FORM AND RECORDS

10.1 Source Data Verification

Study monitors will perform ongoing source document verification to confirm that critical protocol data (ie, source data) entered into the CRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at the pharmacy, laboratories, and medico-technical departments involved in a clinical trial.

Source documents that are required to verify the validity and completeness of data entered into the CRFs must never be obliterated or destroyed.

To facilitate source document verification, the investigator(s) and institution(s) must provide the sponsor direct access to applicable source documents and reports for trial-related monitoring, sponsor audits, and IEC/IRB review. The investigational site must also allow inspection by applicable regulatory authorities.

10.2 Use of Computerized System

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with FDA requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system (for clinical research purposes) would be one that (1) allows data entry only by authorized individuals; (2) prevents the deletion or alteration of previously entered data and provides an audit trail for such data changes (eg, modification of file); (3) protects the database from tampering; and (4) ensures data preservation.

If a site's computerized medical record system is not adequately validated for the purposes of clinical research (as opposed to general clinical practice), applicable hardcopy source documents must be maintained to ensure that critical protocol data entered into the CRFs can be verified.

10.3 Retention of Records

US FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for Good Clinical Practice (GCP) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply. No records should be disposed of without the written approval of Hutchison MediPharma. Written notification should be provided to Hutchison MediPharma for transfer of any records to another party or moving them to another location.

11 MONITORING

It is understood that the responsible Hutchison MediPharma monitor (or designee) will contact and visit the investigator regularly and will be allowed, on request, to inspect the various records of the trial (CRFs and other pertinent data) provided that patient confidentiality is maintained in accord with local requirements.

It will be the monitor's responsibility to inspect the CRFs at regular intervals throughout the study and to verify the adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to laboratory test reports and other patient records needed to verify the entries on the CRF. The investigator (or deputy) agrees to cooperate with the monitor to ensure that any problems detected during these monitoring visits are resolved.

12 DATA QUALITY

The overall procedures for quality assurance of clinical study data are described in the sponsor or designee Standard Operational Procedures.

Accurate and reliable data collection will be assured by verification and cross–check of the CRFs against the investigator's records by the study monitor (source document verification], and the maintenance of a drug-dispensing log by the investigator.

The sponsor or its agent will be responsible for data management of this study according to data management documents. Any decision to use the CRF as a source document must be stated in the Data Validation Manual and the investigator must be advised of this decision. A comprehensive validation check program will verify the data and discrepancy will be generated accordingly. In the event of discrepant data, the sponsor or its agent will issue data queries to the site and request data clarification. Site is required to respond to all queries and promptly enter date into the EDC system.

The CRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the sponsor and records retention for the study data will be consistent with the sponsor's standard procedures.

In order to facilitate analysis of the biological samples collected in this study, the treatment code will be released to the responsible analytical person when the samples have been received at the analytical site and are ready for assay. The result of the analysis must not be released with individual identification of the patient until the database is closed.

12.1 Assignment of Preferred Terms and Original Terminology

For classification purposes, preferred terms will be assigned to the original terms entered in the CRF, using the most up to date version of MedDRA for AEs and diseases and World Health Organization (WHO) drug terms and procedures dictionary for treatments and surgical and medical procedures.

13 USE OF INFORMATION AND PUBLICATION

13.1 Use of Information

All information regarding fruquintinib and Hutchison MediPharma's operations, such as Hutchison MediPharma's patent applications, formulae, manufacturing processes, basic scientific data, or formulation information, supplied by Hutchison MediPharma and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by Hutchison MediPharma in connection with the development of fruquintinib. This information may be disclosed as deemed necessary by Hutchison MediPharma or its designee to other clinical investigators, other pharmaceutical companies, and to the regulatory agencies. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the investigator is obligated to provide Hutchison MediPharma with complete test results and all data developed in this study and to provide direct access to source data/documents for trial-related monitoring, audits, IEC/IRB review, and regulatory inspection.

The investigator will maintain a confidential patient identification code list of all patients enrolled in the study (by name and patient number). This list will be maintained at the site and will not be retrieved by Hutchison MediPharma or its designee.

13.2 Publication

Core publication(s) will be authored by specified principal investigator(s) who contribute significantly to the implementation and conduct of the study and non-site personnel who contribute substantially to the design, interpretation, or analysis of the study (eg, Hutchison MediPharma or consultants). Hutchison MediPharma scientists making significant contributions to the study will be included in the list of authors. Hutchison MediPharma agrees that before it publishes any results of this study, it shall provide the investigator a pre-publication manuscript for review at least 30 days prior to the submission of the manuscript to the publisher.

The investigators have the right to publish the results of the study, but with due regard to the protection of confidential information. Accordingly, Hutchison MediPharma shall have the right to review and approve any paper for publication, including oral presentation and abstracts, which utilize data generated from this study. At least 30 days before any such paper or abstract is presented or submitted for publication, a complete copy shall be given to Hutchison MediPharma for review. Hutchison MediPharma shall review any such paper or abstract and give its comments to the author(s) promptly. The investigator shall comply with Hutchison MediPharma's confidential information in any such paper and agrees to withhold publication of the same for an additional 30 days in order to permit Hutchison MediPharma to obtain patent or other proprietary rights protection, if Hutchison MediPharma deems it necessary.

This confidential information shall remain the sole property of Hutchison MediPharma, shall not be disclosed to others without the written consent of Hutchison MediPharma, and shall not be used except in the performance of this study.

It is understood by the investigator that the information developed in the clinical study will

be used by Hutchison MediPharma in connection with the development of fruquintinib and, therefore, may be disclosed as required to other clinical investigators, other pharmaceutical companies, or to regulatory agencies. It is understood that there is an obligation to provide Hutchison MediPharma with complete test results and all data resulting from this study and to provide direct access to source data/documents for study related monitoring, audits, IEC/IRB review, and regulatory inspection.

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Appendix A Study Schedule of Events

Procedure \ Date	Screening		Treatment[2]							Treatment Completion[3]	Follow-up
			Cycle 1				Cycle 2-3		Cycle 4 and onwards		
	Day -28 to Day -1	Day -7 to Day -1	Day 1	Day 8 (±1d)	Day 15 (±1d)	Day 22 (±1d)	Day 1 (±3d)	Day 15 (±3d)	Day 1 of each subsequent cycle (±3d)	30 (±7) days after permanent treatment discontinuation	Every 12 (±2) weeks from Treatment Completion Visit
Informed consent[1]	X										
Tumor assessment **(Dose Escalation, Expansion Cohorts C, D, E)**	X		Screening, then every 8 (±1) weeks thereafter (eg C3D1, C5D1, C7D1, etc.)							X[4]	
Tumor assessment **(Dose Expansion Cohorts A and B only)**	X		Screening, C2D1, C3D1 C4D1, and every 8 (±1) weeks thereafter (eg C6D1, C8D1, C10D1, etc.)							X[4]	
Medical history, demographics	X										
Concomitant medication[5]	X	X	X	X	X	X	X	X	X	X	
ECOG performance status		X	X		X		X	X	X	X	
Vital signs[6]		X	X	X	X	X	X	X	X	X	
Complete physical examination[7]		X									
Limited physical examination[7]			X	X	X	X	X	X	X	X	
Height	X										
Hematology[8]		X		X	X	X	X	X	X	X	

Procedure \ Date	Screening		Treatment[2]							Treatment Completion[3]	Follow-up
			Cycle 1				Cycle 2-3		Cycle 4 and onwards		
	Day -28 to Day -1	Day -7 to Day -1	Day 1	Day 8 (±1d)	Day 15 (±1d)	Day 22 (±1d)	Day 1 (±3d)	Day 15 (±3d)	Day 1 of each subsequent cycle (±3d)	30 (±7) days after permanent treatment discontinuation	Every 12 (±2) weeks from Treatment Completion Visit
Coagulation assay (aPTT, INR)		X		X	X	X	X	X	X	X	
Chemistry panel[9]		X		X	X	X	X	X	X	X	
Urinalysis[10]		X		X	X	X	X	X	X	X	
Echocardiogram[11]	X		X (Every 12 weeks ± 1 week after the first dose)							X	
Thyroid function test[12]	X						X		X	X	
Serum pregnancy tests [13]		X								X	
Urine pregnancy tests[13]							X		X		
Specific tumor markers[14] **Dose Escalation, Expansion Cohorts C, D, E)**	X		Screening, then every 8 (±1) weeks thereafter: C3D1, C5D1, C7D1, etc								
Specific tumor markers[14] **Dose Expansion Cohorts A and B only)**			Screening, C2D1, C3D1 C4D1, and every 8 (±1) weeks thereafter								
12-lead electrocardiogram[15]		X	X		X		X		X	X	
PK plasma sampling			PK samples are being collected on Days 1, 2, 14, and 15 of Cycle 1 for Expansion Cohorts B, C, D, and E. Refer to Appendix D for								

Procedure \ Date	Screening		Treatment[2]							Treatment Completion[3]	Follow-up
			Cycle 1				Cycle 2-3		Cycle 4 and onwards		
	Day -28 to Day -1	Day -7 to Day -1	Day 1	Day 8 (±1d)	Day 15 (±1d)	Day 22 (±1d)	Day 1 (±3d)	Day 15 (±3d)	Day 1 of each subsequent cycle (±3d)	30 (±7) days after permanent treatment discontinuation	Every 12 (±2) weeks from Treatment Completion Visit
			specific timepoints								
Adverse event[16]	X	X	X	X	X	X	X	X	X	X	
Fruquintinib treatment			Once daily, 3 weeks on/ 1 week off								
Survival follow up[17]											X

Note:

1. A written informed consent form should be obtained prior to any protocol-specific procedure or test. Tests completed within 28 days prior to enrollment can be used for screening and do not need to be repeated (except hematology, coagulation test, clinical chemistry, or urinalysis results).
2. Unless otherwise indicated, the visit window during the treatment period will be ± 3 days (± 1 day during cycle 1).
3. Patients who complete or prematurely discontinue the study need to return to the study site for a follow-up at 30 (±7) days after the decision to discontinue treatment permanently. Ongoing AEs will be followed until the event has resolved to baseline grade, the event is assessed as stable by the investigator, new anti-tumor treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or when it has been determined that the study treatment or participation is not the cause of the AE.
4. The treatment completion visit tumor assessment can be omitted if treatment ended because of disease progression or the patient had a tumor assessment within 14 days prior to the last dose of study drug.
5. Concomitant medication includes any prescribed or over-the-counter medicines. All medication used by patients within 7 days before screening and 30 days after study treatment completion should be recorded. At each visit, all medication used since the prior visit should be recorded.

6. Vital signs include blood pressure, heart rate, respiratory rate, and temperature. For patient with a baseline history of antihypertensive medications, blood pressure should be monitored at 3 hours (±2 hours) after the daily doses of anti-hypertensive medication.

7. Please refer to Section 6.3.2 for the assessments that should be completed as part of the Complete and Limited Physical Exams.

8. Hematology consists of complete blood count, including red blood cell count, hemoglobin, hematocrit, reticulocyte count, white blood cell count with differential (neutrophils, bands, lymphocytes, eosinophils, monocytes, basophils, and other cells), and platelet count.

9. The chemistry panel includes blood urea nitrogen, creatinine and creatinine clearance, sodium, potassium, chlorine, bicarbonate, calcium, magnesium, phosphorus, glucose, alanine aminotransferase, bilirubin (total), aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, total cholesterol, triglycerides, uric acid, protein (total) and albumin.

10. Urinalysis includes pH, glucose, protein, and blood. A 24-hour urine should be collected from all patients with >1+ proteinuria for quantitative test of urine protein during the screening. If protein ≥2+ during the period of study treatment, a 24-hour urine test should be conducted within 1 week.

11. MUGAs are permitted if echocardiograms cannot be performed.

12. Includes free T3, free T4, and thyroid-stimulating hormone (TSH).

13. Women of childbearing potential will receive a serum pregnancy test during screening and within 30 days after treatment completion, and a urine pregnancy test on Day 1 of each 28-day cycle beginning at Cycle 2. If pregnancy is suspected, additional tests should be completed. In the case of menopausal women, the date of menopause onset should be recorded.

14. CA125 level for patients with ovarian cancer, PSA for patients with prostate cancer, or other tumor markers (as appropriate) should be obtained as clinically indicated or with each tumor assessment.

15. On Days 1 and 15 in Cycle 1, ECG should be performed at pre-dose and at 3 hours (± 15 minutes) post-dose (around C_{max} after single dose and at steady state in order to evaluate concentration-QT relationship for fruquintinib). Untimed ECG will be conducted on Day 1 of each cycle from Cycle 2 and onward.

16. After informed consent, all SAEs and concomitant medications will be collected. After initiation of study drug, all AEs and SAEs will be collected until 30 days following 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.

17. **For subjects in Expansion Cohorts B, C, D, and E** - Survival follow-up (by telephone) should be performed every 12 (±2) weeks from the date of the Treatment Completion visit. All subsequent anti-tumor therapy and information about ongoing or unresolved study drug-related SAEs will be collected. For the patients that discontinue the study without PD, all available tumor assessment results during survival follow-up will be recorded in the CRF 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 survival follow-up will be performed.

Appendix B 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 housework, 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 C Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST Version 1.1)

Quick Reference:

http://ctep.cancer.gov/guidelines/recist.html

Patient Eligibility

Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined as the presence of at least one measurable lesion.

In studies where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

Methods 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 follow-up. CT is the best currently available and reproducible method to measure lesions selected for response assessment. MRI is also acceptable in certain situations (eg, for body scans but not for lung).
- Lesions on a chest X-ray may be considered measurable lesions if they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- Clinical lesions will only be considered measurable when they are superficial and ≥10 mm in diameter, as assessed using calipers. For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- Ultrasound (US) should not be used to measure tumor lesions.
- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete response.
- Cytology and histology can be used in rare cases (eg, for evaluation of residual masses to differentiate between Partial Response and Complete Response or evaluation of new or enlarging effusions to differentiate between Progressive Disease and Response/Stable Disease).
- Use of endoscopy and laparoscopy is not advised. However, they can be used to confirm complete pathological response.

Baseline Disease Assessment

All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

Measurable 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 of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm; when CT scans have slice thickness >5 mm, the minimum size should be twice the slice thickness).
- 10 mm caliper measurement by clinical exam (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 short axis when assessed by CT scan (CT scan slice thickness is recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

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 measurable if the soft tissue component meets the definition of measurability described above.

"Cystic lesions" thought to represent cystic metastases can be considered measurable 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.

Non-measurable Lesions

Non-measurable lesions are all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with 10 to <15 mm short axis), 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, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques. Blastic bone lesions are non-measurable.

Lesions with prior local treatment, such as those situated in a previously irradiated area or in an area treated with 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.

Target Lesions

- All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, as well as their suitability for reproducible repeated measurements.
- All measurements should be recorded in metric notation using calipers if clinically assessed.

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 diameters, which will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. If lymph nodes are to be included in the sum, only the short axis will contribute.

Non-target Lesions

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

Evaluation of 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 (this may include the baseline sum). The sum must also demonstrate an absolute increase of at least 5 mm.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Special Notes on the Assessment of Target Lesions

Lymph nodes identified, as target lesions should always have the actual short axis measurement recorded even if the nodes regress to below 10 mm on study. 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": While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small. However, sometimes lesions or lymph nodes become so faint on a CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure", in which case a default value of 5 mm should be assigned.

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 maximal longest diameter for the "coalesced lesion".

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR / Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker levels above normal limits.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions. When patient has measurable disease, 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 such that, even in 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.

When patient has only non-measurable disease: 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, a useful test that can be applied is to consider if the increase in overall disease burden based on change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease. Examples include an increase in a pleural effusion from "trace" to "large" or an increase in lymphangitic disease from localized to widespread.

New Lesions

The appearance of new malignant lesions denotes disease progression:

- The finding of a new lesion should be unequivocal (ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor, especially when the patient's baseline lesions show partial or complete response).
- 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.
- A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and disease progression.

It is sometimes reasonable to incorporate the use of ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) scanning to complement CT 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:

Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is PD based on a No FDG-PET at baseline and a positive FDG-PET at follow-up:

- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if 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 at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Time Point Response

Below is a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline: Patients with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall Response
CR	CR	No	CR
CR	Non-CR /non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD NE	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; PR = Partial Response; SD = Stable Disease; PD = Progressive Disease; NE = Not Evaluable

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. However, in all other circumstances, (ie, in randomized phase 2 or 3 trials or 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.

Missing Assessments and Inevaluable Designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE 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 most likely happen in the case of PD.

Reporting of Results

- All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient

will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

- All the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.
- All conclusions should be based on all eligible patients.
- Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (eg, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.
- The 95% confidence intervals should be provided.

Appendix D Handling and Shipment of Pharmacokinetic Samples

Blood samples will be taken for pharmacokinetic evaluation by cannula or direct venipuncture at the time points listed in Appendix D-1 (dose escalation phase) and Appendix D-2 (dose expansion phase). The exact times and dates of blood sampling are to be recorded in the CRFs.

Blood samples (2 mL) for fruquintinib pharmacokinetics will be collected into sodium heparinate vacutainers. The tubes will be immediately inverted gently at least 5 times to mix the blood and then placed in ice bath prior to centrifugation. The tubes will be centrifuged at approximately 1000 g and 4ºC for 10 minutes, after which the plasma will be transferred immediately into 2 clean prelabeled tubes. Approximately 0.5 mL plasma will be placed in each tube (Tube A and Tube B). After the tubes are tightly capped, the samples should be stored immediately at -20°C or -80°C. The whole process of plasma collection should be completed within 2 hours of the blood sampling. According to the present results of plasma stability, fruquintinib can be stored at -20°C and at -80°C for 133 days. For long-term storage, it is recommended that the plasma samples be stored at -80°C.

Each sample will be identified by date of collection, study number, patient number and initials, and sample time point identifier (i.e. 30 minutes, 1 hour, 4 hours etc.). Tube B samples must be labeled as "duplicate."

All plasma samples will be shipped on dry ice to the central laboratory within 30 days of sample collection. The dry ice should be sufficient to keep the samples frozen during the whole shipment period. The samples of Tube B are shipped out after the prior batch of Tube A has been received safely by the central laboratory. Tube A samples will be used for bioanalysis. Tube B samples will be stored in -80°C freezer for future use. The laboratory should be notified at least 1 day prior to the arrival of the sample and be provided shipping details and tracking numbers for the shipment.

Prior to shipment, a PK sample requisition form (containing the details of each sample/label identification included in the shipment) will be prepared. All sample correspondence must contain the study number, study drug, and Site references (including emergency contact details and responsible shipment coordinator). All of the sample details on this log must match the details included on the individual sample labels, as each sample label will be checked against the list by Centre Laboratories' sample coordination personnel. The log should be reviewed by the preparer and a second individual for accuracy and signed/dated by both individuals. To avoid sample mix-ups or misidentification, the samples in the shipment will be sorted by patient number and sample time using segmented cartons.

Table D-2 PK Sampling Time Points (Dose Escalation Phase and Cohort A of Dose Expansion Phase)

Visit Cycle	Time Point
Cycle 1, Day 1	Pre-dose (≤10 minutes)
	Post-dose 1 hour ±±(± 5 minutes)
	Post-dose 2 hours ±±(± 15 minutes)
	Post-dose 4 hours ±±(± 30 minutes)
	Post-dose 8 hours ±±(± 60 minutes)
Cycle 1, Day 2	Pre-dose (≤10 minutes)
Cycle 1, Day 14	Pre-dose (≤10 minutes)
	Post-dose 1 hour ±±(± 5 minutes)
	Post-dose 2 hours ±±(± 15 minutes)
	Post-dose 4 hours ±±(± 30 minutes)
	Post-dose 8 hours ±±(± 60 minutes)
Cycle1, Day 15	Pre-dose (≤10 minutes)
Cycle1, Day 21	Pre-dose (≤10 minutes)
	Post-dose 1 hour ±±(± 5 minutes)
	Post-dose 2 hours ±±(± 15 minutes)
	Post-dose 4 hours ±±(± 30 minutes)
	Post-dose 8 hours ±±(± 60 minutes)
Cycle 1, Day 22	Post-dose 24 hours ±±(± 60 minutes) on Day 21

Table D-2 PK Sampling Time Points (Cohort B, C, D, and E of Dose Expansion Phase)

Visit Cycle	Time Point
Cycle 1, Day 1	Pre-dose (≤10 minutes)
	Post-dose 1 hour ±±(± 5 minutes)
	Post-dose 2 hours ±±(± 15 minutes)
	Post-dose 4 hours ±±(± 30 minutes)
	Post-dose 8 hours ±±(± 60 minutes)
Cycle 1, Day 2	Pre-dose (≤10 minutes)
Cycle 1, Day 14	Pre-dose (≤10 minutes)
	Post-dose 1 hour ±±(± 5 minutes)
	Post-dose 2 hours ±±(± 15 minutes)
	Post-dose 4 hours ±±(± 30 minutes)
	Post-dose 8 hours ±±(± 60 minutes)
Cycle1, Day 15	Pre-dose (≤10 minutes)

Appendix E Prohibited Concomitant Medications that Have a Known Risk of QT prolongation and/or Torsades des Pointes (TdP)

The list is continuously updated online at www.crediblemeds.org or www.qtdrugs.org

Generic Name	Brand Names (Partial List)	Drug Class
Amiodarone	Cordarone, Pacerone, Nexterone	Antiarrhythmic
Anagrelide	Agrylin, Xagrid	Phosphodiesterase 3 inhibitor
Arsenic trioxide	Trisenox	Anticancer
Azithromycin	Zithromax, Zmax	Antibiotic
Chloroquine	Aralen	Antimalarial
Chlorpromazine	Thorazine, Largactil, Megaphen	Antipsychotic / Antiemetic
Cilostazol	Pletal	Phosphodiesterase 3 inhibitor
Ciprofloxacin	Cipro, Cipro-XR, Neofloxin	Antibiotic
Citalopram	Celexa, Cipramil	Antidepressant, SSRI
Clarithromycin	Biaxin, Prevpac	Antibiotic
Cocaine	Cocaine	Local anesthetic
Disopyramide	Norpace	Antiarrhythmic
Dofetilide	Tikosyn	Antiarrhythmic
Domperidone	Motilium, Motillium, Motinorm Costi, Nomit	Antinausea
Donepezil	Aricept	Cholinesterase inhibitor
Dronedarone	Multaq	Antiarrhythmic
Droperidol	Inapsine, Droleptan, Dridol, Xomolix	Antipsychotic / Antiemetic
Erythromycin	E.E.S., Robimycin, EMycin, Erymax, Ery-Tab, Eryc Ranbaxy, Erypar, Eryped, Erythrocin Stearate Filmtab, Erythrocot, E-Base, Erythroped, Ilosone, MY-E, Pediamycin, Zineryt, Abboticin, Abboticin-ES, Erycin, PCE Dispertab, Stiemycine, Acnasol, Tiloryth	Antibiotic
Escitalopram	Cipralex, Lexapro, Nexito,	Antidepressant, SSRI
Flecainide	Tambocor, Almarytm, Apocard, Ecrinal, Flécaine	Antiarrhythmic
Fluconazole	Diflucan, Trican	Antifungal
Haloperidol	Haldol	Antipsychotic
Ibutilide	Corvert	Antiarrhythmic
Levofloxacin	Levaquin, Tavanic	Antibiotic
Methadone	Dolophine, Symoron, Amidone, Methadose, Physeptone, Heptadon	Opioid agonist

Generic Name	Brand Names (Partial List)	Drug Class
Moxifloxacin	Avelox, Avalox, Avelon	Antibiotic
Ondansetron	Zofran, Anset, Ondemet, Zuplenz, Emetron, Ondavell, Emeset, Ondisolv, Setronax	Antiemetic
Oxaliplatin	Eloxatin	Antineoplastic Agent
Papaverine HCl (Intra-coronary)	none	Vasodilator, Coronary
Pentamidine	Pentam	Antifungal
Pimozide	Orap	Antipsychotic
Procainamide	Pronestyl, Procan	Antiarrhythmic
Propofol	Diprivan, Propoven	Anesthetic, general
Quinidine	Quinaglute, Duraquin, Quinact, Quinidex, Cin-Quin, Quinora	Antiarrhythmic
Sevoflurane	Ultane, Sojourn	Anesthetic, general
Sotalol	Betapace, Sotalex, Sotacor	Antiarrhythmic
Thioridazine	Mellaril, Novoridazine, Thioril	Antipsychotic
Vandetanib	Caprelsa	Anticancer

Source: www.crediblemeds.org or www.qt.drugs.org

Appendix F Fruquinitinib and Concomitant Medication

Fruquintinib is not a substrate of efflux transporters. Fruquintinib showed dose-dependent inhibition on P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Based on the data for digoxin transport (mediated by P-gp) and estrone-3-sulfate transport (mediated by BCRP), the IC_{50} on P-gp and BCRP was estimated to be 4.60 and 1.29 μM, respectively.

According to the present metabolism data, cytochrome P450 enzymes CYP3A4/5 play an important role in the metabolism of fruquintinib. Fruquintinib had no marked reversibly inhibitory effects on CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5 (IC_{50} >10 μM) and no induction of CYP1A2, [redacted] and CYP3A4 at the tested concentration of 10 μM. No marked time-dependent inhibition was observed for CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5.

A series of CYP3A4 strong inducers and strong inhibitors are listed in Tables F-1 and F2 below. Patients who received a CYP3A4 strong inducer or strong inhibitor within 2 weeks (3 weeks for hyperforin perforatum treatment) prior to the first dose of the study drug will not be allowed to participate in the study.

Typical substrates of P-gp and BCRP are listed in Table F-3 below. During the study, substrates of P-gp and BCRP, and strong inducers and inhibitors of CYP3A4/5 are avoided to be administered concomitantly with fruquintinib, unless investigators consider it necessary. In this case, efficacy reduction and toxicity increases resulting from the interaction should be closely monitored.

Not all the medications are listed in the following tables. Other drugs known to possibly affect CYP3A4 activity and to be substrates of P-gp and BCRP should be used with cautions. When combining fruquintinib with other drugs the prescription information of all concomitant medications should be reviewed.

Table F-1 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 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 F-2 Typical Strong Inducers of CYP3A4

Strong Inducers of CYP3A4
Avasimibe
Carbamazepine
Enzalutamide
Mitotane
Phenobarbital
Phenytoin
Rifabutin

Rifampicin
Enzalutamide
St. John's wort

Table F-3: Typical Substrates of P-gp and 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 G Guideline to Interpreting the Causality Question

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug without treatment of the reported event?
- No alternative cause. The AE cannot be reasonably explained by another etiology, such as the underlying disease, other drugs, other host or environmental factors.
- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? HMPL would not normally recommend or support a rechallenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where 1 or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

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.

Appendix H 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. T his 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 7.1.2), 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 CRFs 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:
    - Haematology
    - Clinical biochemistry: ALT, AST, bilirubin (including total bilirubin and direct bilirubin), ALP, albumin, prothrombin time 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.

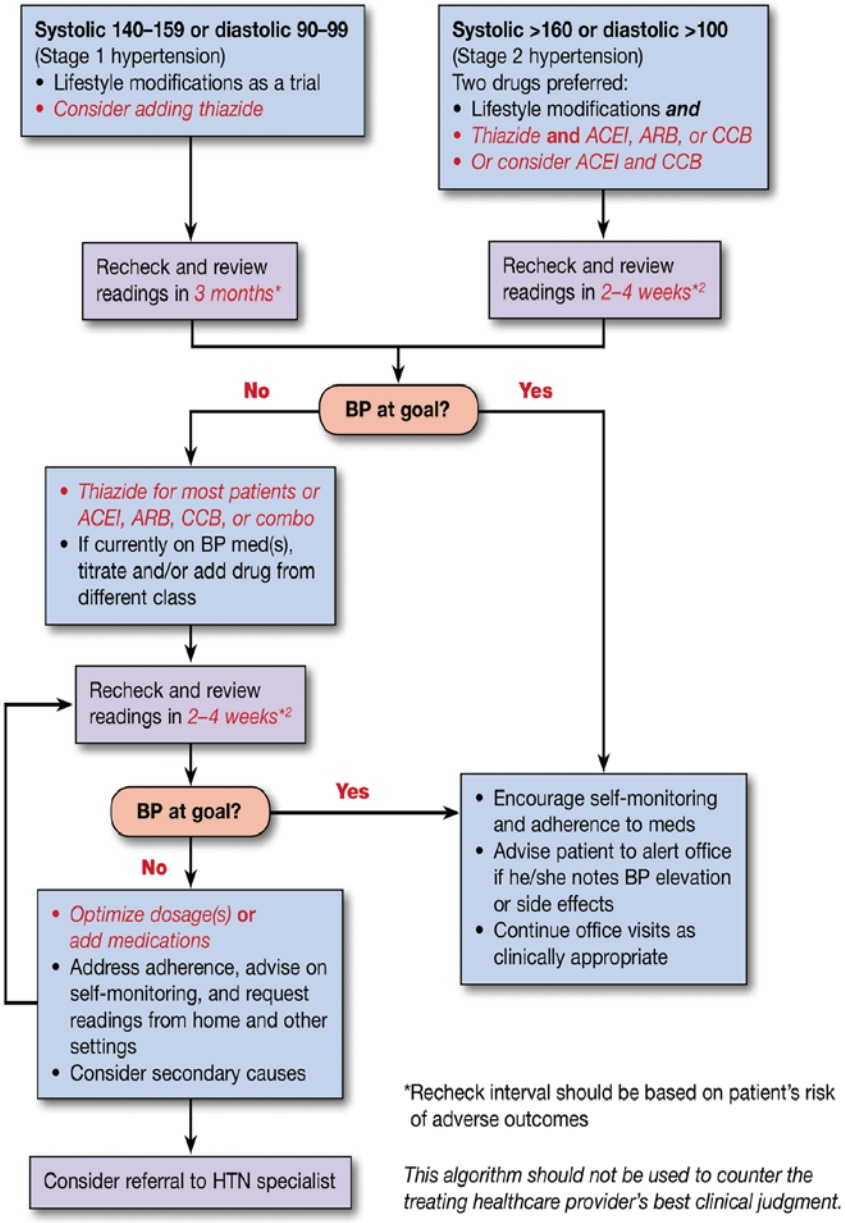
Appendix I Management of Hypertension in Patients Receiving Fruquintinib

Hypertension is a common AE that has been reported in patients taking angiogenesis inhibitors (Izzedine, et al 2009[15]), 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, please see a summary of the most recent AHA/ACC hypertension treatment guidelines.

Controlling Hypertension in Adults[1]



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

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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.
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Appendix J Clinical Management of Severe or Serious Hemorrhagic Events

If hemorrhagic events are evaluated as severe (CTCAE Grade ≥3) or serious adverse events, fruquintinib treatment should be discontinued or interrupted immediately, and appropriate treatment measures initiated to control bleeding (e.g. 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 5.2.2.1, Table 13, Dose Adjustment for Hemorrhage at any Site). 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 serious adverse event after taking fruquintinib, the investigator is required to report the event in an expedited fashion (within 24 hours of first awareness) to sponsor (see Table 12 and Section 7.2 Expedited Reporting Requirements).

See the **Management Flowchart** below for guidance on the management of severe or serious hemorrhage at any site.

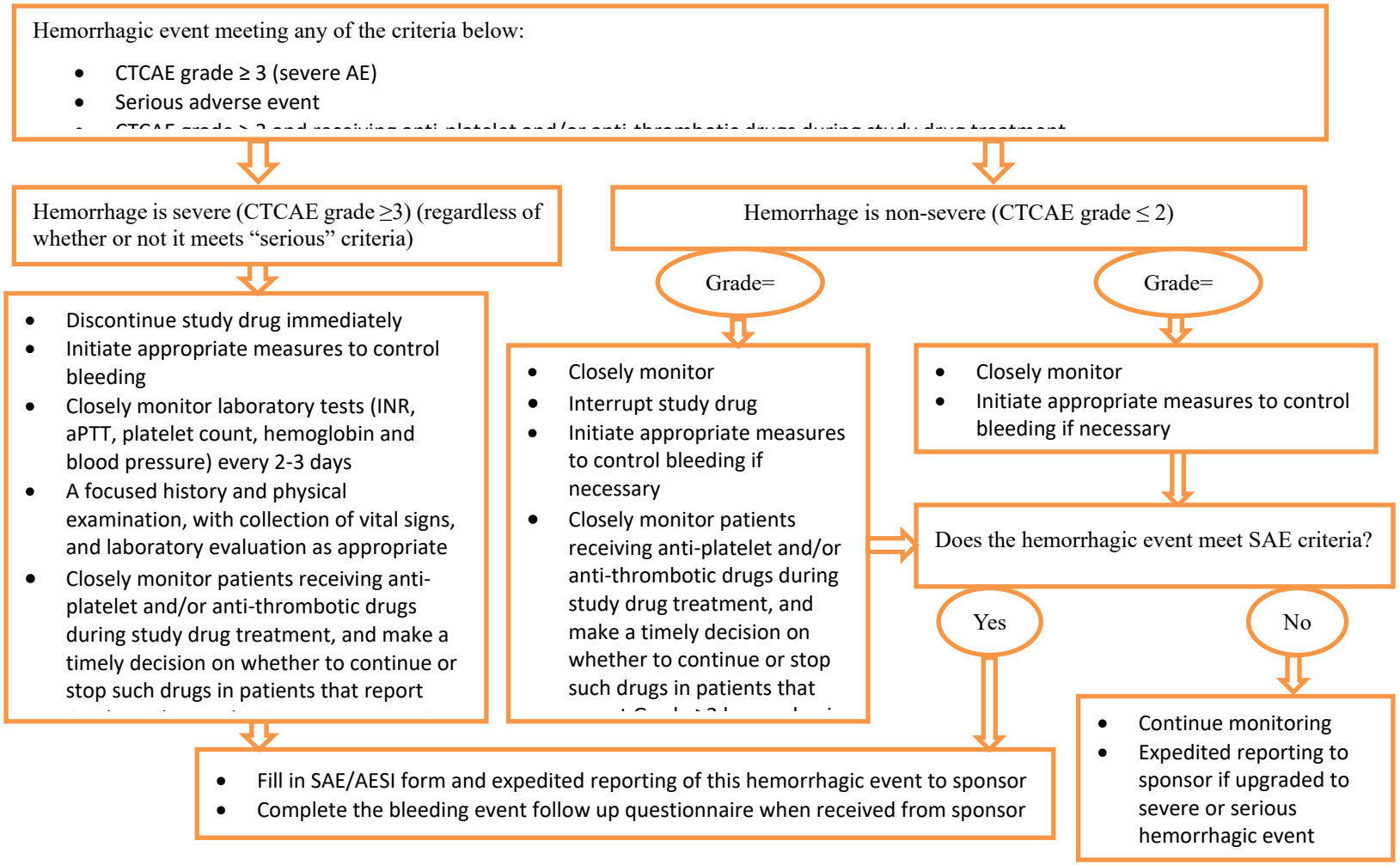
Recommended Data Collection for Severe or Serious Hemorrhagic Events:

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 (e.g. warfarin)
        - NSAIDs (e.g. aspirin)
        - Anti-platelet drugs (e.g. clopidogrel/glycoprotein GPIIb/IIIa inhibitors/dipyridamole)
        - Other anticoagulants (e.g. 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, prothrombin time, 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).

Severe or Serious Hemorrhagic Events Management Flow Chart



Appendix K Protocol Amendment History

Amendment 3, Version 3:

The protocol was amended on July 2, 2018 to add a cohort of 30 patients with metastatic colorectal cancer (mCRC) to the expansion phase of this study. At the time of writing the Amendment 3, the Safety Review Committee (SRC) had determined that the recommended Phase 2 dose (RP2D) of fruquintinib is 5 mg QD (3 weeks on/1 week off each 28-day cycle). The study population in the expansion phase therefore included both the originally planned cohort of 6 patients with advanced solid tumors of any type (Cohort A) and a new cohort of 30 patients with metastatic colorectal cancer mCRC (Cohort B). The basis for adding 30 patients with mCRC was the positive Phase 3 study FRESCO conducted in China that demonstrated a significantly increased overall survival in patients with mCRC treated with fruquintinib compared to placebo, and led to approval of fruquintinib for this indication by the CFDA. Another reason for Amendment 3 was to correct the terminology used in the original protocol to describe the dose escalation phase of the study as a safety run-in phase. The correct terminology was changed to "dose escalation phase" because the study was not prospectively designed as the safety-run in phase in a Phase 2 trial.

The changes in Amendment 3 are summarized in the table below.

Section Number	Section Title	Description of Changes
Not applicable	Signature page, Declaration of Sponsor	Personnel changes: 1. [redacted] has replaced [redacted] as the signatory on behalf of Hutchison MediPharma (US) Inc. 2. [redacted], and [redacted] of Hutchison MediPharma Limited, has replaced [redacted] as the signatory on behalf of Hutchison MediPharma, Limited (Shanghai, China)
Not applicable	Protocol title	Changed Protocol of Clinical Trials to **Clinical Study Protocol** in keeping with industry terminology.
Not applicable	Title page; Declaration of Investigator; Synopsis, Study Title	Title change: A Multi-Center, Open-Label, Phase 1/1b Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics, **and Anticancer Activity** of fruquintinib in **Patients with** Advanced Solid Tumors **of any Type, and in Patients with Refractory Metastatic Colorectal Cancer**
Section 1.3.2	Clinical Safety	Added **Table 3, Identified Risks in Patients Treated with Fruquintinib,** and **Table 4, Potential Risks in Patients Treated with Fruquintinib**, with cross-reference to fruquintinib IB edition 10 (finalized November 22, 2018)

Section Number	Section Title	Description of Changes
Synopsis Section 1.3.3 Section 1.4	Synopsis Clinical Efficacy Study Rationale	**Added a dose expansion phase comprising 6 patients with solid tumors of any type (Cohort A) and 30 patients with refractory metastatic colorectal cancer (mCRC).** **Added that the rationale for enrolling 30 patients with refractory mCRC in the dose expansion phase (Cohort B) is the outcome of a placebo-controlled, Phase 3 (study 2013-013-00CH1 [FRESCO]) of fruquintinib as third-line or higher treatment for patients with mCRC. FRESCO demonstrated a significantly longer OS and PFS for fruquintinib compared to placebo and an acceptable safety profile. The CFDA approved fruquintinib for third-line or higher treatment of patients with mCRC.** Details are provided in the tracked-changes version of Amendment 3.
Section 2	Synopsis Study Objectives and Endpoints	**To create a new first-level heading titled Study Objectives and Endpoints and specify the *objectives and the associated endpoints* of the dose escalation phase and the dose expansion phase under a single second-level heading for each of the respective phases.**
Section 2.1	Dose Escalation Phase	**To add a heading under which the objectives and endpoints of the dose escalation phase are specified.**
Section 2.1.1	Primary Objective	**The primary objective of the dose escalation phase is to evaluate the safety and tolerability of fruquintinib in patients with advanced solid tumors and to determine the recommended Phase 2 dose (RP2D).**
Section 2.1.2	Primary Endpoint	**To specify that the primary endpoint of the dose escalation phase is the incidence of DLT in each cohort. DLT is defined in Section 2.1.2**
Section 2.1.3	Secondary Objectives	Added that the secondary objectives are: • **To evaluate the PK characteristics of multiple-dose fruquintinib and to investigate the metabolite profile of fruquintinib in the plasma of patients with solid tumors.** • **To evaluate the anticancer activity of fruquintinib in patients with solid tumors according to RECIST Version 1.1.**
Section 2.1.4	Secondary Endpoints	Added that the secondary endpoints are: • **The primary PK parameters: maximum plasma concentration (C_{max}), time to reach maximum concentration (T_{max}), terminal half-life ($t_{1/2}$), area under the concentration-time curve in a selected time interval (AUC_{0-t}), area under the concentration-time curve in the time interval from 0 to infinity ($AUC_{0-\infty}$), apparent clearance (CL/F), apparent volume of distribution (V_z/F) during the terminal phase according to CL/F/Ke, and the accumulation index based on AUC.** • **The objective response rate (ORR), disease**

Section Number	Section Title	Description of Changes
		control rate (DCR), duration of response (DoR), PFS overall survival (OS) and percentage change in tumor size from baseline according to RECIST V. 1.1
Section 2.2	Dose Expansion Phase	**To add a heading under which the objectives and endpoints of the dose expansion phase are specified**
Section 2.2.1	Primary Objective	**To add that the primary objective of the dose expansion phase is to evaluate the anticancer activity of fruquintinib at the recommended Phase 2 dose (RP2D) from the dose escalation phase, in patients with advanced solid tumors and in patients with metastatic colorectal cancer mCRC who have either progressed on, or had intolerable toxicity from at least 1 FDA-approved third-line therapy (trifluridine/tipiracil or regorafenib). Progression is assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1**
Section 2.2.2	Primary Endpoint	To specify that **progression free survival (PFS) at 12 weeks is the primary endpoint of the dose expansion phase.**
Section 2.2.3	Secondary Objective	To specify that the secondary objectives of the dose expansion phase are: • **To evaluate anticancer efficacy (ORR, DCR, DoR, PFS, and OS)** • **To evaluate the pharmacokinetic (PK) characteristics of multiple dose fruquintinib and to investigate the metabolite profile of fruquintinib in the plasma of patients with advanced solid tumors and in patients with mCRC.** **To evaluate the safety of fruquintinib in patients with advanced tumors and in patients with mCRC.**
Section 2.2.4	Secondary Endpoints	To specify that the secondary endpoints of the dose expansion phase are: • **The objective response rate (ORR), disease control rate (DCR), duration of response (DoR), PFS overall survival (OS) and percentage change in tumor size from baseline according to RECIST V. 1.1** • **The primary PK parameters include: maximum plasma concentration (Cmax), time to reach maximum concentration (Tmax), terminal half-life (t1/2), area under the concentration-time curve in a selected time interval (AUC0-t), area under the concentration-time curve in the time interval from 0 to infinity (AUC0-∞), apparent clearance (CL/F), apparent volume of distribution (Vz/F) during the terminal phase according to CL/F/Ke, and the accumulation index based on AUC.** • **Safety: AEs, physical examinations, vital signs, laboratory test results, 12-lead electrocardiogram,**

Section Number	Section Title	Description of Changes
		and echocardiogram.
Section 3.1 and Section 3.1.2	Description of the Study; Dose Expansion Phase	Changed description to read as follows: **This is an open-label study of fruquintinib comprised of a dose escalation phase in patients with advanced solid tumors of any type, and a dose expansion phase in patients with advanced solid tumors of any type and in patients with refractory mCRC. Patients with refractory mCRC have progressed on, or had intolerable toxicity from, at least 1 FDA-approved third-line therapy (trifluridine/tipiracil or regorafenib).**
Section 3.2	Sample Size	To specify that approximately **50** patients will be enrolled in this 2-phase study: **14** in the dose escalation phase and 36 in the dose expansion phase (**6 patients with advanced solid tumors of any type and 30 patients with mCRC**).
Section 3.4	Safety Review Committee	To define the role of the **Safety Review Committee** as follows: **safety monitoring and evaluation for dose escalation decisions SRC upon completion of the of the DLT observation period of the last patient in each cohort. The SRC is chaired by the Sponsor's fruquintinib Clinical Program Leader, members will include the principal investigators (PIs), the Sponsor's PK scientist, medical monitor, and the CRO's medical monitor.**
Section 3.6	Patient Discontinuation	To **modify the criteria for the discontinuation of study drug treatment** and to add **criteria for early discontinuation of study drug treatment**. Details are provided in the tracked-changes version of Amendment 3.
Section 4	Patient Selection	Changed patient population as follows: "patients with locally advanced or metastatic solid tumors" to "**patients with locally advanced or metastatic solid tumors of any type, and patients with refractory mCRC**".
Section 4.1	Inclusion Criteria (Criterion 4)	Specified that the criterion for enrollment in the dose escalation phase is histologically or cytologically documented, locally advanced or metastatic solid malignancy **of any type** (except squamous NSCLC) that has progressed on approved systemic therapy and for which no effective therapy or standard of care exists.
Section 4.1	Inclusion Criteria (Criterion 4)	**Added the dose expansion phase** and specified that patients will be enrolled in 1 of 2 cohorts. For **Cohort A**, the entry criterion is identical to that of the dose escalation phase. For **Cohort B, the entry criterion is defined as histologically or cytologically documented mCRC in patients who have progressed on, or had intolerable toxicity with at least 1 FDA-approved third-line systemic therapy (trifluridine/tipiracil or regorafenib.** **A definition of treatment failure was also added** and can be found in the tracked-changes version of Protocol Amendment 3.
Section 4.2	Exclusion Criteria (Criterion 8)	Changed text as follows: Risk International Normalized Ratio (INR) >1.5 or activated partial thromboplastin time (aPTT) >1.5 X ULN, **unless the patient is currently**

Section Number	Section Title	Description of Changes
		receiving or intending to receive anticoagulants for prophylactic purposes.
Section 4.2	Exclusion Criteria (Criterion 9)	Changed text as follows: Risk of, active hemorrhage; history or presence of active gastric/duodenal ulcer or ulcerative colitis, active hemorrhage of an unresected gastrointestinal tumor, **history of perforation of fistulas**; or any other condition that could possibly result in gastrointestinal tract hemorrhage or perforation **within 6 months prior to screening.**
Section 4.2	Exclusion Criteria (Criterion 16)	Changed text as follows: Patients who have ever received a VEGFR inhibitor, **except for patients with mCRC enrolled in the dose expansion phase.**
Section 4.2	Exclusion Criteria (Criterion 23)	Changed text as follows: **Any unresolved toxicities from a previous antitumor treatment greater than CTCAE v.4.03 Grade 1** (except for alopecia)
Section 4.2	Exclusion Criteria (Criterion 25)	Changed exclusion of patients with liver disease as follows: **Known clinically significant history of liver disease, including cirrhosis, current alcohol abuse or active viral hepatitis. For patients with evidence of chronic hepatitis B ((HBV), the HBV viral load must be undetectable on suppressive therapy, if indicated. Patients with a history of hepatitis C virus (HCB) must have been treated and cured. Patients with HCV who are currently on treatment are eligible if they have an undetectable HCV viral load.**
Section 4.2	Exclusion Criteria (Criterion 29)	Changed text as follows: **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/ patients requiring steroids within 4 weeks prior to start of study treatment will be excluded.**
5.1.3	Packaging and Drug Labeling	Removed **expiry date** from description of product labeling because this information is not required by the US FDA.
5.1.6	Dose and Administration (Declaration of RP2D)	Added the following paragraph (note: text refers to dose escalation phase): **After the SRC review of Cohort 2, the RP2D was declared as 5 mg QD, 3 weeks on/1 week off each 28-day cycle. Patients from Cohort 1 who remain in the study may have their fruquintinib dose escalated to 5 mg QD at the discretion of the investigator and with the agreement of the Sponsor.**
5.1.6	Dose and Administration (Foods and/or drugs to avoid on PK sampling days)	Added the following test to the paragraph beginning with "On the days of PK sampling:" **The patient is encouraged to avoid, or minimize the use of caffeine-containing foods or drinks, tobacco, tobacco products, and alcohol during the entire study. If the patient cannot avoid taking any of the above-listed substances during the study, it should be regarded as a habit and documented as demographic data.** Also added: **The following substances are prohibited during the study: grapefruit or grapefruit juice, illegal drug use, or excessive (>1 drink/day) alcohol use.**
Section 5.2.2.1	Dose Modification	• Changed title of Section 5.2.2.1 to read as follows: Dose

Section Number	Section Title	Description of Changes
	Sequence by Starting Dose and for General Hematologic and Non-hematologic Toxicity	Modification **Sequence by Starting Dose and** for General Hematologic and Non-Hematologic Toxicity • Added **Table 7, Dose Modification by Starting Dose**, and **Table 8, Dose Modification for Hematologic and Non-hematologic Toxicity,** Added the following text: • **Patients starting at 5 mg QD are allowed to have two 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. Patients starting at 3 mg QD are allowed to have one reduction, ie, from 3 mg QD to 2 mg QD. The lowest dose level permitted in the study is 2 mg (see Table 7).**
5.3.1	Concomitant Therapies	The following text was changed: • Patients who are receiving ~~**low-dose**~~ warfarin or Coumadin-like products should have their INR monitored and maintained at **the lower third of the therapeutic range (ie, 2.0-2.3) unless a higher INR is required for anti-thrombotic efficacy**.
Section 6.1.2	Physical Examination	Added the following text to the paragraph describing the limited physical examination: **In order to assess changes from baseline and screen for new abnormalities, the limited physical examination should assess for new or changed skin lesions, enlarged nodes, palpable masses, hepatomegaly, and splenomegaly. Patient-reported symptoms should be directed to address the symptoms.**
Synopsis Section 6.2 and Appendix A, Study Flowchart (Table and Footnote 4)	Synopsis Tumor Assessment and assessment of specific tumor markers in each phase	Specified in Section 6.2 that **the schedule of tumor assessments is** different **in the dose escalation and dose expansion phases of the study.** Added to the text of Section 6.2 and to Appendix A, Study Flowchart, **the schedule of tumor assessments in the dose escalation phase assessments and specific tumor markers in the dose escalation phase (Screening, then every 8 (±1) weeks thereafter: C3D1, C5D1, C7D1, etc).** Added to the text of Section 6.2 and to Appendix A, Study Flowchart, **the schedule of tumor assessments and specific tumor markers in the dose expansion phase (Screening, then every 8 (±1) weeks thereafter: C2D1, C3D1, C4D1, etc)** Added the following text: **Response assessments will be performed by the investigator using physical and image-based evaluation.**
Section 7.1.2	Reporting of Dose Limiting Toxicity	**The following paragraph has been added to Section 7, Safety Plan:** **7.1.2 Investigators are required to report DLT events to the Sponsor within 48 hours of first awareness. The communication must include an email that describes the event and indicates which DLT criterion was met (see Section 3.1.1 c, Definition of a Dose-Limiting Toxicity). The Sponsor's medical monitor must confirm that the event meets the DLT definition and communicate this**

Section Number	Section Title	Description of Changes
		back to the investigator by email. A notification of each DLT event will be distributed by email to all investigators shortly after confirmation. DLT events are again reviewed together with other safety data and PK data, at the SRC meeting upon completion of the DLT window of each dose cohort.
Section 7.1.8	Recording of Adverse Events (Hospitalization, Prolonged Hospitalization, or Surgery)	Changed the text to read as follows: **The investigator must document any** AE that results in hospitalization **unless the patient is hospitalized for 1 or more of the following reasons:** • **To undergo** an efficacy measurement for the study • **To undergo** a diagnostic or elective surgical procedure for a preexisting medical condition that has not changed • **To** receive scheduled therapy for the target disease of the study
Section 8.1	Analysis Populations	Added text to define the **Efficacy Analysis Set (EAS) as all patients who have received at least 1 dose of fruquintinib and have had at least 1 post-baseline tumor assessment. All efficacy endpoints will be analyzed will based on this analysis set.**
Section 8.5	Efficacy Analysis	• Added text **to identify the efficacy endpoints, including the objective response rate (ORR), duration of response (DoR), progression free survival (PFS), and overall survival (OS).** • Added text **to specify that efficacy data will be listed and summarized by dose cohort and disease type.** • Added text **to specify that ORR and DCR will be summarized with percentages and 95% exact confidence intervals. The PFS rate at 12 weeks and its 95% confidence intervals will be estimated by the Kaplan-Meier method. PFS, DoR, and OS will be summarized descriptively using Kaplan-Meier medians and quartiles. Percentage change in tumor size from baseline will be determined for patients with measurable disease at baseline and derived at each visit by the percentage change in the sum of the diameters of target lesions (TLs) compared to baseline. Best percentage change in tumor size will be summarized using descriptive statistics and presented using a waterfall plot.** • Added text to stipulate that **a best overall response of PR or CR, changes in tumor measurements must be confirmed by repeat assessments no less than 4 weeks after the criteria for response are first met.** • Added the definitions of **best overall response (BOR), disease control rate (DCR) PFS at 12 weeks, and analysis of median PFS using all data available up to the analysis cut-off point.** Details are provided in the tracked-changes version of Protocol Amendment 3.
Section 8.6	Determination of Sample Size	**Dose Escalation Phase:** Added text to specify that **the total number of patients enrolled will depend on the number of dose escalations**

Section Number	Section Title	Description of Changes
		and the need to further characterize individual cohorts treated with single-agent fruquintinib at the RP2D. **Dose Expansion Phase:** Added text to specify that the PFS rate is the primary efficacy endpoint for Cohort B (patients with refractory mCRC). Thirty patients will be recruited to have at least 25 evaluable patients in Cohort B. **The true positive PFS rate and the true negative PFS rate at 12 weeks in a cohort of at least 25 evaluable patients. Determination is based on the PFS rates in the FRESCO study.**
Appendix A	Study Flowchart **(Footnote 7)**	**Added details of physical examination to be completed as part of the tumor assessment.**
To correct various grammatical and typographical errors in the previous version of the protocol (Amendment 2) and to add the date of 3 December 2018 to the footers.		

Amendment 2, Version 2:

This amendment to protocol 2015-013-00US1 was written for the following reasons: (1) to provide updated safety information and additional guidance to the investigator on the management of severe or serious hemorrhagic events; (2) inclusion and exclusion clarifications/modifications as discovered during the conduct of the study; and (3) many minor changes were made to improve clarity and consistency within the protocol. The minor changes in the protocol text, which may include punctuation, grammar corrections or text edited for greater clarity or detail are not included in this document, however, these changes are captured in the accompanying tracked changes document. Header and/or footer changes are mentioned once but are throughout the document.

The changes in Amendment 2 are summarized in the table below.

	Prior version: v1.1	Current version: v2.0	Reason for Amendment
1	**Page 1 and page footer:** Amendment 1; Version 1.1; Date: 31 July 2017	**Page 1 and page footer:** Version 2.0; Date: 2 July 2018	Protocol version and date change. This is a major amendment; therefore, the version number increases from 1.1 to 2.0. It is also called Amendment 2.
2	**Page 3:** Sponsor Medical Monitor for the Trial: [redacted] Clinical Development and Regulatory Affair Department Hutchison MediPharma Limited [redacted]	**Page 4:** Sponsor Medical Monitor for the Trial: [redacted] Clinical Development and Regulatory Affair Department Hutchison MediPharma Limited [redacted]	Personnel change. Moved the information page after the signature page.

	Prior version: v1.1	Current version: v2.0	Reason for Amendment
3	**Page 5: Study Design** 1. Safety monitoring and evaluation for dose escalation will be carried out by the Safety Review Committee (SRC) which is comprised of the site PIs, the CRO's medical monitor, and the sponsor's medical monitor. 2. If 2 or more patients at the 5 mg QD dose level experience DLT, study will be terminated and the expansion phase of the study will not be conducted.	**Page 6: Study Design** 1. Safety monitoring and evaluation for dose escalation will be carried out by the Safety Review Committee (SRC) upon completion of the DLT observation period of each cohort. The SRC is comprised of the site principal investigators (PIs), a PK scientist, the CRO's medical monitor and the sponsor's medical team member, safety scientist. Adverse event (AE) and PK data will be evaluated together when determining fruquintinib dose escalation with reference to fruquintinib PK and safety characteristics in Chinese patients in trials conducted previously. 2. If 2 or more patients at the 5 mg QD dose level experience DLT, the SRCwill discuss the next dose	1. Clarification as to the timing of the SRC review. Update to include a PK scientist and safety scientist into SRC membership. Delete duplicated information and combine to a paragraph. 2. SRC discussion instead of terminating the study, if 2 or more DLTs happen at 5 the mg QD dose level.
4	**Page 7: Study Treatment** …until disease progression, death, intolerable toxic reaction, or at investigator's discretion that the patient can no longer benefit from the study treatment.	**Page 7: Study Treatment** … until disease progression, death, intolerable toxicities, or at investigator's discretion that the patient can no longer benefit from the study drug.	Consistency in the use of the term "study drug" as an alternative to the term "fruquintinib." Other alternative terms (e.g., "study treatment," "study medication" or "IP") are removed.
5	**Page 7-8 and 36: Inclusion Criteria** 1. 18-75 years of age 2. Body weight ≥ 45kg 4. … the last dose of prior systemic anti-cancer therapy must have been administered ≥ 4 weeks prior to initiation of study treatment, and for whom no effective therapy or standard of care exists. 5. Have measurable disease per RECIST Version 1.1 (expansion phase only)	**Page 7-8 and 35: Inclusion Criteria** 1. ≥ 18 years of age; 2. Body weight ≥ 40kg; 4. … the last dose of prior systemic anti-cancer therapy must have been administered ≥ 4 weeks (unless specifically noted in exclusion criteria) prior to initiation of study drug, and for whom no effective therapy or standard of care exists. Have measurable disease per RECIST Version 1.1 (expansion phase only). Lesions that received radiotherapy are not measurable per RECIST v 1.1.	1. Remove the upper age limit to include adult subjects of any age that otherwise meet all inclusion no exclusion criteria. . 2. Reduce lower limit of body weight for inclusion 4. Clarification of prior anti-cancer therapy washout: ⩾ 4 weeks with reference to exceptions in exclusion criteria Clarification of RECIST v. 1.1 criteria for lesions treated with radiotherapy.

	Prior version: v1.1	Current version: v2.0	Reason for Amendment
6	**Page 8 and 37: Exclusion Criteria** 1.	**Page 8 and 36: Exclusion Criteria** 1. Blood transfusion within 1 week before enrollment for the purpose of increasing the likelihood of eligibility is not allowed;	1. Clarification to exclude patients with blood transfusion during the week before enrollment to avoid a temporary measure to meet the minimum hemoglobin concentration (9.0 g/dL).
7	**Page 8 and 37: Exclusion Criteria** 5. Serum creatinine clearance < 60 mL/min;	**Page 8 and 36: Exclusion Criteria** 5. 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 Cockraft-Gault equation as follows: Clcr (ml/min) = [(140 - age) x (weight in kg) x 0.85 if female] ÷ [72 x (serum creatinine in mg/dL)].	5. Specifies the methods by which creatinine clearance can be measured or estimated and indicates the upper limit of serum creatinine permitted at screening.
8	**Page 8 and 37: Exclusion Criteria** 6. Urine dipstick for proteinuria > 2 +. Patients discovered to have ≥ 1 + proteinuria on dipstick urinalysis at baseline should undergo a 24-hour urine collection and must demonstrate ≤ 1 g of protein in 24 hours;	**Page 8 and 36: Exclusion Criteria** 6. Urine dipstick protein ≥2+ and 24-hour urine protein ≥1.0 g/24-h. Patients with greater than 1+ proteinuria on urinalysis must undergo a 24-hour urine collection;	6. Clarification of exclusion criteria for proteinuria by semi-quantitative (urinalysis) and quantitative (24-hour urine) methods.
9	**Page 8 and 37: Exclusion Criteria** 8. International Normalized Ratio (INR) > 2 or activated partial thromboplastin time (aPTT) > 1.5 ULN, except if the patient is currently receiving or intending to receive anti-coagulants for therapeutic purposes (prophylactic use is allowed).	**Page 9 and 36: Exclusion Criteria** 8. International Normalized Ratio (INR) >1.5 or activated partial thromboplastin time (aPTT) > 1.5 × ULN.	8. Decrease the upper limit of INR at screening from 2.0 to 1.5. Clarification of indications for anti-thrombotic therapy permitted at study entry. Both measures are to reduce the risk of hemorrhagic events on study.
10	**Page 9 and 37-38: Exclusion Criteria** 9.	**Page 9 and 37: Exclusion Criteria** 9. History of perforation or fistulas;	9. Exclusions for GI disorders broadened to include patients with a history of GI perforation or fistulas.

	Prior version: v1.1	Current version: v2.0	Reason for Amendment
11	**Exclusion Criteria** This criterion was added.	**Page 9 and 37: Exclusion Criteria** 16. Patients who have ever received a VEGFR inhibitor.	16. Such drugs are excluded because they target the same molecule as fruquintinib. Patients treated with VEGFR inhibitors previously are unlikely to respond to fruquintinib
12	**Page 9 and 38: Exclusion Criteria** 16. Systemic anti-neoplastic therapies within 4 weeks prior to the initiation of investigational treatment, including chemotherapy, radical radiotherapy, hormonotherapy, biotherapy and immunotherapy;	**Page 9 and 37: Exclusion Criteria** 17. Systemic anti-neoplastic therapies (except for those described in Exclusion 18) or other investigational therapies within 4 weeks prior to the first dose of study drug, including chemotherapy, radical radiotherapy, hormonotherapy, biotherapy and immunotherapy;	Note: Original Exclusion Criteria #16 is now #17. 17. Now includes a reference to exceptions to the exclusion criteria based on prior systemic anticancer therapy.
13	**Exclusion Criteria** This criterion was added.	**Page 10 and 37: Exclusion Criteria** 18. Systemic small molecule targeted therapies (e.g., tyrosine kinase inhibitors) within 5 half-lives or 4 weeks (whichever is shorter) prior to the first dose of study drug;	Note: Original Exclusion Criteria #18 is now #21 due to added criteria. 18. Small molecule tyrosine kinase inhibitors are an exception to the standard 4-week washout period for prior systemic anti-cancer therapies. Tyrosine kinase inhibitors usually wash out in < 2 weeks; 5 half-lives is expected to be < 4 weeks.
14	**Exclusion Criteria** This criterion was added.	**Page 9 and 37: Exclusion Criteria** 20. Brachytherapy (i.e., implantation of radioactive seeds) within 60 days prior to the first dose of study drug.	20. This criterion is added because of the potentially increased risk of severe or serious hemorrhage after brachytherapy.
15	**Page 9 and 38: Exclusion Criteria** 18. Use of strong inducers or inhibitors of CYP3A4 within 2 weeks before the first dose of study treatment (3 weeks for St John's Wort). See Appendix F for a list of such medications	**Page 10 and 37: Exclusion Criteria** 21. Use of strong inducers or inhibitors of CYP3A4 within 2 weeks before the first dose of study drug (3 weeks for St John's Wort); P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) substrate within 2 weeks before the first dose of study drug. See Appendix F for a list of such medications.	2. Drugs affected by P-gp and BCRP transporters are added to the list of excluded drugs because of the potential for fruquintinib increasing the exposure to the drugs by affecting the absorption and disposition of the drugs.

	Prior version: v1.1	Current version: v2.0	Reason for Amendment
16	**Page 9 and 38: Exclusion Criteria** 19. Surgery prior to enrollment within 28 days prior to the initiation of study treatment or unhealed surgical incision;	**Page 10 and 38: Exclusion Criteria** 22. Surgery or invasive procedure (i.e., procedure that includes a biopsy) within 60 days prior to the first dose of study drug or unhealed surgical incision;	Note: Original Exclusion Criteria #19 is now #21 due to added criteria. 21. Invasive procedures with biopsy are added to surgery as exclusions; the duration is set at 60 days for invasive procedures and extended to 60 days for surgery. These exclusions are to reduce the risk of severe or serious hemorrhagic events while on study drug.
17	**Page 10 and 38: Exclusion Criteria** 21. Known human immunodeficiency virus (HIV), hepatitis A, B or C infection except for fully recovered Hepatitis A. Previous medical history of hepatitis B virus (HBV) infection regardless of drug control, HBV DNA ≥104 ×copy number or ≥2000 IU/mL;	**Page 10 and 38: Exclusion Criteria** 24. Known human immunodeficiency virus (HIV) infection; Known clinically significant history of liver disease, including cirrhosis or known hepatitis A, B or C infection except for fully recovered Hepatitis A. Previous medical history of hepatitis B virus (HBV) infection regardless of drug control, HBV DNA ≥104 × copy number or ≥2000 IU/mL; current alcohol abuse;	Exclusion criteria were broken up into two separate criteria
18	**Exclusion Criteria** This criterion was added.	**Page 10 and 38: Exclusion Criteria** 27. Tumor invades large vascular structure, e.g., pulmonary artery, superior or inferior vena cava.	27. Exclusion added because of the increased risk of severe (Grade ≥ 3) or serious (SAE) hemorrhage.
19	**Page 10 and 38: Exclusion Criteria** 25. Central nervous system (CNS) metastatic disease or prior cerebral metastasis;	**Page 10 and 38: Exclusion Criteria** 29. History or presence of Central nervous system (CNS) metastatic disease;	Note: Original Exclusion Criteria #25 is now #29 due to added criteria. 29. Clarifies that either current or past CNS metastatic disease is an exclusion.
20	**Exclusion Criteria** This criterion was added.	**Page 10 and 38: Exclusion Criteria** 30. No other malignancy, except for non-melanoma skin cancer, during the 5 years prior to screening;	30. More than one invasive malignancy in the same patient could lead to confusion about which disease is active and interfere with efficacy assessment.

	Prior version: v1.1	Current version: v2.0	Reason for Amendment
21	**Page 10 and 38: Exclusion Criteria** 27. Received investigational treatment in another clinical study within 4 weeks prior to the initiation of investigational treatment;	This criterion was deleted.	This was deleted, and more specific criteria were added for clarification (see #16,17 & 18).
22	**Exclusion Criteria** This criterion was added.	**Page 10 and 38: Exclusion Criteria** 33. Known hypersensitivity to fruquintinib or any of its excipients.	33. This was erroneously omitted in prior versions of the protocol.
23	**Page 11: Statistical Analysis** All variables obtained at each observation time point will be summarized descriptively by dose cohort, except for certain time points for which a description is not required by the protocol. For continuous variables, summary statistics will include the number of patients (n), mean, standard deviation (SD), minimum and maximum. For categorical variables, summary statistics will include the number and percentage of patients in each category.	**Page 11: Statistical Analysis** By-subject listings will be created for important variables from each CRF module. Summary tables for continuous variables will contain at least the following statistics: N (number in population), mean, standard deviation, median, minimum, and maximum. Summary tables for categorical variables will include: N, n, and percentage.	The revised description clarified only important variables rather than all variables will be listed in by-subject listings. For continuous variables, an additional statistic "median" as added to summary statistics. For categorical variables, both total N and non-missing n will be presented
24	**Page 12: Safety Assessment** AE severity will be graded according to the NCI CTCAE (version 4.03). AEs will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). The frequency of treatment-emergent AEs (TEAEs) will be summarized by MedDRA System Organ Class (SOC) as well as Preferred Term (PT). The incidence of TEAEs, SAEs, AEs of special interest, AEs leading to dose interruption, reduction, or treatment discontinuation will be presented by a system organ class and preferred term; by relationship to investigational product and by toxicity grade for each dose level in both study phases.	**Page 12: Safety Assessment** The severity of all AEs will be graded by the investigator according to the NCI CTCAE, version 4.03. AEs will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Treatment- emergent AEs (TEAEs) will be classified by MedDRA System Organ Class (SOC) and specified by Preferred Term (PT). The incidence of TEAEs, SAEs, AEs of special interest, AEs leading to dose interruption, reduction, or study drug discontinuation will be summarized for each dose level in both study phases. For the laboratory assessments, such as hematological, serum biochemistry, and urine data will be programmatically graded according to CTCAE severity grade. Summary tables will be	This section was re- written to specify that the investigator grades the severity of AEs The description of how laboratory assessments will be handled is presented in more detail, including those parameters where a CTCAE scale does not exist. This was not included in such detail previously.

	Prior version: v1.1	Current version: v2.0	Reason for Amendment
	Shifts in laboratory test results will be summarized hierarchically according to the NCI CTCAE (version 4.03) grade or normal ranges if no CTCAE grade is provided for a particular analyte. When abnormal laboratory results are counted at the patient level, the worst value reported during study treatment will be chosen.	presented to show the number of subjects by CTCAE severity grade with corresponding percentages. For parameters for which a CTCAE scale does not exist, the frequency of subjects with values below, within, and above the normal ranges will be summarized. Shift tables for hematology and serum biochemistry will also be presented showing change in CTCAE severity grade from baseline to worst grade post-baseline.	
25	**Page 13: Efficacy** All patients who receive at least one dose of fruquintinib and have at least one post-baseline tumor assessment will be included in the evaluable for respone set (ERS). The overall response rate (ORR) and disease control rate (DCR) will be summarized by dose cohort with percentages and 95% exact confidence intervals for ERS. If the sample size permits, duration of response in the ERS and progression free survival (PFS) in the SAS will be summarized by the dose cohort descriptively using Kaplan-Meier medians and quartiles.	**Page 12-13: Efficacy** All SAS patients who have at least one post-baseline tumor assessment will be included into the response evaluable analysis set (REAS). The overall response rate (ORR) and disease control rate (DCR) will be summarized by dose cohort with percentages and 95% exact confidence intervals for REAS. If sample size permits, PFS and DoR will be summarized by dose cohort descriptively using Kaplan- Meier medians and quartiles. Percentage change in tumor size will be determined for patients with measurable disease at baseline and is derived at each visit by the percentage change in the sum of the diameters of TLs compared to baseline.	This section was edited for grammar and content. The patient population REAS was defined in a simpler way when treating it as a subset of SAS. The change in tumor size for those patients with measurable baseline disease will be characterized to provide a metric by which to measure possible efficacy.
26		**Page 18-19: Abbreviations and Definitions** The following were added to this table: ALP, APTT, BUN, DBil, EC, FDG-PET, IEC- IRB, INR, CTCAE, PFS, PT, RECIST, TBil, TLs, TSH, ULN, VEGF, VEGRF	These abbreviations and definitions are added in this amendment.
27	**Page 33: Section 3.1 Description of the study.** The study is comprised of 2 phases	**Page 31: Section 3.1 Description of the study.** The study is comprised of 2 phases: the Safety run-in phase and the Expansion phase.	Elaboration of the names of the two phases.

	Prior version: v1.1	Current version: v2.0	Reason for Amendment
28	**Page 33: Section 3.1, 5th bullet.** • If 2 or … will not be conducted. If 2 or more patients at the 5mg QD dose level experience DLT, the study will be terminated the expansion phase of the study will not be conducted.	**Page 31: Section 3.1, 5th bullet.** If 2 or … will not be conducted. If 2 or more patients at the 5mg QD dose level experience DLT, the SRC will discuss the next dose level.	Verbiage was added to indicate the next step in the study if the conditions in the 5th bullet item are met. Previously it stated the study will end, which is not correct the next step will be discussed by the SRC.
29	**Page 34: Section 3.1, 1th bullet on the page.** • At the discretion of the investigators, patients who have completed the DLT observational window (Cycle 1, Days 1-28) and are deemed to be benefiting from fruquintinib treatment may continue fruquintinib treatment at the assigned dose until disease progression, death, or intolerable toxicity.	**Page 32: Section 3.1.** Bullet deleted.	This bullet point duplicates bullet point 10 on page 42; therefore, it is deleted.
30	**Page 35: Section 3.3** It is planned to have about 3 sites to participate in the study.	**Page 34: Section 3.3** It is planned to have up to 5 sites to participate in the study.	Sponsor may increase the number of participating sites to 5 if enrollment targets are not met.
31	**Page 35: Section 3.4, Safety Review Committee** safety data review and to determine the next step for dose escalation or de- escalation	**Page 34: Section 3.4, Safety Review Committee** …safety data review and to determine the next step for dose escalation or dose expansion.	There is no “de- escalation” of dose in the study. The term is corrected to “dose expansion.”
32	**Page 35: Section 3.4, Safety Review Committee** Regular safety data review will be conducted at pre- defined intervals and at the end of the first treatment cycle of a dose cohort.	**Page 34: Section 3.4, Safety Review Committee** Regular safety data review will be conducted at pre- defined intervals and at the end of the DLT observation period (i.e., first treatment cycle) of a dose cohort.	Clarification that safety data review should be done at the end of the DLT observation period for all patients in a particular dose cohort.
33	**Page 39: Section 5.1.4 Drug Storage** … under appropriate storage conditions.	**Page 39: Section 5.1.4 Drug Storage** … under appropriate storage conditions (10-30 º C).	The temperature range for drug storage was added for completeness.

	Prior version: v1.1	Current version: v2.0	Reason for Amendment
34	**Page 40: Section 5.1.5 Drug Accountability, 2nd paragraph** …standard operating procedure or returned to Hutchison MediPharma with appropriate documentation…	**Page 39: Section 5.1.5 Drug Accountability, 2nd paragraph** …standard operating procedure or returned to Hutchison MediPharma or a Hutchison identified entity with appropriate documentation…	Verbiage added to indicate that study drug may be returned either directly to an HMP employee, or to a person or organization designated by Hutchison to receive drug for destruction.
35	**Page 40: Section 5.1.6 Dose and Administration, 3rd paragraph** On the days of PK sampling, patients should avoid high-fat meals for the entire day and avoid consumption of any liquids other than water (up to 200ml) within the period of 1 hour before and after drug administration. No caffeine containing foods or drinks, no grapefruit or grapefruit juice, or recreational drugs will be allowed during the PK assessment period (Cycle 1).	**Page 40: Section 5.1.6 Dose and Administration, 3rd paragraph** On the days of PK sampling, patients should avoid high-fat meals for the entire day and avoid consumption of any liquids other than water (up to 200ml) within 1 hour before or after drug administration. No grapefruit, grapefruit juice, or recreational drugs will be allowed during the PK assessment period (Cycle 1), and no caffeine-containing foods or drinks may be taken on the days that PK samples are drawn.	It was clarified that caffeine containing foods should be avoided only on days PK samples are to be drawn. Previously it was indicated that no caffeine was to be consumed during the entire 1st cycle which was incorrect.
36	**Page 41: Section 5.2.2.1 Dose Modification for general….4th & 5th sentence.** A patient is allowed to have dose reduction no more than twice, i.e., from 3mg QD to 2 mg QD for patients taking the 3mg QD regimen, and from 5mg QD to 4 mg QD for patients escalated to 5 mg QD. Patients that were reduced from 5mg to 4mg QD can have a second dose reduction to 3mg QD.	**Page 41: Section 5.2.2.1 Dose Modification for general…., 4th & 5th sentence.** A patient is allowed to have dose reduction no more than twice, i.e., from 3mg QD to 2 mg QD for patients taking 3mg QD regimen, and from 5mg QD to 4 mg QD for patients taking 5 mg QD regimen. Patients that were reduced from 5mg to 4mg QD can have a second dose reduction to 3mg QD. Patients taking 3mg QD regimen can only have dose reduction once (from 3mg to 2mg QD).	Dose reduction directions for subjects with toxicities are clarified. Directions for dose reduction for patients receiving the 3 mg dose are now included.
37	**Page 42: Section 5.2.2.2 Dose Modification and Treatment….,** Title of section now reads: Dose Modification and Treatment Suggestions for selected AEs	**Page 41: Section 5.2.2.2 Dose Modification and Treatment….,** Title of section now reads: Dose Modification and Treatment Suggestions for selected identified risks	The term “identified risks” is more accurate than “selected AEs”.

	Prior version: v1.1	Current version: v2.0	Reason for Amendment
38	**Page 42-43, Table 8, Dose Modification for Proteinuria** No foot note	**Page 42, Table 8, Dose Modification for Proteinuria[a]** The following note was added to the end of the table: a: If protein ⩾ 2+ during the period of study treatment, 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.	The conditions under which a 24-hour urine test should be conducted are clarified.
39	**Page 43, Table 9, Dose Modification for Hypertension, AE Grading and Definitions, Grade 3** Grade 3: SBP ⩾ 160mm Hg or DBP ⩾ 100mm Hg; or symptomatic increase in DBP by >20mmHg	**Page 43, Table 9, Dose Modification for Hypertension, AE Grading and Definitions, Grade 3** Grade 3: SBP ⩾ 160mmHg or DBP ⩾ 100mmHg; or more than one drug or more intensive therapy are used	Another criterion is added to define a Grade 3 AE of hypertension, i.e. more than one drug or more intensive therapy are used to manage the AE.
40	**Page 44, Table 11, Dose Adjustment for Hemorrahage at any site.**	**Page 44, Table 11, Dose Adjustment for Hemorrahage at any site.** The following notes were added to the end of the table for Grade 3 events: a: Refer to Appendix J for clinical management of severe or serious hemorrhage. b: 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 (See section 5.3.1 Concomitant therapy).	Elaboration of instructions is added to guide the investigator on the management of hemorrhagic AEs, which are associated with this class of drugs (VEGF or VEGFR inhibitors)

	Prior version: v1.1	Current version: v2.0	Reason for Amendment
41	**Page 45, Section 5.3.1 Concomitant Therapies, 1st paragraph.** Last sentence of the section was moved to the end of the first paragraph.	**Page 45, Section 5.3.1 Concomitant Therapies, 1st paragraph.** The following sentence was added to the end of the paragraph: All concomitant medications should be reported to the investigator and recorded on the appropriate CRF.	This sentence was added to the 1st paragraph and deleted from below.
42	**Page 45, Section 5.3.1 Concomitant Therapies, 1st bullet.** • Patients who are receiving low-dose warfarin or coumadin-like products should have their INR monitored and maintained at ≤1.5	**Page 45, Section 5.3.1 Concomitant Therapies, 1st bullet.** • Patients who are receiving low-dose warfarin or coumadin-like products should have their INR monitored and maintained at ≤2.0	Upper limit of INR changed to ≤2.0 for prophylactic use of anticoagulation, which is at the lower end of the therapeutic range for prevention and treatment of thrombosis, in order to minimize the risk of hemorrhage.
43	**Page 46, Section 5.3.1 Concomitant Therapies, 1st paragraph.**	**Page 46, Section 5.3.1 Concomitant Therapies, 1st paragraph.** The investigator should closely monitor patients receiving anti-platelet and/or anti-thrombotic drugs with INR, aPTT and platelet count 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 (See Appendix J for additional information on the clinical management of severe or serious hemorrhagic AEs).	This paragraph was added to instruct investigators to closely monitor coagulation-related lab results and consider whether anti-platelet and/or anti-thrombotic concomitant medications should be continued in the event of Grade ≥2 hemorrhagic events at any site. This is designed to mitigate the risk of severe (Grade ≥ 3) and serious (SAEs) hemorrhagic AEs
44	**Page 47, Section 6.1, Safety Assessments, Vital Signs Assessment, 1st paragraph, 3rd sentence.** For patients with a baseline history of antihypertensive medications, blood pressure should be monitored at 3 hours (±2 hours) after the daily doses of anti-hypertensive medication.	**Page 47, Section 6.1, Safety Assessments, Vital Signs Assessment, 1st paragraph, 3rd sentence.** For patients with a baseline history of hypertension, or those who develop hypertension during the study, blood pressure should be monitored daily by the patient at home, at 3 hours (±2 hours) after the daily doses of anti-hypertensive medication, and the results recorded in a blood pressure diary. Patients monitoring their blood pressure should bring their	Clarification that patients with hypertension must monitor their blood pressure at home and keep a diary of the results.

	Prior version: v1.1	Current version: v2.0	Reason for Amendment
		diary to each study visit.	
45	**Page 48, Cardiac Monitoring, 1st paragraph, 1st sentence.** Left ventricular ejection fraction (LVEF) assessed via ultrasonic cardiogram and 12-lead.	**Page 48, Cardiac Monitoring, 1st paragraph, 1st sentence.** Left ventricular ejection fraction (LVEF) assessed via echocardiogram and 12- lead…	The more appropriate term in the U.S. for this cardiac imaging modality is "echocardiogram."
46	**Page 48, Section 6.2 Efficacy Assessment** The baseline tumor assessment can be comleted within 28 days prior to first administration of study drug. All measurable and evaluable lesions should be assessed and documented at this visit, using physical…	**Page 49, Section 6.2 Efficacy Assessment** The section was titled "Tumor Assessment" and the window of ± 7 days was added. 1st sentence of the 1st paragraph now reads: The baseline tumor assessment can be completed within 28 days prior to first administration of study drug. All measurable and evaluable lesions should be assessed and documented at this visit ± 7 days, using physical…	The window of assessment was added for procedural clarification.
47	**Page 61, Section 6.2 Efficacy Assessment, paragraph 4** Disease status will be assessed using RECIST version 1.1 (see Appendix C). At the investigator's discretion, other methods of assessment of measurable disease as per RECIST may be used. Includes assessment of PSA levels for patients who have prostate cancer at each cycle. Includes assessment of CA-125 levels for patients who have ovarian cancer at each cycle. The same imaging procedure used to define measurable lesions at baseline must be used throughout the study for each patient.	**Page 49, Section 6.2 Efficacy Assessment, now paragraphs 4&5** Disease status will be assessed using RECIST version 1.1 (see Appendix C). The same imaging procedure used to define measurable lesions at baseline must be used throughout the study for each patient. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST may be used. Examples of other assessment methods include tumor markers, such as PSA and CA-125 levels for patients with prostate and ovarian cancer, respectively. However, tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete response.	Paragraph 4 was broken up into two separate paragraphs. It was clarified that tumor assessment methods in addition to standard imaging, e.g., tumor markers, may be used as part of the assessment, as described in RECIST v 1.1. It is clarified that tumor markers alone cannot be used to assess a tumor response, and additional detail is provided to describe how tumor markers can be considered in the overall assessment of tumor responses.

	Prior version: v1.1	Current version: v2.0	Reason for Amendment
48	**Page 50, Section 7.1.1 Adverse Events and Serious Adverse Events (SAEs)**	**Page 51, Section 7.1.1** The section was renamed to **7.1.1 Adverse Events** and broken up to distinguish between SAEs and AEs. The following section was added: **7.1.2 SAEs and other Expedited Reporting of Adverse Events.** Section 7.1.2. was subdivided into the following sections: **7.1.2.1 SAE definition**, **7.1.2.2 Potential Drug-Induced Liver Injury (DILI)**, and **7.1.2.3 Severe Hemorrhagic Events**	This section was divided to improve the organization of content, and to add a specific section for Severe Hemorrhagic Events.
49	**Page 50-51, Section 7.1.1, bullet list: A serious adverse event is any AE that is any of the following:**	**Page 51, 7.1.2.1 SAE definition** The following bullet point was added to the end of the list: If AEs meet any of the above serious criteria, the AEs should be reported to sponsor as an SAE no more than 24 hours after awareness of the SAE.	The bullet point was added to specify the time window for reporting SAEs to the Sponsor.
50	**Not applicable, section added.**	**Page 52, 7.1.2.3 Severe Hemorrhagic Events** When hemorrhagic events meet NCI CTCAE $\geqslant$ grade 3 severity (regardless of whether it is serious or non- serious), the event should be reported to the sponsor no more than 24 hours after first awareness of the event. The management of severe or serious hemorrhagic events will be conducted according to Appendix J.	This section instructs investigators to report any hemorrhagic event with Grade $\geqslant$ 3, regardless of whether it is serious or non-serious, within the same time window as all SAEs.
51	**Page 52, Section 7.1.3 Adverse Events Reporting Period.** After initiation of study medications, all AEs and SAEs regardless of attribution will be collected until 30 days following the last dose of study treatment or a new treatment of anti-tumor therapy, whichever is earlier.	**Page 53, Section 7.1.4 Adverse Events Reporting Period.** 2nd paragraph, first sentence: After initiation of study drug, all AEs and SAEs (including non-serious potential DILI and non-serious severe hemorrhagic events), regardless of attribution….	This modification specifies that non-serious drug-induced liver injury (DILI) AEs and non- serious severe (grade $\geq$ 3) hemorrhagic events are reported according to the same schedule as SAEs.

	Prior version: v1.1	Current version: v2.0	Reason for Amendment
52	**Page 55, Pregnancy section, 1st paragraph, 2nd sentence.** The investigator should report all pregnancies within 24 hours to the sponsor.	**Page 56, Pregnancy section, 1st paragraph, 2nd sentence.** The investigator should report all pregnancies within 24 hours to the sponsor (the reporting period for pregnancy continues up to 30 days after completion of the study drug).	Clarification of the duration of the reporting period for pregnancy.
53	**Page 55, Section 7.2 Expedited Reporting Requirements for Serious Adverse Events** · Serious adverse events · Potential Drug-Induced Liver Injury regardless of seriousness · Pregnancies SAEs occurring beyond the abovementioned time limit, if considered related to the study investigational drug, should also be reported to the sponsor.	**Page 57, 7.2 Expedited Reporting Requirements, bullet points clarified and added:** · Serious adverse events (from informed consent to 30 days following the last dose of study drug or a new treatment of anti-tumor therapy) · Potential Drug-Induced Liver Injury regardless of seriousness • Severe hemorrhagic events (NCI CTCAE grade ≥ 3), regardless of seriousness · Pregnancies SAEs occurring beyond the abovementioned time limit (30 days after the discontinuation of the study drug), if considered related	The group of AEs for which Expedited Reporting is required is expanded beyond SAEs and pregnancies to include non-serious DILI events, and non-serious severe (grade ≥ 3) hemorrhagic events. In addition, the duration of time after the last dose of study drug is extended to 30 days (if not related) or longer than 30 days (if related) for reporting all of these events. .
54	**Page 56, Section 8, Statistical Analysis.** The final analysis will be based on patient data collected through study discontinuation or study termination. All summaries will be presented by assigned dose level.	**Page 58, Section 8, Statistical Analysis. The introduction to this section was rewritten:** All statistical analysis will be performed under the direction of Hutchison MediPharma personnel. Any data analysis carried out independently by the investigator should be submitted to Hutchison MediPharma prior to publication or presentation. The final analysis of study data will be based on all patient data up to the time when either all patients have discontinued the study or the study has been terminated. Details of the statistical analysis and data reporting will be provided in the Statistical Analysis Plan (SAP) document finalized prior to database lock. Data will be summarized using descriptive statistics (continuous	The introduction to this section was rewritten to specify that all statistical analyses should be performed under the direction of Hutchison MediPharma personnel. In addition, more information is provided on how the data will be summarized and finalized, on the requirement of completion of the SAP before database lock, and on the description of how missing data will be treated in the statistical analyses.

	Prior version: v1.1	Current version: v2.0	Reason for Amendment
		data) and/or contingency tables (categorical data) for demographic and baseline characteristics, efficacy measurements, safety measurements, and pharmacokinetic measurements. Information regarding compliance with efficacy testing and data missingness will be documented. Graphical techniques (eg, waterfall plots, Kaplain-Meier curves) will be used when such methods are appropriate and informative. The baseline value used in each analysis will be the last (most recent) pre-treatment value. Analyses will be based upon the observed data unless methods for handling missing data are specified. Analyses will be performed using SAS® (Version 9.1 or higher).	
55	**Page 56, Section 8.1, Analysis Populations. 3rd bullet.** Evaluable for Response Set (ERS): This population includes all dosed tpatients who have measurable tumor lesions at baseline. Tumor evaluation related endpoints other than PFS will be summarized based on this specific population.	**Page 59, Section 8.1, Analysis Populations. 3rd bullet.** Response Evaluable Analysis Set (REAS): All SAS patients who have at least one post-baseline tumor assessment will be included in the REAS. Tumor evaluation related endpoints will be summarized based on this analysis set.	A better description of the REAS was provided. It was made clear that all patients that have at least one post baseline assessment will be included. This was not clear previously.
56	**Page 56, Section 8.2, Analysis of the Conduct of the Study. This entire section was rewritten.** Enrollment, major protocol violations, and discontinuations from the study will be summarized by dose level. Demographic and baseline characteristics, such as age, sex, race/ethnicity, weight, type of malignancy, duration of malignancy, site of metastatic disease, and baseline ECOG performance status, will be summarized	**Page 59, Section 8.2, Analysis of the Conduct of the Study. This entire section was rewritten.** A patient listing of all treated patients will be generated to describe site, subject number, screening date, first dosing date, duration of study treatment, analysis set in which the patient included and disposition. In the patient disposition listing, reason for study drug discontinuation will be included. A table will be created to summarize these categories in terms of number and percent for each of the	A more detailed description of this section was provided with a more accurate description of listings to be generated for the study conduct analysis.

	Prior version: v1.1	Current version: v2.0	Reason for Amendment
	using means, standard deviations, medians, and ranges for continuous variables, and proportions for categorical variables. All summaries will be presented overall and by dose level. Study drug administration data will be listed by dose level, and any dose modifications will be flagged. Means and standard deviations will be used to summarize the total dose of fruquintinib received.	analysis set defined above. Patient demographics and baseline characteristics, such as age, sex, race/ethnicity, weight, type of malignancy, duration of malignancy, site of metastatic disease, and baseline ECOG performance status, will be listed and summarized. All summaries will be presented overall and by dose level. Major protocol deviations related to study inclusion or exclusion criteria, conduct of the trial, subject management, or subject assessment will be listed. Study drug administration data will be listed by dose level, and any dose modifications will be flagged. Descriptive information will be provided regarding number of initialized cycles, total days of study drug exposure, actual days of study drug taken, cumulative dose of study drug, dose intensity and relative dose intensity and the number and timing of prescribed dose reductions and interruptions.	
57	**Page 57, Section 8.3, Safety Analysis.** AE severity will be graded according to the NCI CTCAE (version 4.03). AEs will be coded with Medical Dictionary for Drug Regulatory Activities (MedDRA). The frequency of AEs will be summarized by MedDRA System Organ Class (SOC) as well as Preferred Term (PT). The incidence of TEAEs, SAEs, AEs of special interest, AEs leading to dose interruption, reduction, or treatment discontinuation will be presented by a system organ class and preferred term; by relationship to investigational product and by toxicity grade for each dose level in both	**Page 59, Section 8.3, Safety Analysis. Paragraph 2 and 3.** AE severity will be graded by the investigator according to the NCI CTCAE (version 4.03). If a CTCAE criterion does not exist, the grade corresponding to the appropriate adjective will be used by the investigator to describe the maximum intensity of the adverse event: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life threatening), or Grade 5 (fatal). All AEs will be coded with Medical Dictionary for Drug Regulatory Activities (MedDRA). All AEs will be listed. The focus of safety data summarization will be on treatment-emergent adverse events (TEAEs), which are defined as adverse event that	Paragraph 2 of the original section was revised. The paragraph was split into two paragraphs and edited for content. The 2nd paragraph now includes the process by which investigators are to grade AEs in the event there is not a CTCAE criterion for the AE intensity observed. Details regarding AE listings and TEAEs were provided and edited for content.

	Prior version: v1.1	Current version: v2.0	Reason for Amendment
	study phases. Changes in laboratory data will be summarized by grade using the NCI CTCAE, v4.03. When counting abnormal laboratory results at patient level, the worst value during study treatment will be chosen.	occurs or worsen in the period extending from the first dose of study drug to 30 days after the last dose of study drug in this study. TEAEs will be summarized as the number of patients and corresponding percentage by MedDRA System Organ Class (SOC) as well as Preferred Term (PT).	
58	**Page 58, Section 8.5, Tumor Assessment** Tumor-assessment related endpoints, ORR, DCR and DoR will be summarized based on ERS. PFS will be summarized for SAS. Objective Response Rate (ORR) The objective response rate (ORR) will be estimated only for patients with disease that is measurable by RECIST (v.1.1, see Appendix C). The ORR is defined as the number (%) of patients with at least one response of CR or PR at a study visit that is confirmed at least 4 weeks later. Data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR. However, any CR or PR which occurs after the patient has received an anticancer therapy other than fruquintinib anticancer will not be included in numerator of the ORR calculation. Progression Free Survival (PFS) Progression free survival (PFS) is defined as the time from date of first dosing until the date of an objective disease progression as defined by RECIST 1.1 or death (by any cause in the absence of progression) regardless of whether the patient withdraws from the fruquintinib therapy. Patients	**Page 61, Section 8.5, Tumor Assessment** Objective Response Rate (ORR) The objective response rate (ORR) is defined as the percentage of patients with at least one best overall response of CR or PR according to RECIST 1.1. ORR will be calculated based on the REAS. Proportions of subjects with ORR will be presented by dose group along with exact confidence intervals. Progression Free Survival (PFS) Progression free survival (PFS) is defined as the time from date of first dose of study drug until the date of an objective disease progression as defined by RECIST 1.1 or death for any reason. Patients who have not progressed or died at the time of analysis will be censored at the time of the last tumor assessment. The censoring rule for PFS will be detailed in the Statistical Analysis Plan (SAP). PFS will be summarized by dose cohort descriptively using Kaplan-Meier medians and quartiles. Duration of Response (DoR) Duration of response (DoR) is defined as the time from date of the first objective response complete response (CR) or partial response (PR), which evever comes first, until the occurene of documented disease progression or of death in the absence of disease progression. If a patient does not progress following a response, then the	This section was edited and rewritten for clarity and simplification. In addition, provided more details on the statistical analysis methods for the endpoints.

	Prior version: v1.1	Current version: v2.0	Reason for Amendment
	who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment. However, if the patient progresses or dies after two or more consecutive missed tumor assessment visits, the patient will be censored at the time of the latest evaluable RECIST assessment. If the patient has no evaluable tumor assessment visits after first dose of study treatment or does not have evaluable baseline tumor assessment data the patient will be censored on the date of first dosing unless they die within two tumor assessment visits of baseline. Patients who start new anticancer treatment initiated prior to documented disease progression or death on study, will be censored at the date of last evaluable tumor assessment prior to or on date of new anticancer treatment. Duration of Response (DoR) Duration of response (DoR) will be defined as the time from the date of the first documented response, (that is subsequently confirmed) until the date of the documented progression or of death in the absence of disease progression. Then, the end of response should coincide with the date of progression or death from any cause used for the PFS endpoint.	duration of response will be censored at the same time of PFS.	
59	**Page 58, Section 8.5, Tumor Assessment** Not applicable, section added.	**Page 61, Section 8.5, Tumor Assessment** Change in Tumor Size. Percentage change in tumor size will be determined for patients with measurable disease at baseline and is derived at each visit by the percentage change in the sum of the diameters of target lesions compared to baseline. Best percentage change in tumor size will be summarized using descriptive	The methodology in RECIST v 1.1 for assessing thechange in tumor size is added.

	Prior version: v1.1	Current version: v2.0	Reason for Amendment
		statistics and waterfall plot.	
60	**Page 61-62, Section 12, Data Quality. 3rd paragraph and 5th paragraph.** 3rd paragraph: The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC with use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor or its agent will request data clarification from the sites, which the sites will resolve electronically in the EDC system. 5th paragraph deleted/rewritten: A comprehensive validation check program will verify the data and discrepancy reports will be generated accordingly for resolution by the investigator. Throughout the study the Study Management Team will review data according to the Data Validation Manual (Any decision to use the CRF as a source document must be stated in the Data Validation Manual and the investigator must be advised of this decision).	**Page 64-65, Section 12, Data Quality. 3rd paragraph.** The Sponsor or its agent will be responsible for data management of this study according to data management documents. Any decision to use the CRF as a source document must be stated in the Data Validation Manual and the investigator must be advised of this decision. A comprehensive validation check program will verify the data and discrepancy will be generated accordingly. In the event of discrepant data, the Sponsor or its agent will issue data queries to the site and request data clarification. Site are required respond to all queries and promptly enter date into the EDC system.	The 3rd and 5th paragraphs were combined and edited for content and rewritten more succinctly and for clarity.
61	**Page 67, Notes to Study Flow Chart, Note #4.** All measurable and evaluable lesions should be assessed and documented at this visit, using physical examination and image-based evaluation.	**Page 69, Notes to Study Flow Chart, Note #4. 2nd sentence & the following sentence was added to the end of the note.** 2nd sentence: All measurable and evaluable lesions should be assessed and documented at this visit +/- 7 days, using physical examination and image-based evaluation. Added sentence: At the investigator's discretion, other methods of assessment of measurable disease as per RECIST	Lesion assessment windows are added to specify when they should be done in relation to the study visit schedule. The sentence added to note #4 provides guidance to investigators on the optional use of tumor assessment methods other than imaging, e.g., tumor markers, that are described in RECIST v 1.1.

	Prior version: v1.1	Current version: v2.0	Reason for Amendment
		may be used. Examples of other assessment methods include tumor markers, such as PSA and CA-125 levels for patients with prostate and ovarian cancer, respectively. However, tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete response.	Many of the footnotes were edited for clarity and grammar.
62	**Page 68, Notes to Study Flow Chart, Note #15.** Adverse Events and Concomitant Medications are collected continuously from the time of informed consent until 30 days after study completion, but represented at study visits on this study flow chart.	**Page 70, Notes to Study Flow Chart, Note #15.** After informed consent, all SAEs and concomitant medications will be collected. After initiation of study drug, all AEs and SAEs will be collected until 30 days following 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.	Changed the AE reporting period from first dose of study instead of informed consent, and keep it consistent with Section 7.1.4.
63	**Page 77, Table PK Sampling Time Points.** Cycle 1, Day 1 Pre-dose 10 minutes Cycle 1, Day 2 Pre-dose 10 minutes Cycle 1, Day 14 Pre-dose 10 minutes Cycle1, Day 15 Pre-dose 10 minutes Cycle1, Day 21 Pre-dose 10 minutes Cycle 1, Day 22 Pre-dose 10 minutes	**Page 79, Table PK Sampling Time Points.** Windows to the sampling time points were adjusted. Cycle 1, Day 1 Pre-dose (≤ 10 minutes) Cycle 1, Day 2 Pre-dose (≤ 10 minutes) Cycle 1, Day 14 Pre-dose (≤ 10 minutes) Cycle1, Day 15 Pre-dose (≤ 10 minutes) Cycle1, Day 21 Pre-dose (≤ 10 minutes) Cycle 1, Day 22 Post-dose 24 hours (± 60 minutes) on Day 21	The modifications provide specific windows to those time points in the sample schedule that did not have a window defined.

	Prior version: v1.1	Current version: v2.0	Reason for Amendment
64	**Page 78, Appendix E. Prohibited Concomitant Medications that have a Known Risk of QT prolongation and/or Torsades des Pointes (TdP).** The list is continuously updated online at www.crediblemeds.org or www.qtdrugs.org. The investigator should consult both the list below and one of the above referenced web sites to be sure none of the concomitant medications are prohibited because of a known risk of QT prolongation and/or TdP.	**Page 80, Appendix E Prohibited Concomitant Medications that have a Known Risk of QT prolongation and/or Torsades des Pointes (TdP).** The list is continuously updated online at www.crediblemeds.org or www.qtdrugs.org	The second sentence was deleted for brevity. It is clear from the section title what this list is intended for.
65	**Page 80, Appendix F Fruquintinib and Potential Drug-Drug Interactions**	**Page 84, Appendix F Fruquintinib and Concomitant Medication**	The section was renamed.
66	**Not applicable, Appendix J was added.**	**Page 91-93, Appendix J, Clinical Management of severe or serious hemorrhagic events.**	This appendix was added to provide detailed guidance to investigators on the management of severe (Grade ≥ 3) or serious (SAE) hemorrhagic events to mitigate the risk and impact of such events on study patients. A flow chart is included.