STATISTICAL ANALYSIS PLAN

2013-013-00CH1

FRUQUINTINIB RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER PHASE III CLINICAL TRIAL TO COMPARE EFFICACY AND SAFETY IN COMBINATION WITH BSC VS. BSC IN ADVANCED COLORECTAL CANCER PATIENTS WHO HAVE PROGRESSED AFTER SECOND-LINE CHEMOTHERAPY (FRESCO)

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	06NOV2015	Yiru Wang	Not Applicable – First Version
1.1	24NOV2015	Yiru Wang	1. Subgroup analysis based on BMI category was added for TEAE overview summary, SAE summary ,TEAE leading to drug discontinuation and TEAE with CTCAE grade >= 3; 2. Methods for handling ties was specified for OS and PFS analysis
2.0	28APR2016	Yiru Wang	1. Definition of PPS updated. 2. Add by center enrolment summary. 3. MedDRA version updated 4. Comparison of eCRF and IWRS VEGF inhibitors and K-Ras mutation status was added 5. Compliance category changed; 6. Add details for handling ties for efficacy analysis 7. Subgroup analysis added for efficacy analysis 8. Add summary table for laboratory data 9. Add hepatobiliary laboratory abnormalities
3.0	14NOV2016	Ni Guan	1. Definition of Concomitant procedure and medication updated to any procedure/medication taken on or after first dosing of treatment through-out the study until 30 days after

			last dose. 2. Summary of exposure and compliance information only for overall rather than both cycle 1 and overall 3. Additional sensitivity analysis was added for OS 4. Censoring rule for PFS primary analysis updated to include censoring of new anti-cancer therapy. 5. Algorithm for exposure and compliance were modified 6. Add CTCAE grading for laboratory part 7. ECG baseline criteria for shift table modified.

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1. LIST OF ABBREVIATIONS

Terms and Abbreviations	Definition
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine Aminotransferase/Glutamic-Pyruvic Transaminase
APTT	Activated Partial Thromboplastin time
AST	Aspartate Aminotransferase/Glutamic-Oxalacetic Transaminase
BOR	Best Overall Response
BSC	Best Supportive Care
CCR	Creatinine Clearance Rate
CEA	Carcino-Embryonic Antigen
CMH	Cochran-Mantel-Haenszel
CR	Complete Response
CS	Clinically Significant
CTC AE	Common Terminology Criteria For Adverse Event
CTMS	Clinical Trial Management System
DCR	Disease Control Rate
DMC	Data Monitoring Committee
DOR	Duration of Response
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic Case Report Form
EGFR	Epidermal growth factor receptor
ENR	All Subjects Enrolled
HR	Hazard Ratio
INR	International Normalized Ratio
LLQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute

NCS	Not Clinically Significant
NE	Not Evaluable
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progressive Free Survival
PLT	Blood platelet count
PP	Per Protocol
PR	Partial Response
PT	Preferred Term
QD	*Quaque Die*/Once Daily
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SCr	Serum Creatinine
SD	Stable Disease
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
Std	Standard Deviation
TSH	Thyroid stimulating hormone
ULN	Upper Limit of Normal
ULQ	Upper Limit of Quantification
VEGF	Vascular Endothelial Growth Factor
WHO DDE	World Health Organization Drug Dictionary Enhanced

Note: Standard units such as mg and mL as used in the text are not included in the abbreviations list.

2. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol 2013-013-00CH1. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol version4.0, dated 12JUN2016.

3. STUDY OBJECTIVES

To compare the efficacy and safety of Fruquintinib plus best supportive care (BSC) versus placebo plus BSC in patients with advanced colorectal cancer who were ineffectively treated by second-line and above standard chemotherapy.

4. STUDY DESIGN

4.1. GENERAL DESCRIPTION

This is a randomized, double-blind, placebo-controlled, multicenter Phase III clinical trial to compare the efficacy and safety of Fruquintinib plus best supportive care (BSC) versus matching placebo plus BSC in patients with advanced colorectal cancer ineffectively treated by second-line and above standard chemotherapy.
Approximately 400 subjects will be enrolled into this study and the study will be stopped when around 280 OS events are observed. After checking the eligibility criteria, subjects will be randomized into either Fruquintinib plus BSC group (treatment group) or placebo plus BSC group (control group) at a ratio of 2:1. Stratified randomization will be performed based on prior Vascular Endothelial Growth Factor (VEGF) inhibitors treatment (yes vs. no) and K-Ras gene status (wild type vs. mutant type).

- Treatment group: Subjects will receive Fruquintinib 5mg orally, once daily (QD), plus BSC for 3 weeks on/1 week off.
- Control group: Subjects will receive matching placebo 5mg orally, QD, plus BSC for 3 weeks on/1 week off.

Subjects will receive study treatment with each cycle of 4 weeks (A treatment cycle is 28 days, including 3 weeks of treatment and 1 week of drug break) until the occurrence of progressive disease (PD), death, unacceptable toxicity, withdrawal of consent, or other conditions that meet the End of Treatment criteria.

Baseline tumor evaluation should be completed within 3 weeks before the first dose using CT/MRI. Post-baseline tumor evaluations shall be performed every 8 weeks until the occurrence of PD. Subjects' safety assessment and drug accountability will be performed by each treatment cycle. Continuous drug safety monitoring and assessment will be performed through the whole study period (including a 30-day observation period after the end of

treatment). Safety parameters include adverse event (AE), laboratory parameter changes, vital signs and electrocardiogram (ECG) changes. Besides, the medication and survival follow up after PD will be recorded.

If any subject develops PD, it will be considered as the end of treatment. The subjects who, according to the investigator's discretion, can still benefit from the study treatment after developing PD can continue to take the prior investigational product (Fruquintinib or matching placebo, neither of the investigator, sponsor and the subjects know which investigational product the subject is receiving) after the investigator's consultation with the sponsor and approval by leading PI. The sponsor then will only provide investigational products and free examination for safety evaluation; and during which data other than SAE, safety data, drug use and survival status will not be collected.

All subjects who discontinue the treatment for any reason will be followed up for survival until recording as death, except for patients' withdrawal consent and clearly expressed to refuse follow-up. The survival state will be evaluated every 2 months after the end of treatment. A last evaluation of survival will be performed at the end of study. No evaluation of survival will be conducted after the completion of the study.

4.2. SCHEDULE OF EVENTS

Schedule of events can be found in Section 5: Assessment Plan and Procedures of the protocol.

4.3. CHANGES TO ANALYSIS FROM PROTOCOL

- Subgroup analysis of AE, OS, and PFS are added. See section 8.4 for list of subgroups.
- Adverse events of special interest will be summarized for Safety Analysis Set (SAS). See section 19.1.6 and Appendix 3 for details.
- Added per-protocol set
- Added sensitivity analyses for OS and PFS.
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5. PLANNED ANALYSES

5.1. INTERIM ANALYSES

No formal interim analysis will be performed. However, periodic safety monitoring will be conducted by data monitoring committee (DMC). The 1st Data Monitoring Committee (DMC) data review meeting will occur at approximately 6 months post the first patient enrolled, with at least 100 patients enrolled. The 2nd, also the last DMC data review meeting will occur at approximately 6 months post the first DMC data review meeting. Demographic data, other baseline characteristics and safety data will be summarized as described in a separate DMC SAP and submitted to DMC for review.

5.2. FINAL ANALYSES

The final analysis will be conducted when around 280 OS events have been reached. OS and all the other available data will be analyzed.

6. ANALYSIS SETS

Agreement and authorization of subjects included/excluded from each analysis set will be conducted prior to the unblinding of the study.

6.1. ALL SUBJECTS ENROLLED SET [ENR]

The all subjects enrolled set (ENR) will contain all subjects who provide informed consent for this study.

6.2. INTENTION-TO-TREAT SET [ITT]

The ITT analysis set will be the primary analysis set for the efficacy endpoints. The ITT set will include all randomized subjects. Following the intention-to-treat principle, patient data will be analysed according to randomized treatment. Demographic data and other baseline characteristics will also be summarized for the ITT.

6.3. SAFETY ANALYSIS SET [SAS]

The safety analysis set (SAS) will include all subjects in the ITT set who received at least one administration of study medication and subjects will be classified according to the treatment actually received. The SAS set will be used for analysis of safety endpoints.

If there is any doubt whether a subject was treated or not, they will be assumed treated for the purposes of analysis.

6.4. PER PROTOCOL SET [PP]

The per-protocol set (PP) will include all subjects in the ITT who did not experience any major protocol deviations that may have impact on the OS evaluation. This population will be used for sensitivity analysis of OS to evaluate the robustness of the primary analysis results based on the ITT.

7. GENERAL CONSIDERATIONS

7.1. REFERENCE START DATE AND END DATE AND STUDY DAY

Reference start date is defined as the day of the first administration of study treatment. Day 1 is the day of the first dose of study treatment in Cycle 1, and will appear in every listing where an assessment date or event date appears.

Reference end date is defined as the day of the last administration of study treatment within the subject's last treatment cycle.

Study day will be calculated from the reference start date, and will be used to show start/stop day of assessments and events relative to the first administration of study treatment.

- If the date of the event is on or after the reference start date then:
  - Study day = (date of event – reference start date) + 1.
- If the date of the event is prior to the reference start date then:
  - Study day = (date of event – reference start date).

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings. Study day, and any corresponding durations will be presented based on the imputations specified in Appendix 2: Partial Date Conventions.

In addition to the overall reference start and end date, the start and end of treatment within each cycle will be identified based on the data collected on the electronic Case Report Form (eCRF) "Study Drug Administration (ADMIN)" form and will be used when assigning events or assessments to a particular treatment cycle.

7.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to the reference start date (including unscheduled assessments). In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered baseline, but AEs and medications commencing on the reference start date will be considered post-baseline, that is, treatment-emergent ("worst case" approach). For Subject being randomized but not treated, baseline would be the last non-missing assessment prior to or on randomization date.

7.3. END OF TREATMENT

Unless otherwise specified, end of treatment (EOT) is defined as the latest non-missing measurement taken within 30 days after the reference end date. EOT measurements in general should be recorded at the "End of Treatment" visit and hence the measurement date and the reference end date should coincide. A GAP Period of 30 days is defined to allow for the situation where the assessments do not coincide: if the measurement date is within 30 days after the end of treatment date that measurement is considered as the EOT measurement.

7.4. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries, but will contribute to the best/worst case value where required (e.g. shift table).

In the case of a retest (same visit number assigned), the latest available measurement for that visit will be used for by-visit summaries.

For any subject with early withdrawal assessments available, all early withdrawal assessments related to the specific subject are to be considered in chronological order and are to be:

- Considered as unscheduled.
- Not summarized in the by-visit summaries.
- Only listed in the by-subject data listings.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

7.5. STATISTICAL TESTS

The default significance level will be two-sided 5%; Two-sided 95% confidence intervals will be presented and all tests will be two-sided, unless otherwise specified in the description of the analyses.

7.6. COMMON CALCULATIONS

For quantitative measurements, change from Baseline will be calculated as:

- Change from baseline= Test Value at Visit X – Baseline Value

Percentage change from baseline will be calculated as:

- Percentage change from Baseline= (Test Value at Visit X – Baseline Value) / Baseline Value × 100

7.7. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.2 or higher version.

8. STATISTICAL CONSIDERATIONS

8.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

The following factors are used as stratified factors for randomization.

- Prior use of VEGF inhibitors (yes vs. no)
- K-Ras gene status (wild type vs. mutant type)

The comparison of OS and PFS of Fruquintinib with placebo group by log-rank test, as well as the estimation of Hazard Ratio (HR) by COX model, and the comparison of ORR and DCR of Fruquintinib with placebo group by Cochran-Mantel-Haenszel test will involve the above two stratification factors.

All stratified efficacy analyses will performed based on actual levels of strata collected through eCRF. A sensitivity analysis of OS will be performed based on strata collected through IWRS as stratification factors at randomization. The concordance and discordance between the actual levels and the assigned levels will be summarized in frequency and percentage by treatment group and also listed by treatment group and subject.

8.2. MULTICENTER STUDIES

For this study, treatments were assigned to subjects using a central randomization independent of centers. Since there are 28 centers involved in this study, it is anticipated that subject accrual will be sparse across centers and hence it is not necessary to include center effect in statistical modelling.

8.3. MISSING DATA

Partial primary diagnosis date would be imputed as following: If year is missing, do not impute; if year and month of primary diagnosis date are known but the day of date is unknown, day will be imputed as 15. If only year of the date is known, month and day would be imputed as July 1st.

Partial dates of adverse events and prior/concomitant medication will be handled as described in Appendix 2. Missing efficacy data will be handled as described in section 18.1 and 18.2. In rare case, if year and month of death date are known but the day of date is unknown, day will be imputed as 15. For example, if a patient is reported to die on Dec 2016, the death date will be imputed as 15 Dec 2016.

When a partial new anti-tumor thereapy starting date is reported, every effort will be made to identify the precedence relationship of starting date of new anti-tumor thereapy relative to last dosing date of study drug and the date of disease progression (if happened). According to the confirmed precedence relationship, Partial new anti-tumor therapy date would be impute to the earliest possible date.

8.4. EXAMINATION OF SUBGROUPS

Subgroup analyses will be conducted as stated in the OS analysis and progression free survival sections. It should be noted that the study was not designed to detect treatment differences with high statistical power within subgroups. For OS and PFS subgroup analysis, if a subgroup is too small, it may be pooled with others. If the number of events in a subgroup is not sufficient, analysis will not be performed.

The following subgroups will be assessed for OS and PFS:

- Age (years):
  - <65
  - ≥65
- Gender:
  - Male
  - Female
- Baseline Eastern Cooperative Oncology Group Performance Status (ECOG PS):
  - 0
  - 1
- Time from 1st Metastatic Diagnosis to Randomization:
  - ≤18 months
  - >18 months
- Number of Prior Treatment Line on or above Metastatic Disease:
  - ≤3
  - >3
- Previous Chemotherapy Lines
  - 2 or 3
  - >3
- Prior VEGF Inhibitor Treatment:
  - Yes
  - No
- Prior Use of Epidermal Growth Factor Receptor (EGFR) Inhibitors
  - Yes
  - No
- Prior target treatment (Except for VEGFR)
  - No anti-VEGF or anti-EGFR
  - Anti-VEGF, or anti-EGFR, or both
    - Anti-VEGF and no anti-EGFR
    - Anti-EGFR and no anti-VEGF
    - Both anti-VEGF and anti-EGFR
- K-Ras Gene Status:
  - Wild Type
  - Mutant Type
- Primary Tumor Site:
  - Colon
  - Rectal

- Colon and rectal
- Primary Tumor Location
  - Left (Splenic flexure, descending colon, transverse colon, sigmoid colon and rectum)
  - Right (Cecum, ascending colon and hepatic flexure)
  - Both Left and Right
- Metastasis Tumor Site:
  - Single
  - Multiple
- Liver Metastasis:
  - Yes
  - No

Note: The values of stratification factors used for subgroup analysis are actual values of strata collected through eCRF.

For subgroup analysis of safety data, analysis by BMI category (<18.5, ⩾18.5 and <24 and ⩾24) will be performed for the following summary tables:

- TEAE overview summary
- SAE summary
- Summary of TEAE leading to drug discontinuation
- Summary of TEAE with CTCAE grade ⩾3.

8.5. MULTIPLE COMPARISION/MULTIPLICITY

There are no requirements for multiplicity adjustments in this study. The overall Type I error rate is two-sided 0.05 for the primary analysis of OS and all secondary analyses.

9. OUTPUT PRESENTATIONS

Appendix 1 details the conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures and listings to be provided by Quintiles Biostatistics.

Continuous variables will be summarized using descriptive statistics, i.e., number of subjects (n), mean, median, standard deviation (Std), 25th and 75th percentiles (Q1, Q3), minimum and maximum.

Qualitative variables will be summarized by count(s) and percentages (%). Unless otherwise stated, the calculation of percentages will either be based on the total number of subjects in the relevant analysis set with data available or relative to the total number of subjects included in the relevant analysis set.

10. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent will be accounted for in this study.

Subject disposition, withdrawals will be presented for the ENR set.

11. PROTOCOL DEVIATIONS

Apart from the directly programmatic checks from the information collected on the study database, the study team will discuss, identify and classify eligibility criteria or post-entry deviations from Clinical Trial Management System (CTMS) system monitoring reports prior to database lock.

Subjects who experience any of the following major protocol deviation criteria will not be included in per-protocol population.:

- Deviation from inclusion criteria 1-4 and 7
- Deviation from exclusion criteria 8-9, 11, 19, 21
- Randomized patients who failed to receive treatment
- Patients who were treated with the incorrect study treatment versus as randomized
- Patients who has received additional concurrent antineoplastic therapy (see section 6.5 of study protocol for details)
- Patients who did not complete 1 cycle treatment due to reasons other than disease progression or death or safety reasons or investigators' decision for subjects best interest or study close out, in other words, due to withdrawing informed consent or lost to follow-up or poor compliance

All subjects with major protocol deviation (except for subjects with incorrect study medication) will be identified and confirmed at blinded data review meeting prior to database lock. Major protocol deviations leading to exclusion of subjects from PP set will be summarized by each category for ITT set. All major protocol deviations identified at blinded data review meeting will be listed. A flag indicating whether the PD will lead to exclusion of subjects from PP set will be added to the listing. Subjects with inclusion/exclusion criteria deviations will be listed separately.

12. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be summarized for the ITT set.

No statistical testing will be carried out for demographic or other baseline characteristics.

The following demographic and other baseline characteristics will be reported for this study:

- Age (years) - Calculated relative to date of informed consent; <65 vs. ≥65
- Gender
- Race
- Ethnicity

- Baseline ECOG PS
- Baseline Weight (kg)
- Height (cm)
- Baseline BMI (kg/m^2)

12.1. DERIVATIONS

- BMI (kg/ m^2) = Weight (kg)/ Height $(m)^2$
- Age (Years): Calculated relative to the date of informed consent. Age (Years) is to be calculated using the following SAS® code:
    - Age (Years) = int((intck('month', <date of birth>, <date of IC>) - (day(<date of IC >) < day(<date of birth>))) / 12)

13. MEDICAL HISTORY AND ONCOLOGY HISTORY

Medical history will be summarized by system organ class (SOC) and preferred term (PT) for the ITT. Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 19.1 (MedDRA v19.1) or higher will be used for coding the medical history terms. Number and percentage will be presented in frequency tables, ordered by primary SOC and PT in descending order of total frequency. For SOCs or PTs with the same total frequency, categories will be sorted alphabetically.

Oncology history information will be presented for the ITT. The following oncology history information will be summarized for the study:

- Time since primary diagnosis to randomization (years)
- Stage of disease at the time of diagnosis
- Primary site at the time of diagnosis (colon, rectal, colon-rectal)
- Primary site at the time of diagnosis
    - Left (Splenic flexure, descending colon, transverse colon, sigmoid colon and rectum)
    - Right (Cecum, ascending colon and hepatic flexure)
    - Both Left and Right
- Metastasis (yes, no)
- Metastatic site (single, multiple)
- Liver metastasis (yes, no)
- Time from 1st metastatic diagnosis to randomization (months)
- Time from 1st metastatic diagnosis to randomization (<18 months; ≥18 months)
- Prior use of VEGF inhibitor (yes, no)
- Prior use of EGFR inhibitors (yes, no)
- Prior target treatment (Except for VEGFR) (No anti-VEGF or anti-EGFR, （Anti-VEGF, or anti-EGFR, or both）； Anti-VEGF and no anti-EGFR, Anti-EGFR and no anti-VEGF, Both anti-VEGF and anti EGFR)
- Prior use of fluorouracil, oxaliplatin and irinotecan
- K-RAS gene status (wild type, mutant type)
- Prior oncology treatment (chemotherapy and medication, radiation therapy, surgery and procedures)
- Prior treatment lines on or above metastatic disease (2 or 3 , >3)

- Prior chemotherapy lines ((≤3, >3)
- Time since last chemotherapy to randomization

Note: The summary of prior use of VEGF inhibitor and K-RAS gene status will be based on the actual values of strata collected through eCRF.

Metastatic (yes, no) will be obtained from ONC_HX form of the eCRF.

Metastatic site (single, multiple) will be determined based on information collected on TAR and NTAR forms of the eCRF.

The liver metastasis information refers to TAR and NTAR forms, with the response of "Screening" of "Please specify the Visit" item and use "Tumor Location" to determine if subject has liver metastasis or not.

13.1. DERIVATIONS

- Duration from 1st metastatic diagnosis to randomization (months) = (Date of randomization – Date of 1st metastatic) / 30.4375

If the date with known year and month but unknown day, day 15 will be imputed. If both day and month are missing, July 1st will be imputed.

14. MEDICATIONS AND PROCEDURES

Medications will be coded using World Health Organization Drug Dictionary (WHO DD), version 01Sep2016. Surgery and procedure will be coded using Medical Dictionary for Regulatory Activities (MedDRA), version 19.1. All medications and procedures will be listed.

Concomitant procedures is defined as procedures underwent on or after the first day of study therapy and no later than 30 days following the last dose of study therapy. Concomitant Procedures will be summarized by system organ class (SOC) and preferred term (PT) for the SAS.

Concomitant medications is defined as medications other than study medications which are taken at any time on-treatment, i.e. on or after the first day of study therapy and no later than 30 days following the last dose of study therapy. Concomitant medications will be summarized by reason for use and preferred term (PT) for the SAS. .

- See Appendix 2 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior or concomitant, the medication will be classified by the worst case; i.e. concomitant.
- 'Prior' medications are medications which started prior to the first dose of study medication.
- 'Concomitant' medications or procedures are those which:
    - Started prior to the first dose of study treatment and ended on or after the first dose of study treatment;

- Started on or after the first dose of study treatment but no later than 30 days following last dose of study medication

15. STUDY MEDICATION EXPOSURE

The extent of exposure to the study medication will be presented for the SAS. The following variables will be summarized by treatment group:

- Total duration of exposure (months)
- Actual duration of exposure (months)
- Cumulative dose (mg)
- Average daily dose (mg/day)
- Dose intensity (mg/day)
- Relative dose intensity (RDI)
- Number and percentage of subjects experiencing drug interruption or dose reduction
- Number and percentage of subjects with drug interruption
- Frequency of drug interruptions
- Number and percentage of subjects with any dose reduction
- Number of subjects with dose reduction from 5mg to 4mg
- Number of subjects with dose reduction from 4mg to 3mg
- Frequency of dose reductions

All subjects will be assumed receiving BSC. Therefore, no summary or listing will be presented for BSC.

15.1. DERIVATIONS

The start date and stop date of administration and dose level in each cycle will be taken from the eCRF "Study Drug Administration" form of the eCRF. The treatment is given 5mg QD per day and it is assumed that for each cycle the subject should take medication in the first 3 weeks followed by 1 week off treatment.

- Total duration of Exposure (months) = ((Stop date of administration in cycle 1 – Start date of administration in cycle 1) +1+(Stop date of administration in cycler 2 – Start date of administration in cycle 2)+1+...+(Stop date of administration in cycle N – Start date of administration in cycle N)+1)/((365.25/12). Drug interruption is not taken into account in the derivation of this measurement.
- Actual duration of Exposure (months) = The sum of days with non-zero dosing/(365.25/12). Dose interruption will be excluded from actual duration of exposure.
- Cumulative dose (mg) = The sum of the total dosage that the subject actually received during an exposure period. For patients who do not receive any study drug the cumulative dose will be set to zero.
- Average daily dose (mg/day) = Cumulative dose (mg) / (Actual duration of exposure* 365.25/12). For patients who do not receive any study drug, the average daily dose is set to zero.
- Dose intensity (mg/day) = Cumulative dose (mg) / (Total duration of exposure*365.25/12). For patients who do not receive any study drug, the DI is set to zero.

- Relative dose intensity = Dose intensity (mg/day) / planned dose intensity (mg/day). The planned dose intensity for Fruquintinib or matching placebo is 5mg/day.

16. STUDY MEDICATION COMPLIANCE

Compliance to study medication will be assessed using Relative Dose Intensity (RDI) as described in section 15.1.

17. SUBSEQUENT ANTI-TUMOR THERAPY

Number and percentage of subjects with any subsequent anti-tumor therapy, number of subsequent anti-tumor therapies, number and percentage of subjects with a specific type of therapy (chemotherapy, radiotherapy, surgery, other), number and percentage of subjects treated with a specific type of drug (VEGF target drug ,EGFR inhibitor, VEGFR inhibitor) , time from randomization until initiation of first subsequent therapy, and time from last dose of study treatment until initiation of first subsequent therapy will be summarized. A summary of anti-tumor therapy relative to progression will also be presented. An accompanying listing will be produced.

18. EFFICACY OUTCOMES

Tumors should be evaluated according to the standard of Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. Either computed tomography (CT) or magnetic resonance imaging (MRI) evaluation method can be used, but should be consistently used during the entire study period for a given patient. If a tumor assessment is done within 21 days prior to the first dose in the same hospital using the same method and same machine, it can be used as baseline tumor assessment. Tumors will be evaluated every 8 weeks until the occurrence of PD. Should the subject interrupt the medication due to AEs or other reasons, the evaluation should be conducted as scheduled. For suspected cases of PD before the start of the next scheduled assessment, additional tumor assessments should be done.

18.1. PRIMARY EFFICACY

18.1.1. PRIMARY EFFICACY VARIABLE & DERIVATION

The primary efficacy variable is OS.

The OS refers to the time interval between the randomization date and the date of death (any cause). The final known date of survival will be used as the censoring date for subjects who have not been reported to have died by the time of analysis cut-off date.

18.1.2. PRIMARY ANALYSIS OF PRIMARY EFFICACY VARIABLE

The primary analysis of OS will be based on ITT set. As stated in section 8.1, strata based on actual levels of strata collected through eCRF will be used in the primary analyses.

The primary comparison of OS between the two groups is to be performed using log-rank test stratified by prior use of VEGF inhibitor (yes vs. no) and K-Ras gene state (wild type vs. mutant type). When OS is statistically significantly longer for the treatment group than for the control group, under a two-sided significance level of 0.05, the study result can be declared positive.

The median and quartiles for OS and the survival rates at 3, 6, 9, 12, and 18 months, together with their two-sided 95% confidence intervals will be estimated for each treatment group using the Kaplan-Meier method, and the OS over time in the two treatment groups will be presented graphically by the Kaplan-Meier curves.

Furthermore, the treatment effect will be characterised by the "treatment/control" HR estimated using a stratified Cox proportional hazards model. The estimated HR and corresponding two-sided 95% confidence interval (CI) will be presented.

In addition, duration to follow-up for overall survival would be compared between two groups by Kaplan Meier method. Duration to follow-up refers to the time interval between randomization date and last date known to be alive for subjects who have not yet been reported to have died by the time of analysis. Subjects who were reported to have died would be censored at death date.

The SAS procedure LIFETEST will be used for log-rank test and Kaplan-Meier estimation, and the SAS procedure PHREG will be used for fitting the Cox proportional hazards model analysis. A STRATA statement will be used to implement the stratified analyses in both procedures.

The SAS procedure PHREG will be used for Cox proportional hazards model analysis. Efron method will be used to handle ties. Breslow is SAS default, however it does not do well when data are heavily tied. Efron is preferred over Breslow [Allison, Paul D. 2010].

18.1.3. SENSITIVITY ANALYSIS OF PRIMARY EFFICACY VARIABLE

The following sensitivity analyses for OS , conducted in the ITT population (unless otherwise noted) , will be performed.

a. As a sensitivity analysis to assess the impact of stratification, the two treatment groups will be compared using unstratified log-rank test. The hazard ratio together with associated 95% confidence interval obtained using the unstratified Cox regression model will also be presented.
b. Stratified log-rank test and stratified Cox proportional hazards model analysis as described in section 18.1.2 will be repeated for the ITT set, except that strata data used in the analysis are strata collected through IWRS as stratification factors.
c. As an exploratory analysis, a stratified Cox regression model with actual strata collected through eCRF will be fitted to evaluate the effect of other baseline demographic or disease characteristics on the estimated

hazard ratio. This model will include a set of potential prognostics/predictive factors as described in section 8.4. Factors included in the model will be assessed for co-linearity and a stepwise selection process will be applied to identify a final subset of prognostics/predictive factors in the model. Once the subset has been established (retaining factors significant at the 10% level), treatment will be added to the final model to assess its effect.
An exploratory analysis of treatment by factor interactions using the stratified Cox regression model will be conducted, using the factors identified in the final model above.

In addition, to assess the robustness of the OS endpoint, the primary analyses as described in section 18.1.2, i.e. the stratified log-rank test, Kaplan-Meier estimates, and hazard ratio obtained from Cox proportional model will be repeated for PP set.

18.1.4. SUBGROUP ANALYSIS

To assess consistency of treatment effect in OS in different subsets, subgroup analyses of OS will be performed. For each subgroup, the number of subjects and events at the time of analysis, median OS from Kaplan-Meier[KM] estimate), hazard ratios and 95% CI from an unstratified Cox proportional hazards model with treatment as the only covariate will be presented for the ITT set. A forest plot will be used to present these subgroup results. For the list of subgroups, please see Section 8.4.

18.2. SECONDARY EFFICACY

18.2.1. SECONDARY EFFICACY VARIABLES & DERIVATIONS

The secondary efficacy variables include PFS, ORR, DCR, DOR and duration of SD.

18.2.1.1. Progression Free Survival (PFS)

Baseline tumor evaluation should be completed within 3 weeks before the first dose. After randomization, tumor assessments in both treatment arms are to be performed within a time window of ±3 days around the scheduled visits (every 8 weeks). Unscheduled scans may be performed when disease progression is suspected.

PFS is defined as the time from randomization until the date of objective disease progression or death (by any cause in the absence of progression). Subjects 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 subject progresses or dies after two or more consecutive missed tumor assessment visits, the subject will be censored at the time of the latest evaluable RECIST assessment. If the subject has no evaluable tumor assessment visits after randomization or does not have evaluable baseline tumor assessment data the subject will be censored on the date of randomization unless they die within two tumor assessment visits of baseline. If new anticancer treatment is initiated prior to documented disease progression or death on study, the subject will be censored at date of last evaluable tumor assessment prior to or on date of new anticancer treatment. The above censoring

rules for primary analysis of PFS are summarized in table 1. Another set of censoring rules for sensitivity analysis are also presented in table 1. The only difference from the primary analysis is that it considers initiation of new anticancer treatment as PD event for subjects without documented PD or death.

Two consecutive missed/non-evaluable tumor assessment visits is defined as no evaluable tumor assessment within 118 days ([2*(8 weeks+3 days window time) of randomization or the previous evaluable RECIST 1.1 measurement. Note: 118 days allows for two visits 8 weeks apart plus an allowable 3 days visit window.

The PFS time will always be derived based on scan/assessment dates not visit dates. If PD is documented between scheduled visits, the actual date of documented progression will be used as an uncensored value in the analysis of PFS.

RECIST assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

- Date of progression will be determined based on the **earliest** of the dates of the component that triggered the progression
- When censoring a subject for PFS the subject will be censored at the **latest** of the dates contributing to a particular overall visit assessment

Table 1 Censoring Scheme for Analysis of Progression-Free Survival

No.	Situation	Primary Analysis	Sensitivity
1	No progression and no death	Censored at date of last evaluable tumor assessment	Censored at date of last evaluable tumor assessment
2	No baseline tumor assessments unless they die within two tumor assessment visits from randomization	Censored at date of randomization	Censored at date of randomization
3	No on study tumor assessment unless they die within two tumor assessment visits from randomization	Censored at date of randomization	Censored at date of randomization
4	Documented progression other than situation 6	Progressed at date of first documented progression per RECIST 1.1	Progressed at date of first documented progression per RECIST 1.1
5	Death without progression other than situation 6	Progressed at date of death	Progressed at date of death
6	Death or progression after two or more consecutive missed/non-evaluable tumor assessments	Censored at date of last evaluable tumor assessment before missed tumor assessments	Censored at date of last evaluable tumor assessment before missed tumor assessments
7	New anticancer treatment started prior to documented disease progression or death on	Censored at date of last evaluable tumor assessment prior to or on date of new anticancer treatment	**Progressed at date of new anticancer treatment, however if the new anticancer treatment was**

	study		**initiated** after two or more consecutive missed/non-evaluable tumor assessments, subjects will be censored at date of last evaluable tumor assessment before missed tumor assessments

PFS (in months) will be calculated as (first event date – randomization date +1) /30.4375 when a subject is deemed to experience a PFS event or calculated as (date of last evaluable tumor assessment - randomization date +1) /30.4375 when a subject is deemed to be censored, according to the rules specified in Table 1.

18.2.1.2. Objective Response Rate (ORR)

ORR is defined as the proportion of subjects whose best overall response (BOR) from baseline is either a CR or PR per RECIST 1.1 criteria for the ITT set. In order to protect against potential bias raised by measurement error as much as possible, response confirmation would be involved to determine the best overall response according to the algorithm described in RECIST guideline 1.1.

BOR is determined by the best response designation recorded between the date of randomization and the date of objectively documented progression or the date of subsequent anti-cancer therapy, whichever occurs first. For subjects without documented progression or subsequent anticancer therapy, all available response designations will contribute to the BOR determination. Complete or partial responses would be claimed only if criteria are met at subsequent visit for the corresponding situation exhibited in table 2. The subsequent visit should, generally, no less than 53 days (8 weeks minus 3-day window) from the visit at which the tumor response is to be confirmed. In addition, duration between randomization and the visit at which SD is to be claimed must be at a minimum of 53 days (8 weeks minus 3-day window).

Although the inclusion criteria #9 requires measurable disease at baseline, it is likely that patients with no measurable disease at baseline were recruited into the study by mistake. In that case, a sensitivity analysis of ORR will be calculated and analyzed for patients with only measurable disease at baseline.

Table 2 CR and PR confirmation rule for Best Overall Response

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD if SD duration of no less than 53 days from randomization was met , otherwise, PD
CR	PD	SD if SD duration of no less than 53 days from randomization was met, otherwise, PD
CR	NE	SD if SD duration of no less than 53 days from randomization was met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD

PR	PD	SD if SD duration of no less than 53 days from randomization was met, otherwise, PD
PR	NE	SD if SD duration of no less than 53 days from randomization was met, otherwise NE
NE	NE	NE

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR. Such situation would rarely occur for this study, thus 'CR' would be considered as real complete response which meet all the criteria described in RECIST 1.1 unless otherwise specified.

18.2.1.3. Disease Control Rate (DCR)

DCR is defined as the proportion of subjects whose best overall response (BOR) from baseline is either a CR, PR or SD per RECIST 1.1 criteria for the ITT set.

The best response of stable disease (SD) can be assigned if SD criteria were met at least once after randomization at a minimum interval of 53 days (8 weeks -3 days).

Although the inclusion criteria #9 requires measurable disease at baseline, if patients with no measurable disease at baseline entered the study, a sensitivity analysis of DCR will be calculated and analyzed for patients with only measurable disease at baseline.

18.2.1.4. Duration of Response (DOR)

Duration of response is defined as the time (month) from the **first time** that the objective response reaches CR or PR, whichever comes first, until the occurrence of PD or death (if the death of the subject occurs before recording the PD). The DOR is just applied to patients whose BOR is CR or PR. The calculation is performed based on the actual completion date of tumor scan. The end of response should coincide with the date of progression or death from any cause used for the PFS event. If a subject does not progress following a response, then their duration of response will use PFS censoring time.

18.2.1.5. Duration of Stable Disease

Duration of SD is only for evaluation of subjects with BOR of SD. It is defined as time (months) from date of randomization to the time of first record of PD or death (if death of the subject occurs before recording of PD). The calculation is performed based on the actual completion date of the tumor scan. The end of SD should coincide with the date of progression or death from any cause used for the PFS event. If a subject does not progress following a SD, then their duration of SD will use PFS censoring time.

18.2.2. MISSING DATA METHODS FOR SECONDARY EFFICACY VARIABLES

When no imaging/measurement is done at all at a particular time point, the subject is not evaluable (NE) at that time point. If only a subset of lesion measurements is made at an assessment, the subject 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. See Appendix 2 in protocol for specification.

18.2.3. ANALYSIS OF SECONDARY EFFICACY VARIABLES

18.2.3.1. Primary Analysis of PFS

The primary analysis of PFS will be based on ITT set. As stated in section 8.1, actual levels of strata collected through eCRF will be used for stratified analyses.

The primary comparison of PFS between the two groups is to be performed using stratified log-rank test for the ITT set; specifically, treatment efficacy expressed by the HR and associated two-sided 95% CI will be estimated from a stratified COX model . Stratification factors are the same as that of OS. The median and quartiles for PFS and the PFS rates at 1, 3 and 6 months, together with their two-sided 95% confidence intervals will be estimated for each treatment group using the Kaplan-Meier method, and the Kaplan-Meier curves for PFS will be presented.

The source of progression event (death versus progression) will be summarized by treatment group.

The status of subjects who are censored in the primary analysis of PFS will be tabulated for each treatment group using the following categories:

- Censored RECIST progression : RECIST progression event occurred > 118 days after last evaluable RECIST assessment (or date of randomisation in absence of evaluable baseline RECIST assessment)
- Censored death: Death occurred > 118 days after last evaluable RECIST assessment (or randomisation)
- No baseline tumor assessment and no death happened within two tumor assessment visits from randomization
- No on-study tumor assessment and no death happened within two tumor assessment visits from randomization
- Initiation of new anti-cancer therapy before disease progression or death
- Progression free at time of analysis : Subjects known to be alive without RECIST progression at data cut-off date. This excludes patients alive without evaluable baseline RECIST assessment or evaluable on-study RECIST asessment.
- Lost to follow-up at last evaluable RECIST assessment.
- Withdrawn consent at last evaluable RECIST assessment.

Sensitivity Analysis

As a sensitivity analysis to assess the impact of stratification, the two treatment groups will be compared using unstratified log-rank test. The hazard ratio together with associated two-sided 95% confidence interval obtained using the unstratified Cox regression model will also be presented. For this sensitivity analysis, the censoring rules as described in Table 1 for primary analysis will be used.

In addition, the primary analysis as described in 18.2.3.1 will repeated for PFS endpoint using a different set of

censoring rule as described in Table 1 for sensitivity analysis.

Subgroup Analysis
Subgroup analyses of PFS will be performed in the same way as OS. All assignments of censoring and progression will be same as in the primary method of derivation for PFS.

18.2.3.2. Analysis of ORR and DCR

The analysis of ORR and DCR will be based on the ITT set. Actual levels of strata collected through eCRF will be used for the stratified analyses, where applicable.

The exact 95% CI for the estimated ORR and DCR will be calculated for each treatment group using the Clopper-Pearson method. The Cochran-Mantel-Haenszel (CMH) test, with strata as specified above, will be used to compare the ORR and DCR between treatment groups. The results from the stratified CMH analysis will be expressed in terms of the odds ratio and its associated CI and p-value. If the number of objective response or disease control is not sufficient to utilize CMH test, the stratified exact test will performed instead. Exact confidence limits for the common odds ratio will be presented.

PROC FREQ with BINOMIAL option in EXACT statement in SAS will be used to calculate the CI of the ORR and DCR for each treatment group. PROC FREQ with CMH option in TABLE statement will be used for CMH test. PROC FREQ with COMOR option in EXACT statement will be used to execute stratified exact test.

18.2.3.3. Analysis of DOR and Duration of SD

Duration of response only applies for patients who have responded to the treatment. Descriptive analysis will be adopted for DOR. For each treatment group, results will be presented by Kaplan-Meier estimates and distribution curves. Similar analysis method will also be used for duration of SD.

19. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the SAS. Safety endpoints include AEs, laboratory results (hematology, clinical chemistry, clinical urinalysis and stool for occult blood), vital signs (blood pressure, heart rate, respiratory rate, and temperature), weight, ECG and echocardiography (UCG) and ECOG PS.

In general, the safety summary tables will only include “on-treatment” events/assessment, i.e. those collected on or after the first date of study treatment and collected no later than 30 days after the date of last study treatment administration, unless otherwise specified.

There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified with the relevant section.

19.1. ADVERSE EVENTS

The AEs will be classified coded using MedDRA central coding dictionary, version 19.1.

Treatment-emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or after the first dose of study medication and no later than 30 days after the date of last study treatment administration. An exception is that study drug related SAE collected later than 30 days after the last treatment date will be treated as TEAEs. This definition is aligned with protocol AE/SAE data collection procedure.

See Appendix 2 for handling of partial dates for AEs. In the case where it is not possible to classify an AE as treatment-emergent or not, the AE will be classified by the worst case; i.e. treatment-emergent.

An overall summary of number of subjects and number of events within each of the categories described in the sub-section below, will be provided as specified in the templates.

Listings will include TEAEs and Non-TEAEs. TEAEs (Y/N) will be flagged in the listings.

19.1.1. ALL TEAES

Incidence of TEAEs will be presented by SOC and then PT and also broken down further by maximum severity and relationship to study medication. Number (n) and percentage (%) will be presented with the percentage calculated relative to the total number of subjects in the SAS.

19.1.1.1. Severity

The severity of all TEAEs shall be graded according to 5 grades (Grade 1 to Grade 5) in accordance with the national cancer institute common terminology criteria for adverse event (NCI CTC AE) V4.03 as defined in the following document:
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

The TEAEs not listed in NCI CTC AE shall be determined as mild/moderate/severe/life-threatening or incapacitating/fatal (increasing severity), according to Table 6 in the study protocol.

TEAEs starting after the first dose of study medication with a missing severity will be classified as severe. If a subject reports a TEAE more than once within that SOC/PT, the AE with the highest severity will be used in the corresponding severity summaries.

AEs classified as grade 3 or higher will be summarized. Incidence rates (frequencies and percentages) by SOC and PT will be prepared.

19.1.1.2. Relationship to Study Medication

Relationship, as indicated by the Investigator, is classified as “unrelated”, “unlikely related”, “possibly related” and “related” (increasing strength of relationship). TEAEs with a missing relationship to study medication will be regarded as “possibly related” to study medication. If a subject reports the same AE more than once within that

SOC/PT, the AE with the strongest relationship to study medication will be used in the corresponding relationship summaries. Relationship would be summarized as "Related" and "Unrelated". Adverse events with investigator indicated drug-event relationship of "Unrelated" and "Unlikely related" are classified as "Unelated" with the study medication, while adverse events with drug-event relationship documented as "Possibly related" and "Related" are considered as "Related" with the study medication.

19.1.2. TEAEs Leading to Drug Discontinuation

TEAEs leading to permanent discontinuation of study medication will be identified as those records with a response of "Drug permanently discontinued" to the item "Action taken with the study drug" on the "Adverse Event/Serious Adverse Event (AE/SAE)" form of the eCRF.

For TEAEs leading to drug discontinuation, summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared.

19.1.3. Serious Adverse Events

Serious adverse events are those events with a response of "Yes" for the item "Does the Adverse Event meet seriousness criteria?" on the AE/SAE form.

Summaries of incidence rates (frequencies and percentages) of serious AEs by SOC and PT will be prepared. The SOC and PT should be sorted by descending frequency of the total number of subjects with at least one SAE.

19.1.4. Adverse Events Leading to Drug Interruption or Dose Reduction

TEAEs leading to drug interruption or dose reduction will be identified as those records with a response of "Drug interrupted" or "Dose reduced" to the item "Action taken with the study drug" on the AE/SAE form of the eCRF.

For TEAEs leading to drug interruption or dose adjustment, summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared.

19.1.5. Adverse Events Leading to Death

TEAEs leading to Death are those events with "Final Outcome" response recorded as "Fatal" on the Adverse Events page of the eCRF.

A summary of TEAEs leading to death by SOC and PT will be prepared.

19.1.6. Adverse Events of Special Interest (AESI)

The adverse events of special interest (AESI) will be summarized using Standardised MedDRA Queries (SMQ) terms for each disease category. Incidence rates (frequencies and percentages) will be presented by treatment arm. See

Appendix 3 for listing of PT terms included in SMQ for AESI. Time to treatment emergent AESI would also be summarized by treatment arm for each disease category. Time to AESI is defined as time interval from date of randomization to the earliest onset date/ date became serious among AEs within the same disease category.

AESI will be identified by sponsor medical team and then summarized by Quintiles Biostatistics.

19.2. DEATHS

If any subjects die during the study, as recorded on the "Death" form, the information will be presented in a summary table and a data listing for overall and on treatment period (from first dose to 30 days after last dose).

19.3. LABORATORY EVALUATIONS

Results from the local laboratory will be included in the reporting of this study for hematology, urinalysis, stool occult blood test, blood clinical biochemistry, routine thyroid function test and carcino-embryonic antigen (CEA).

The laboratory assessments to be included in the outputs are in Protocol Section 5.3.3.2.

Data recorded by the laboratory will be converted to the International System of Units (SI) and all presentations will use SI units. Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (LLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

Baseline is defined as the last evaluation (including post-randomization evaluation) prior to the first dose of study drug.

The following summaries will be provided for laboratory data:

- Summary of quantitative lab test results and changes from baseline by scheduled visit
- Summary (frequency and percentage) of laboratory CTCAE grade by scheduled visit and worst post-baseline result
- Shift table from baseline to worst post-baseline CTCAE grade
- Summary of abnormality assessed by investigator by scheduled visit and worst post-baseline result. Shift table from baseline to worst post-baseline value according to abnormality assessed by investigator

All lab data will be listed by subject and visit.

19.3.1. LABORATORY SPECIFIC DERIVATIONS

Creatinine clearance rate (Ccr) should be calculated by using the serum creatinine (SCr) values according to the formulations:

- Male: Ccr (umol/L) = [(140 - age) × weight (kg)] / [0.818 × Scr (umol/L)]
- Female: Ccr (umol/L)= [(140 - age) × weight (kg)] / [0.818 × Scr (umol/L)] × 0.85

The unit of the creatinine clearance will be converted to SI unit: umol/L.

19.3.2. CTCAE GRADING FOR LABORATORY DATA

To identify laboratory values of potential clinical importance, laboratory results will be graded according to NCI CTCAE Ver. 4.03, where applicable. All grading will be based on lab values (being direct or some derived, corrected values) only, regardless of its interventional or symptomatic consequences.

Some modifications to the grading system will be applied:

- Grade 5 refers to fatal outcomes, which cannot be determined solely by lab values, therefore will not appear in the grading system.
- A further category denoted Grade 0 would include all other laboratory values except missing values.
- Missing results shall be graded as missing.

For some specific parameters with CTCAE grading in both high and low direction (e.g., calcium, glucose, magnesium, potassium, sodium), CTCAE in high and low directions will be presented separately, i.e. hyper for higher values of concern and hypo for lower values of concern.

19.3.3. LABORATORY REFERENCE RANGES HIGH/LOW CRITERIA AND INVESTIGATOR'S ASSESSMENT

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

In addition to the high and low quantitative laboratory assignments (as identified by means of the laboratory reference ranges), quantitative safety (and other) laboratory assessments will also be evaluated as normal/abnormal, not clinically significant (NCS)/abnormal, clinically significant (CS).

19.3.4. HEPATOBILIARY LABORATORY ABNORMALITIES AND SUBJECTS WITH VALUES OUTSIDE A PRE-SPECIFIED THRESHOLD

Treatment emergent hepatobiliary laboratory abnormalities defined as values outside pre-specified thresholds will be summarized and listed by treatment. Treatment emergent is defined as any disorder/event recorded on the eCRF which started on or after the start date of treatment and within 30 days following the date of last dose of study medication.

The pre-specified thresholds are:

1. Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 3x upper limit of normal (ULN) and ≤ 5x ULN
2. AST and/or ALT > 5x ULN
3. Total bilirubin elevations > 2x ULN
4. AST and/or ALT of > 3x ULN and total bilirubin > 2x ULN
5. HY'S LAW LAB. CRITERIA: AST and/or ALT > 3x ULN and total bilirubin > 2x ULN and ALP < 2x ULN

19.4. ECG EVALUATIONS

Results from the ECG will be included in the reporting of this study.

The following ECG parameters will be reported for this study:

- PR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- QTc Interval (msec)
- Overall assessment of ECG (Investigator's judgment):
    - Normal
    - Abnormal , NCS
    - Abnormal , CS

The following summaries will be provided for ECG data:

- Actual and change from baseline by visit (for quantitative measurements)
- Table and listing of subjects meeting markedly abnormal criteria (worst post-baseline QTc values and change from baseline)
- Summary of abnormality assessed by investigator by scheduled visit and worst post-baseline result
- Shift from baseline to worst post-baseline value according to abnormality assessed by investigator

19.4.1. ECG MARKEDLY ABNORMAL CRITERIA

Markedly abnormal quantitative ECG measurements will be identified in accordance with the following predefined markedly abnormal criteria for each cycle:

- Absolute values for QTc interval will be classified as:
    - > 450 msec
    - > 480 msec
    - > 500 msec
- Change from Baseline for QTc interval will be classified as:
    - >30 msec increase from baseline
    - >60 msec increase from baseline

19.5. VITAL SIGNS

The following vital signs measurements will be reported for this study:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Heart rate (beats/min)
- Breath (breaths/min)

- Temperature (°C)

The following summaries will be provided for vital signs data:

- Actual and change from baseline by visit
- Shift table of worst post-baseline category from baseline

19.5.1. VITAL SIGNS SPECIFIC DERIVATIONS

For Oral Body Temperature (°C), conversions to oral route will be made as follows:

- Axillary: +0.5°C
- Oral: No Adjustment

19.5.2. CATEGORIES FOR INCREASES OR DECREASES IN VITAL SIGNS AND BODY WEIGHT

Summary tables for vital signs and body weight are presented, which display the baseline value category and on-treatment worst category (both the increase and decrease of the values are reported) for the absolute change from baseline. The vital sign and body weight data are summarized according to the categories shown below.

Variable	Unit	Baseline Categories	On-Treatment Categories for Increases or Decreases
Systolic blood pressure	mmHg	≤ 140	Absolute change from baseline of: > 0 - ≤ 20 / > 20 - ≤ 40 / > 40 mmHg
Diastolic blood pressure	mmHg	≤ 90	Absolute change from baseline of: > 0 - ≤ 20 / > 20 - ≤ 40 / > 40 mmHg
Heart rate	Bpm	< 100 / ≥ 100 bpm	Absolute change from baseline of: > 0 - ≤ 20 / > 20 - ≤ 40 / > 40 bpm
Weight	Kg	None (kg)	Percentage change from baseline of < 5% / ≥ 5 - <10% / ≥ 10 - < 20% / ≥ 20%

19.6. PHYSICAL EXAMINATION

The physical examinations results (Normal / Abnormal, NCS / Abnormal, CS) will be presented in a listing.

19.7. OTHER SAFETY ASSESSMENTS

Summary of ECOG performance status by scheduled visit and worst post-baseline value will be presented. Shift of ECOG performance status from baseline to worst post-baseline value will be presented.

Left Ventricular Ejection Fraction (LVEF) results and change from baseline will be summarized by scheduled visit. Investigator's assessment shift table from baseline to post-baseline will also be presented.

20. REFERENCES

International Conference on Harmonization (ICH) E9 Guidelines
CPMP Points to consider on adjustment for baseline covariates
Guidance for industry: E14: clinical evaluation of QT/ QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs.
Eisenhauer EA, Therasse P, Bogaerts J,Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-247.
Allison, Paul D. 2010. Survival Analysis Using SAS: A Practical Guide, Second Edition. Cary, NC: SAS Institute Inc.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

QUINTILES OUTPUT CONVENTIONS

Outputs will be presented according to the Quintiles' general guidelines and template for outputs conventions.

DATES & TIMES

Depending on data available, dates and times will take the form DDMMMYYYY and HH:MM:SS.

SPELLING FORMAT

English US

PRESENTATION OF TREATMENT GROUPS

For outputs, treatment groups will be represented as follows and in that order:

Treatment Group	For Tables, Listings and Graphs
Fruquintinib 5mg orally, QD, plus BSC	Fruquintinib + BSC
Placebo 5mg orally, QD, plus BSC	Placebo + BSC
Screen Failure	Screen Failures

PRESENTATION OF VISITS

For outputs, visits will be represented as follows and in that order:

Long Name (default)	Short Name
Screening (≤21 days prior to 1st dose)	SCR1
Screening (≤7 days prior to 1st dose)	SCR2
Cycle 1 Day 1	C1D1
Cycle 1 Day 8	C1D8
Cycle 1 Day 15	C1D15
Cycle 1 Day 22	C1D22
Cycle 2 Day 1	C2D1
Cycle 2 Day 15	C2D15
Cycle 3 Day 1	C3D1
Cycle 3 Day 15	C3D15
Cycle 4 Day 1	C4D1
...	...

Long Name (default)	Short Name
Cycle X Day 1	CXD1
End of Treatment	EOT
End of Treatment Follow Up	EOTFU
Survival Follow Up	SURV1

LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the template):

- randomized treatment group, first by active dose and then placebo,
- center-subject ID,
- date (where applicable),
- For listings where non-randomized subjects are included, these will appear in a category after the randomized treatment groups labeled “Screen Failure”.

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR TREATMENT-EMERGENCE OF ADVERSE EVENTS:

START DATE	STOP DATE	ACTION
Known	Known	If start date < study med start date, then not TEAE If start date >= study med start date, then determine TEAE according to the definition of TEAE specified in section 19.1
	Partial	If start date < study med start date, then not TEAE If start date >= study med start date, then determine TEAE according to the definition of TEAE specified in section 19.1
	Missing	If start date < study med start date, then not TEAE If start date >= study med start date, then determine TEAE according to the definition of TEAE specified in section 19.1
Partial, but known components show that it cannot be on or after study med start date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study med start date	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then determine TEAE according to the definition of TEAE specified in section 19.1
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then determine TEAE according to the definition of TEAE specified in section 19.1
	Missing	Assumed TEAE
Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date then determine TEAE according to the definition of TEAE specified in section 19.1
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month

START DATE	STOP DATE	ACTION
		are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then determine TEAE according to the definition of TEAE specified in section 19.1
	Missing	Assumed TEAE

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS:

START DATE	STOP DATE	ACTION
Known	Known	Determine prior or concomitant according to the algorithm defined in section 14.
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then determine prior or concomitant according to the algorithm defined in section 14.
	Missing	If stop date is missing, assume it is after study med start date. Then determine prior or concomitant according to the algorithm defined in section 14.
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then determine prior or concomitant according to the algorithm defined in section 14.
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then determine prior or concomitant according to the algorithm defined in section 14.
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and assume the stop date is after study med start date, then determine prior or concomitant according to the algorithm defined in section 14.
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, then determine concomitant according to the algorithm defined in section 14.

START DATE	STOP DATE	ACTION
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then determine prior or concomitant according to the algorithm defined in section 14.
	Missing	Assign as both prior and concomitant

APPENDIX 3. ADVERSE EVENT OF SPECIAL INTEREST (AESI)

AESI	Desciption and Analysis	Preferred Terms
Hepatotoxicity	Analysis methods: 1) Hepatic adverse events are evaluated by the Standardised MedDRA Queries (SMQ) of Hepatic failure, fibrosis, and cirrhosis and other liver damage-related conditions, according to whether the patient had liver metastasis at baseline, and categorized by CTC AE grades; 2) Clinical laboratory abnormalities of liver enzymes and serum bilirubin are also analyzed according to whether the patient had liver metastasis at baseline: (Categorized by 4 items: AST or ALT >3xULN & ≤5xULN; AST or ALT >5xULN; Total Bili. >2xULN; AST or ALT >3xULN and Total Bili.>2xULN; AST/ALT >3xULN, Total Bili. >2xULN and ALP <2xULN).	Acute hepatic failure Acute yellow liver atrophy Ascites Asterixis Bacterascites Biliary cirrhosis Biliary cirrhosis primary Biliary fibrosis Cholestatic liver injury Chronic hepatic failure Coma hepatic Cryptogenic cirrhosis Diabetic hepatopathy Drug-induced liver injury Duodenal varices Gallbladder varices Gastric varices Gastric varices haemorrhage Hepatectomy Hepatic atrophy Hepatic calcification Hepatic cirrhosis Hepatic encephalopathy Hepatic encephalopathy prophylaxis Hepatic failure Hepatic fibrosis Hepatic hydrothorax Hepatic infiltration eosinophilic Hepatic lesion Hepatic necrosis Hepatic steatosis Hepatitis fulminant Hepatobiliary disease Hepatocellular foamy cell syndrome Hepatocellular injury Hepatopulmonary syndrome

		Hepatorenal failure Hepatorenal syndrome Hepatotoxicity Intestinal varices Liver and small intestine transplant Liver disorder Liver injury Liver operation Liver transplant Lupoid hepatic cirrhosis Mixed liver injury Nodular regenerative hyperplasia Non-alcoholic steatohepatitis Oedema due to hepatic disease Oesophageal varices haemorrhage Peripancreatic varices Portal fibrosis Portal hypertension Portal hypertensive enteropathy Portal hypertensive gastropathy Portal triaditis Portal vein cavernous transformation Portal vein dilatation Portopulmonary hypertension Renal and liver transplant Retrograde portal vein flow Reye's syndrome Reynold's syndrome Splenic varices Splenic varices haemorrhage Subacute hepatic failure Varices oesophageal Varicose veins of abdominal wall Anorectal varices

		Anorectal varices haemorrhage Intrahepatic portal hepatic venous fistula Peritoneovenous shunt Portal shunt Small-for-size liver syndrome Spider naevus
Haemorrhage	Any bleeding event, including skin, respiratory, gastrointestinal, genitourinary tracts, brain, tumor or any other site bleeding, or PLT decreased or prothrombin time\APTT\INR prolongation, without a bleeding symptom. Analysis method: The overall incidence of the risk of hemorrhage with Fruquintinib compared to placebo will be evaluated using the MedDRA SMQ of Hemorrhages, and categorized by CTC AE grades.	Blood urine present Blood urine Gastric occult blood positive Occult blood positive Haemorrhage Haematoma Haemorrhagic diathesis Haemorrhagic disorder Spontaneous haemorrhage Haemorrhagic stroke Gastrointestinal haemorrhage Upper gastrointestinal haemorrhage Lower gastrointestinal haemorrhage Gastric haemorrhage Gastroduodenal haemorrhage Gastric ulcer haemorrhage Duodenal ulcer haemorrhage Gastrointestinal ulcer haemorrhage Ulcer haemorrhage Rectal haemorrhage Anal haemorrhage Haematochezia Melaena Gingival bleeding Lip haemorrhage Mouth haemorrhage Mucosal haemorrhage Epistaxis Haemoptysis Pulmonary haemorrhage Respiratory tract haemorrhage

		Haemothorax Pericardial haemorrhage Haematuria Renal haemorrhage Urethral haemorrhage Urinary bladder haemorrhage Menorrhagia Metrorrhagia Postmenopausal haemorrhage Uterine haemorrhage Vaginal haemorrhage Skin haemorrhage Skin ulcer haemorrhage Soft tissue haemorrhage Subcutaneous haematoma Haemorrhage subcutaneous Nail bed bleeding Ear haemorrhage Eye contusion Eye haemorrhage Eyelid bleeding Retinal haemorrhage Hepatic haemorrhage Splenic haemorrhage Haemarthrosis Retroperitoneal haematoma Blood blister Bloody discharge Ecchymosis Contusion Purpura Thrombocytopenic purpura Injection site haemorrhage Injection site haematoma Injection site bruising Infusion site haemorrhage Infusion site haematoma Infusion site bruising Traumatic haemorrhage Wound haemorrhage Tumor haemorrhage Disseminated intravascular coagulation
Hypertension	Any event of hypertension or blood pressure increased, with or without any sign or symptom	Hypertension Blood pressure increased

	Analysis method: The overall incidence of hypertension with Fruquintinib compared to placebo will be evaluated using the MedDRA SMQ of Hypertension. It will be categorized by CTC AE grades.	Blood pressure diastolic increased Blood pressure systolic increased Blood pressure inadequately controlled Blood pressure management Blood pressure orthostatic increased Orthostatic hypertension Essential hypertension Hypertensive crisis Hypertensive emergency Malignant hypertension Hypertensive encephalopathy Labile hypertension Prehypertension Procedural hypertension Renal hypertension Secondary hypertension Systolic hypertension Withdrawal hypertension Blood pressure fluctuation
Thyroid Dysfunction	Any event of hypothyroidism or other thyroid dysfunction; or Lab TSH increase with T3 or T4 decrease, with or without any symptom Analysis method: The overall incidence of thyroid dysfunction with Fruquintinib compared to placebo will be evaluated using the MedDRA SMQ of Hypothyroidism. It will be categorized by CTC AE grades.	Hypothyroidism Thyroid disorder Thyroxine therapy Thyroid therapy Thyroid atrophy Thyroid function test abnormal Thyroxine abnormal Thyroxine decreased Thyroxine free abnormal Thyroxine free decreased Tri-iodothyronine abnormal Tri-iodothyronine decreased Tri-iodothyronine free abnormal Tri-iodothyronine free decreased Iodine uptake abnormal Iodine uptake decreased Tri-iodothyronine uptake abnormal Tri-iodothyronine uptake decreased

		Anti-thyroid antibody positive Anti-thyroid antibody
Proteinuria	Any event of proteinuria, 24hrs urinary protein high, urinary protein test positive Analysis method: The overall incidence of proteinuria with Fruquintinib compared to placebo will be evaluated using a group of MedDRA PTs regarding proteinuria (PT listing will be defined upon the cleaned and coded AE data). It will also be categorized by CTC AE grades.	Protein urine present Proteinuria
Dermatological Toxicity	Any event of hand-foot syndrome or other severe skin reactions Analysis method: The overall incidence of HFS and rash with Fruquintinib compared to placebo will be evaluated using a group of MedDRA PTs regarding HFS and rash (PT listing will be defined upon the cleaned and coded AE data). It will also be categorized by CTC AE grades.	Palmar-plantar erythrodysaesthesia syndrome Palmar erythema Dermatitis bullous Dermatitis allergic Dermatitis psoriasiform Dermatitis acneiform Blister Rash Rash erythematous Rash maculo-papular Skin reaction Skin disorder Skin exfoliation Erythrosis Nail disorder Nail bed bleeding Acute generalised exanthematous pustulosis Cutaneous vasculitis Dermatitis exfoliative generalized Dermatitis exfoliative Drug reaction with eosinophilia and systemic symptoms Epidermal necrosis Erythema multiforme Exfoliative rash Oculomucocutaneous syndrome Skin necrosis Stevens-johnson syndrome

		Toxic epidermal necrolysis Toxic skin eruption Acquired epidermolysis bullosa Blister rupture Bullous impetigo Drug eruption Epidermolysis bullosa Epidermolysis Skin erosion
Cardiac Ischemia and Infarction	A group of Acute Cardiac Syndrome (ACS) relevant symptoms, such as chest pain, tightness or discomfort, accompanied with dyspnoea, nausea, vomiting…, OR Any diagnosis event of angina, ACS ,or cardiac ischemia or infarction Analysis method: The overall incidence of cardiac ischemia and infarction with Fruquintinib compared to placebo will be evaluated using the MedDRA SMQ of Ischaemic heart disease. It will be categorized by CTC AE grades.	Acute coronary syndrome Acute myocardial infarction Angina unstable Blood creatine phosphokinase MB abnormal Blood creatine phosphokinase MB increased Coronary artery embolism Coronary artery occlusion Coronary artery thrombosis Myocardial infarction Myocardial necrosis Troponin increased Troponin I increased Troponin T increased Infarction Blood creatine phosphokinase abnormal Blood creatine phosphokinase increased Cardiac enzymes increased Electrocardiogram ST segment elevation Electrocardiogram ST-T segment elevation Angina pectoris Angina unstable Arteriosclerosis coronary artery Arteriospasm coronary Coronary angioplasty Coronary arterial stent insertion Percutaneous coronary intervention

		Coronary artery bypass Coronary artery disease Coronary artery insufficiency Coronary artery stenosis ECG signs of myocardial ischaemia Ischaemic cardiomyopathy Myocardial ischaemia Prinzmetal angina Subendocardial ischaemia
Arterial/Venous Thromboembolic Events	Any arterial or venous thromboembolic event, including but not limited to, arterial thrombosis, pulmonary embolism, deep vein thrombosis, retinal vein occlusion or thrombosis. Analysis method: The overall incidence of thromboembolic events with Fruquintinib compared to placebo will be evaluated using the MedDRA SMQ of Embolic and thrombotic events. It will be categorized by CTC AE grades.	Acute aortic syndrome Acute myocardial infarction Aortic embolus Aortic thrombosis Arterial occlusive disease Arterial thrombosis Basal ganglia infarction Basilar artery occlusion Basilar artery thrombosis Blindness transient Brachiocephalic artery occlusion Carotid arterial embolus Carotid artery occlusion Carotid artery thrombosis Cerebellar artery occlusion Cerebellar artery thrombosis Cerebral artery embolism Cerebral artery occlusion Cerebral artery thrombosis Cerebral hypoperfusion Cerebrovascular insufficiency Cerebrovascular stenosis Coeliac artery occlusion Coronary artery embolism Coronary artery occlusion Coronary artery reocclusion Coronary artery thrombosis Embolism arterial Femoral artery embolism Femoral artery occlusion Hepatic artery embolism Hepatic artery occlusion Hepatic artery thrombosis Iliac artery embolism Iliac artery occlusion

		Intraoperative cerebral artery occlusion Ischaemic cerebral infarction Ischaemic stroke Lacunar infarction Leriche syndrome Mesenteric arterial occlusion Mesenteric arteriosclerosis Mesenteric artery embolism Mesenteric artery stenosis Mesenteric artery thrombosis Myocardial infarction Myocardial necrosis Papillary muscle infarction Penile artery occlusion Peripheral arterial occlusive disease Peripheral arterial reocclusion Peripheral artery thrombosis Peripheral embolism Popliteal artery entrapment syndrome Post procedural myocardial infarction Pulmonary artery thrombosis Renal artery occlusion Renal artery thrombosis Renal embolism Retinal artery embolism Retinal artery occlusion Retinal artery thrombosis Silent myocardial infarction Spinal artery embolism Spinal artery thrombosis Splenic artery thrombosis Splenic embolism Stress cardiomyopathy Subclavian artery embolism Subclavian artery occlusion Subclavian artery thrombosis Superior mesenteric artery syndrome Thrombotic microangiopathy Thrombotic thrombocytopenic purpura

		Transient ischaemic attack Truncus coeliacus thrombosis Vertebral artery occlusion Vertebral artery thrombosis Visual acuity reduced transiently Axillary vein thrombosis Cavernous sinus thrombosis Cerebral venous thrombosis Deep vein thrombosis Deep vein thrombosis postoperative Embolism venous Hepatic vein occlusion Hepatic vein thrombosis Iliac vein occlusion Inferior vena cava syndrome Inferior vena caval occlusion Intracranial venous sinus thrombosis Jugular vein thrombosis May-Thurner syndrome Mesenteric vein thrombosis Mesenteric venous occlusion Obstetrical pulmonary embolism Obstructive shock Ophthalmic vein thrombosis Ovarian vein thrombosis Paget-Schroetter syndrome Pelvic venous thrombosis Penile vein thrombosis Portal vein occlusion Portal vein thrombosis Post procedural pulmonary embolism Post thrombotic syndrome Postoperative thrombosis Pulmonary embolism Pulmonary infarction Pulmonary microemboli Pulmonary thrombosis Pulmonary vein occlusion Pulmonary veno-occlusive disease

		Pulmonary venous thrombosis Renal vein embolism Renal vein occlusion Renal vein thrombosis Retinal vein occlusion Retinal vein thrombosis Splenic vein occlusion Splenic vein thrombosis Subclavian vein thrombosis Superior sagittal sinus thrombosis Superior vena cava occlusion Superior vena cava syndrome Thrombophlebitis Thrombophlebitis migrans Thrombophlebitis neonatal Thrombophlebitis superficial Thrombosed varicose vein Thrombosis corpora cavernosa Transverse sinus thrombosis Vena cava embolism Vena cava thrombosis Venogram abnormal Venoocclusive disease Venoocclusive liver disease Venous occlusion Venous thrombosis Venous thrombosis limb
Gastrointestinal Perforation	Any event of gastrointestinal perforation. Analysis method: The overall incidence of gastrointestinal perforation with Fruquintinib compared to placebo will be evaluated using the MedDRA SMQ of Gastrointestinal perforation. It will be categorized by CTC AE grades.	Abdominal abscess Abdominal hernia perforation Abdominal wall abscess Abscess intestinal Acquired tracheo-oesophageal fistula Anal abscess Anal fistula Anal fistula excision Anastomotic ulcer perforation Anovulvar fistula Aorto-duodenal fistula Aorto-oesophageal fistula Appendiceal abscess Appendicitis perforated

		Chemical peritonitis Colon fistula repair Colonic abscess Colonic fistula Diverticular fistula Diverticular perforation Douglas' abscess Duodenal fistula Duodenal perforation Duodenal ulcer perforation Duodenal ulcer perforation, obstructive Duodenal ulcer repair Enterocolonic fistula Enterocutaneous fistula Enterovesical fistula Gastric fistula Gastric fistula repair Gastric perforation Gastric ulcer perforation Gastric ulcer perforation, obstructive Gastrointestinal anastomotic leak Gastrointestinal fistula Gastrointestinal fistula repair Gastrointestinal perforation Gastrointestinal ulcer perforation Gastropleural fistula Gastrosplenic fistula Ileal fistula Ileal perforation Ileal ulcer perforation Intestinal fistula Intestinal fistula repair Intestinal perforation Intestinal ulcer perforation Jejunal fistula Jejunal perforation Jejunal ulcer perforation Large intestinal ulcer perforation Large intestine perforation Neonatal intestinal perforation

		Oesophageal fistula Oesophageal fistula repair Oesophageal perforation Oesophageal rupture Oesophageal ulcer perforation Oesophagobronchial fistula Paraoesophageal abscess Peptic ulcer perforation Peptic ulcer perforation, obstructive Perforated peptic ulcer oversewing Perforated ulcer Perineal abscess Perirectal abscess Peritoneal abscess Peritonitis Peritonitis bacterial Procedural intestinal perforation Rectal abscess Rectal fistula repair Rectal perforation Rectoprostatic fistula Rectourethral fistula Retroperitoneal abscess Small intestinal perforation Small intestinal ulcer perforation