Statistical Analysis Plan

2015-0013-00US1

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

Author: [redacted]

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V2.5 (Dated 18Feb2021) for Protocol 2015-013-00US1.

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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OUTPUT TEMPLATES 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
0.1	10Jan2018	[redacted]	Not Applicable – First Version
0.2	15Mar2018	[redacted]	Revise 3.1 section according to protocol version 2 Revise the REAS according to protocol version 2 Add the FAS according to the requirement for analysis Delete the shift table for low, high, normal according to protocol
0.3	24Jan2019	[redacted]	Add the definition of OS and PFS at 12 weeks Revise the population set of REAS to EAS. Add the definition of subsequent anti-cancer therapy. Delete the shift from baseline analysis of ECOG PS. Global changes according to protocol version 3.
1.0	30Jan2019	[redacted]	Upgrade version, no updates.
1.0	17Jan2020	[redacted]	Updating SAP & Shell according to sponsor' comments
1.1	11Feb2020	[redacted]	Updating SAP & Shell according to sponsor' comments
	03Mar2020	[redacted]	Update Table 14.1.1.1, Table 14.1.6.1, source listing of Table 14.1.6.2,
	09Mar2020	[redacted]	Update shell of " Listing 16.2.7.2"
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1.2	15Oct2020	[redacted]	- Revision done for amended protocol V.4.0 -Wording change on replacing 'subject' with 'patient' -Typos -Output Conventions -Revisions were done in almost all sections except for section 4.2, 6, 7.1, 7.2, 7.3.3-7.5, 8, and 14.
2.0	23Nov2020	[redacted]	Revision according to sponsor's comments
	30Nov2020	[redacted]	- Revisions of format and typos - Remove one blank page
	04Dec2020	[redacted]	- Remove section 2.3 to Appendix 1 - Re-number all appendices - Revisions of section 3, 5.7, 6.2, 6.3.1, 6.3.2, 7-12, 13.2, 14, 15.1, 16.1.5, 16.2 - Changes on wording according to sponsor's comments
	08Dec2020	[redacted]	Revise SI unit of: Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase
	09Dec2020	[redacted]	Update Appendix 4
	10Dec2020		Update section 2.4 and 17.4.4

	16Dec2020	[redacted]	- Section 17.7 and corresponding shell - Update some inconsistencies based on shell - Specify cut-off date on header - Separate Table 14.1.1.1 into 2 tables and update footnote separately - Footnote update for some tables - Update Appendix 4 - typo correction
	18Dec2020	[redacted]	Date update
2.2	02Jul2021	[redacted]	Update Appendix 2: Presentation of Treatment Groups
2.3	16Nov2021	[redacted]	Date update
2.4	13Dec2021	[redacted]	- Version and date updated - Updated format of Appendix 4, 5 and 6 - Updated table 2 and AESI description in section 17.2.6 - Removed additional blank - Updated listing 16.2.9.6 Pharmacokinetic Blood Sample (Pharmacokinetic Analysis Set) to listing 16.2.9.6 COVID-19 Visit Impact (Safety Analysis Set)
2.5	18Feb2022	[redacted]	- Version and date updated - Update the AESI list of table in Appendix 5, the old list is the MedDRA 24.0, and the updated list is using MedDRA 24.1.

TABLE OF CONTENTS

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
ATC	Anatomical Therapeutic Classification
BC	Breast Cancer
BMI	Body Mass Index
BOR	Best Overall Response
CEA	Carcino-Embryonic Antigen
CR	Complete Response
CS	Clinically Significant
CTCAE	Common Terminology Criteria for Adverse Event
CTMS	Clinical Trial Management System
DCR	Disease Control Rate
DLT	Dose-Limiting Toxicity
DoR	Duration of Response
DILI	Drug Induced Liver Injury
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic Case Report Form
ENR	All Patients Enrolled Set
HR	Hormone Receptor
INR	International Normalized Ratio
LLQ	Lower Limit of Quantification
mCRC	Metastatic Colorectal Cancer
MedDRA	Medical Dictionary for Regulatory Activities
MUGA	Multi-Gated Acquisition
NCI	National Cancer Institute

NCS	Not Clinically Significant
NE	Not Evaluable
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progressive Free Survival
PID	Percentage Intended Dose
PLT	Blood platelet count
PR2D	Recommended Phase 2 Dose
PR	Partial Response
RD	Relative Dose
PT	Preferred Term
QD	Quaque Die/ Once Daily
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SD	Stable Disease
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
STD	Standard Deviation
TEAE	Treatment-Emergent Adverse Event
TEAESI	Treatment-Emergent Adverse Event of Special Interest
TNBC	Triple-Negative Breast Cancer
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

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol 2015-013-00US1. 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 Version 4.0 (Amendment 4), dated 09 Jan 2020. The Pharmacokinetics (PK) and pharmacodynamics analyses will not be performed by IQVIA Biostatistics (BIOS) and therefore are not documented in this SAP.

1.1. PRIMARY OBJECTIVE

1.1.1. 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).

1.1.2. DOSE EXPANSION PHASE

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

1.2. SECONDARY OBJECTIVES

1.2.1. DOSE ESCALATION PHASE

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 (The detailed analysis method will not be documented in this document).
- To evaluate anticancer activity of fruquintinib in patients with solid tumors according to the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (Eisenhauer et al., 2009).

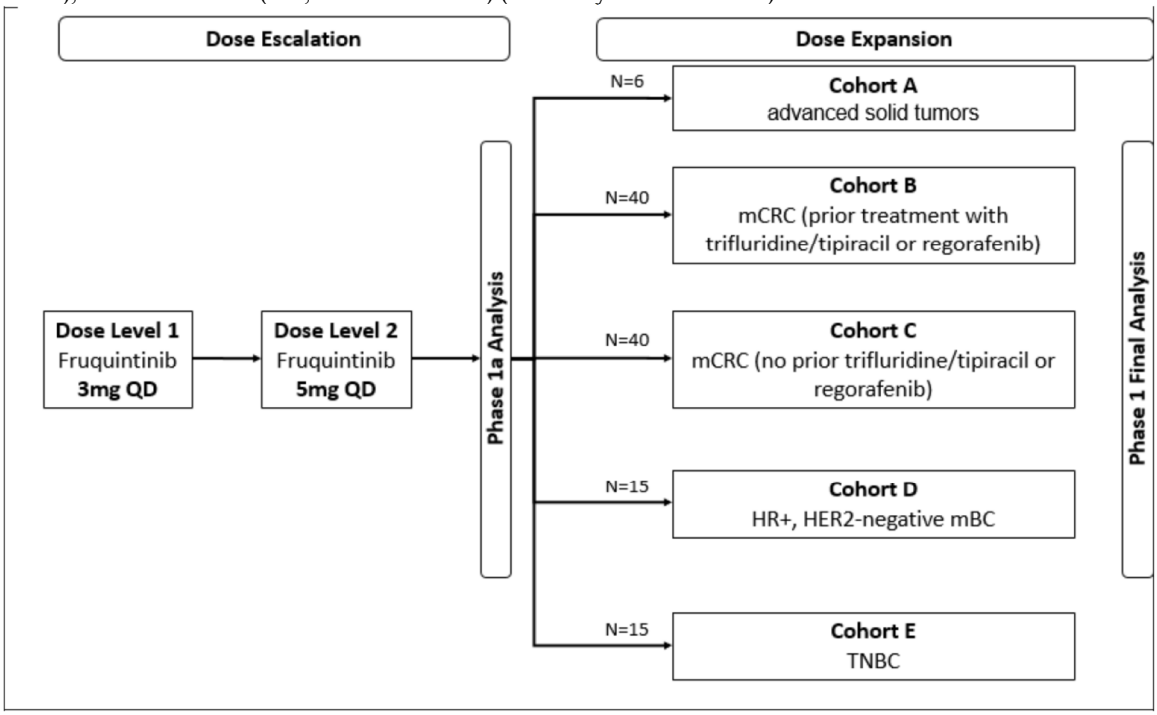
1.2.2. DOSE EXPANSION PHASE

The secondary objectives of the dose expansion phase are:

- To evaluate anticancer efficacy of fruquintinib, as assessed by Objective response rate (ORR), disease control rate (DCR), duration of response (DoR), progression free survival (PFS) and overall survival (OS).
- To evaluate the PK characteristics of multiple dose fruquintinib and to investigate the metabolite profile of fruquintinib in plasma.
- To evaluate the safety of fruquintinib.

2. STUDY DESIGN

The study 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) and in patients with refractory metastatic colorectal cancer (mCRC, Cohort B and C), or breast cancer (BC, Cohort D and E) (see study schema below).



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 and 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 triple-negative breast cancer (TNBC) will be enrolled in the dose expansion phase.

2.1. 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 Maximum Toxicity Dose (MTD) level reached in this trial. 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. The dose levels to be investigated are 3 mg and 5 mg once daily (QD), 3 weeks on/1 week off.

The definition of DLTs and the DLT assessment window is provided in section 17.1 and the definition of a DLT evaluable patient is provided in section 4.3.

To investigate DLT, 6 DLT-evaluable patients will be firstly 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 (i.e. from Day 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). 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 the completion of the dose escalation phase, the SRC will review aggregated safety and PK data and then select a fruquintinib dose as the RP2D for the expansion phase of the trial. Prior to confirmation of a DLT, if a patient has received any prophylactic medical intervention or missed 4 or more fruquintinib dose 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.

Patients will be followed until death or study completion, which is defined as the CRF form "End of Study" is filled.

2.2. 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 TNBC who have progressed on at least one cytotoxic therapy in the metastatic setting

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 serious adverse events (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 National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) V4.03.

In the dose expansion phase, tumor response will be assessed according to RECIST Version 1.1 (Eisenhauer et al., 2009) at screening, and at study visits according the Schedule of Events (Appendix A in the protocol). Confirmation of complete response (CR) and partial response (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.

2.3. STUDY ENDPOINTS

2.3.1. DOSE ESCALATION PHASE

- Primary Endpoints: The primary endpoint of the dose escalation phase is the incidence of DLT in each cohort.
- Secondary endpoints: The objective response rate (ORR), disease control rate (DCR), duration of response (DoR), and progression free survival (PFS) according to RECIST Version 1.1 (Eisenhauer et al., 2009), overall survival (OS) and percentage change from baseline in tumor size.

2.3.2. DOSE EXPANSION PHASE

- Primary endpoint: PFS
- Secondary endpoints:
    - Efficacy analysis: ORR, DCR, DoR, PFS according to RECIST Version 1.1 (Eisenhauer et al., 2009), OS and percentage change in tumor size from baseline.
    - Safety analysis: the incidence and severity of adverse events (AEs), physical examinations, vital signs, laboratory test results, 12-lead electrocardiogram, and echocardiogram.

2.4. CHANGES TO ANALYSIS FROM PROTOCOL

- Change in definition of efficacy analysis set (EAS), in section 4.4.
- Analysis to be performed based on EAS has been revised to exclude PFS and OS in section 4.4.
- Subsequent oncology therapy was not defined in the protocol. The definition and analysis has been added in section 13 of SAP
- Changes on criteria of Hy's Law; "Serum AST or ALT ≥3 × ULN and ALP < 2x ULN and total bilirubin ≥2 × ULN" is changed to be "Hy's Law: Serum AST or ALT > 3 × ULN and ALP < 2x ULN and total bilirubin > 2 × ULN", in section 17.4.4.
- Changes on criteria of drug-induced liver injury (DILI); "Serum AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN" is changed to be "Serum AST or ALT > 3 × ULN together with total bilirubin > 2 × ULN", in section 17.4.4.

3. PLANNED ANALYSES

The timing of analysis for each cohort may be different depending on completion of each cohort, and the final analysis of the study will be conducted at the time of analysis of the last cohort. No formal interim analysis is planned for the study. However, the accrued data from any cohort may be analyzed for internal decision-making purposes; for example, to provide information for a future trial or external data disclosures. Then, the Database Lock (DBL) authorized by sponsor will be planned depending on the purpose of the analysis.

The final analysis will be planned to be carried out after a DBL. The DBL of final analysis is performed according to the study termination criteria (but not limited to) as below:

- The study is completed when all patients have discontinued study drug or the last enrolled patient have completed 1 year of treatment

OR

- If the study is terminated early for reasons including but not limited to:
    - The incidence or severity of adverse events (AEs) in this or other studies indicates a potential health hazard to patients.
    - Patient enrollment is unsatisfactory.

3.1. INTERIM ANALYSIS

No formal interim analysis is planned for the study. However, the accrued data from any cohort may be analyzed for internal decision-making purposes; for example, to provide information for a future trial or external data disclosures. During the analysis, selected summary for safety and anticancer activity of fruquintinib will be performed.

3.2. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics following Sponsor Authorization of this Statistical Analysis Plan and Database Lock for this study.

4. ANALYSIS SETS

Agreement and authorization of patients included/excluded from each analysis set will be conducted prior to database lock.

4.1. ALL PATIENTS ENROLLED SET [ENR]

The analysis set contains all patients who provide the informed consent form for this study.

4.2. SAFETY ANALYSIS SET [SAS] – (ALL TREATED POPULATION)

The analysis set includes all patients who have received at least one dose of fruquintinib. 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 on the initial dose of study drug received.

All safety analyses except for DLT summaries, along with PFS and OS will be based on the SAS.

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

4.3. DOSE-LIMITING TOXICITY EVALUABLE SET [DLT]

The analysis set comprises all SAS patients who are evaluable for DLT assessment. DLT evaluable patients are identified if [Yes] is ticked as the response to “DLT Evaluable Patients” on CRF. DLT set and summaries will only apply to dose escalation phase.

4.4. EFFICACY ANALYSIS SET [EAS]

This analysis set includes all patients who have received at least 1 dose of fruquintinib, have a measurable lesion (target lesions ≥ 10 mm) at the baseline tumor assessment, and either (i) have had at least one post-baseline tumor assessment, or (ii) do not have post-dose tumor assessment but have clinical progression as noted by the investigator, or have died due to disease progression before their first post-baseline tumor scan. All efficacy endpoints (i.e. BOR, ORR, DCR, DoR, and best percentage change from baseline in tumor size), not including PFS and OS, will be summarized based on this analysis set.

5. GENERAL CONSIDERATIONS

5.1. REFERENCE START DATE AND STUDY DAY

Reference start date is defined as the day of the first dose of study medication. Study Day will be calculated from the reference start date and will be used to show start/ stop day of assessments and events. Study day will appear in every listing where an assessment date or event date appears.

If the date of the event is on or after the reference date then:

Study Day = (date of event – reference date) + 1.

If the date of the event is prior to the reference date then:

Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings, but Study Day and any corresponding durations will be presented based on the imputations specified in section 6.3.

5.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to 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, unless additional information collected on eCRF indicate otherwise.

For example, ECG will be considered being performed post-baseline if assessment date coincides with the reference start date but "Time Point" on "ECG (ECG)" form indicates the assessment was performed "Post-dose 3 hours (± 15 minutes)". Adverse Events (AEs) onset on the reference start date and with "Did the adverse event occur prior to the start of study treatment?" in "Adverse Events (AE)" form answered as "No" or not being answered will be considered as post-baseline. Medications commencing the reference start date will be considered post-baseline.

5.3. 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).

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

5.4. WINDOWING CONVENTIONS

The visit-window mapping is described in APPENDIX 4. Visit-based summaries will be based on the windowed visits. All data, whether or not within the visit windows, will be presented in listings.

For windowed visits during the treatment cycles,

- If more than 1 assessment occurs during a visit window, the assessment closest to the scheduled day will be assigned to the windowed visit.
- If two assessments are equidistant from the scheduled day, the later assessment will be assigned to the windowed visit.
- If there are multiple assessments on the same day, the worst case will be used.

For the post-treatment visit, the last assessment in the window will be included in the summary. The window for the post-treatment visit will be "from the last dose date + 8 days to the last dose date + 37 days".

For a patient who prematurely discontinues the study, the premature visit will be slotted accordingly.

5.5. STATISTICAL TESTS

No formal statistical hypotheses will be tested in this study.

Two-sided 95% confidence intervals will be calculated and two-sided, unless otherwise specified in the description of the analyses.

5.6. COMMON CALCULATIONS

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

Test Value at Visit X – Baseline Value

5.7. SOFTWARE VERSION

All analyses will be conducted with SAS version 9.4 or higher based on Enterprise Guide version 7.1.

6. STATISTICAL CONSIDERATIONS

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

No adjustment will be performed.

6.2. MULTICENTER STUDIES

This study is planned to be carried out at up to 10 sites. However, no adjustment in aspect of site effect will be performed. Data from all centers will be pooled for the analysis.

6.3. MISSING DATA

Generally, the missing efficacy and safety data will not be imputed except for the critical missing and partial dates which will be handled as described in this section. In the situation where partial or missing date are imputed, the date will appear partial or missing in the listings, while imputed date will only be used for calculation.

6.3.1. MISSING DATES INFORMATION OF STUDY TREATMENT

When the date of the last dose of study treatment is missing for a patient, all efforts should be made to obtain the date from the investigator. If it is still missing after all efforts, the last dose date collected from the [Study Drug Administration] page of or data cut-off date (if applicable) will be used in the calculation of treatment duration.

6.3.2. MISSING OR INCOMPLETE DATE INFORMATION FOR ADVERSE EVENT DATE

For the purpose of determining whether an adverse event (AE) is treatment emergent (see section 17.2.1), incomplete start dates and/or stop dates will be imputed. Start date will be imputed first when the start date and stop date are both incomplete for a patient. If the field of year is missing or start date of an AE is completely missing, then no value will be imputed. The following rules will be applied to impute the incomplete start date, assuming year is available.

Missing or incomplete start date

- In case the start date of an AE is in the same year as reference start date (when only year is recorded), or the start date is in the same month and year (if only the day is missing) as the reference start date, then the start date of the AE will be imputed by the reference start date or the AE resolution date, whichever occurs earlier.
- If the day and month parts of the AE onset date are missing and occur in the same year as the first dose of study drug, the date of the first dose of study drug will be used as the onset date of the AE. If an AE is observed on different year of first dose, January 1st will be used to complete the onset date of the AE.
- If only the day part of the AE onset date is missing and occurs in the same month and year as the first dose date of study drug, the date of first dose of study drug will be used as the onset date of the AE. Otherwise, the first day of the month will be used to complete the onset date of the AE.
- In all other cases, imputation will not be performed.

Here are some examples.

Incomplete Date of Onset (DD MMM YYYY)	Reference Start Date (DD MMM YYYY)	Imputed Date (DD MMM YYYY)
---------	10Apr2017	---------

Incomplete Date of Onset (DD MMM YYYY)	Reference Start Date (DD MMM YYYY)	Imputed Date (DD MMM YYYY)
-----2017	10Apr2017	10Apr2017
-----2018	10Apr2017	01Jan2018 (because the AE onsets after the reference date)
--Apr2017	10Apr2017	10Apr2017
--Oct2017	10Apr2017	01Oct2017
05---2017	10Apr2017	05---2017

Missing or incomplete stop date

Incomplete stop dates will be imputed to the last possible date:

- If the known part(s) of the AE end date is (are) the same as the death date/ end of study date, the AE end date will be imputed by the death date/ end of study date, whichever occurs earlier.
- In all other cases, the AE end date will be imputed to the last day of the month if only the day is missing or imputed to with 31st December if both day and month are missing.
- If the imputed stop date is before the start date (imputed or non-imputed start date), then the stop date will be imputed using start date.
- If the end date is completely missing or the year part is unknown, the end date will not be imputed.

Here are some examples:

Incomplete AE End Date (DD MMM YYYY)	Date of Death/ End of Study (DD MMM YYYY)	Imputed Date (DD MMM YYYY)
--May2017	Not Available/ Not Available	31May2017
--Sep2017 (known part the SAME as date of death/ end of study)	---------/ 09Sep2017	09Sep2017
-----2017 (known part the SAME as date of death/ end of study)	09Sep2017/ 09Sep2017	09Sep2017
--Jun2017 (known part DIFFERENT from date of death/ end of study)	09Sep2017/ 09Sep2017	30Jun2017
---------	---------/ 09Sep2017	---------
31Dec-----	09Sep2017/ 09Sep2017	31Dec----
-----2018	09Oct2019/ 09Oct2019	31Dec2018

6.3.3. Missing or Incomplete Date Information for Concomitant Medication/ Procedure

The imputation rule is the same as described for adverse event.

6.3.4. Missing or Incomplete Date Information for Primary Diagnosis Date and Metastatic Diagnosis Date

Imputation will only be applied in case the field of year is available. If year and month are known but the day is unknown, day will be imputed as 15. If only year is known, month and day will be imputed to July 1st. If the diagnosis date is completely missing or the year part is unknown, the diagnosis date will not be imputed.

6.3.5. Missing or Incomplete Date Information for Efficacy Data

When a partial new anticancer therapy starting date is reported, every effort will be made to identify the precedence relationship of starting date of new anticancer therapy relative to last dosing date of study drug and the date of disease progression (if happened). According to the confirmed precedence relationship, partial new anticancer therapy date will be imputed to the earliest possible date:

- Day will be imputed as 1 if year and month are known; month and day will be imputed as Jan 1st if only year is known.
- In rare case, if year and month of death date are known but the day is unknown, day will be imputed as 15. For example, if a patient is reported to die on Dec2017, the death date will be imputed as 15 Dec2017.

However, the imputed anticancer start date will be adjusted based on corresponding date in different scenario as shown below, the imputed date will be set to the date according to which it will be adjusted if the originally imputed date is earlier than the corresponding date:

- Adjust based on the date of first dose in case that anticancer therapy starts earlier than both last dosing date and disease progression.
- Adjust based on the last dosing date/the date of disease progression which occurs earlier in case that anticancer therapy is initiated after last dosing date but before disease progression date or vice versa.
- Adjust based on the last dosing date/the date of disease progression which occurs later in case that anticancer therapy is initiated after both last dosing and disease progression.

6.4. Multiple Comparisons/ Multiplicity

There are no requirements for multiplicity adjustments in this study.

6.5. Examination of Subgroups

No subgroup analyses will be performed for this study.

7. OUTPUT PRESENTATIONS

Appendix 2 shows conventions for presentation of data in outputs.

Format and content of summary tables, figures, and listings are presented as mock shells for TFLs and provided by IQVIA Biostatistics.

Continuous variables will be summarized using descriptive statistics including, number of patients (n), mean, median, standard deviation (STD), 25% and 75% quantiles, minimum and maximum. Categorical variables will be summarized with number and percentage and presented in frequency tables. All results will be presented by dose cohort (only in dose escalation phase) or tumor specific cohorts (only in dose expansion phase).

Qualitative variables will be summarized by count(s) and percentages (%).

Percentages will be reported with 1 decimal point; if the count is 0, no percentage will be presented. Value of percentage less than 1% will be presented as "<1%." Value of percentage less than 100% but >99% will be presented as ">99%." Any rounding will be done after all calculations are made.

8. DISPOSITION AND WITHDRAWALS

8.1. ENROLLMENT

Information of all patients who provided informed consent (that is the ENR) will be included in the summary of disposition and withdrawals for this study. A summary table will be generated to provide the following:

- Number of patients who signed the informed consent
- Number of screen failures
- Reason for screen failure
- Number of patients who passed screening
- Number of patients who withdrew consent before study treatment
- Number of patients who received treatment

A separate table will be presented to show the patients included in each analysis set and reason for exclusion from an analysis set.

8.2. PATIENT STATUS AT TREATMENT AND STUDY COMPLETION

Patient status at treatment and study completion will be listed and summarized for SAS. The listing will include individual information (i.e. site and patient number, informed consent information), whether patients discontinued from the treatment and the reasons for the discontinuation, along with the date of first/ last dose, duration of treatment, and the date of discontinuation from the treatment. The same information will be provided for patients who discontinued from the study. The following summaries will be presented:

- Patients still on treatment
- Reason for study drug discontinuation (for study drug)
- Number of patients going into Survival follow-up
- Number and percentage of patients who discontinue the study
- Reason for study discontinuation

A flowchart for disposition will be presented.

9. PROTOCOL DEVIATION

Protocol deviations are recorded as critical, major or minor in Clinical Trial Management System (CTMS) and are classified into 10 categories:

- Administrative Criteria
- Eligibility and Entry Criteria
- Informed Consent Criteria
- IP Compliance
- Laboratory Assessment Criteria
- Regulatory or Ethics Approvals Criteria
- Serious Adverse Event Criteria
- Study Procedures Criteria
- Visit Schedule Criteria
- Other Criteria

Major protocol deviations are those recorded as critical or major.

All subject-level protocol deviations will be presented in listing including deviation date and severity.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the SAS. Data listing will also be provided.

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 consent; summarized as both continuous variable and categorical variable (< 65 vs. ≥ 65 years)
- Gender
- Race
- Ethnicity
- Weight (kg)
- Height (cm)
- BMI (kg/m^2): summarized as both continuous and categorical variable (<18.5, ≥18.5 and <24, ≥24 kg/m^2)
- Baseline ECOG performance status (0, 1, 2, 3, 4, 5)

10.1. DERIVATIONS

BMI (kg/ m^2) = weight (kg)/ height (m)^2

11. SURGICAL AND MEDICAL HISTORY

Medical and surgical history will be coded by MedDRA Version 23.1 or higher and summarized separately for SAS; results will be expressed by system organ class (SOC) and preferred term (PT) in descending order of the frequency in total. For SOCs or PTs with the same frequency, results will be sorted alphabetically.

Individual patient listings of and medical/surgical history will also be provided for the SAS.

12. ONCOLOGY HISTORY

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

- Primary diagnosis of malignancy
- Time since primary diagnosis to first dose of study treatment (months)
- Primary site
- Diagnosis of malignancy at enrollment
- Metastatic status (yes, no)
- Number of metastatic sites: both continuous variable and categorical variable (0, 1, 2, >=3)
- Time since first metastasis diagnosis to first dose of study treatment (months)
- TNM stage at enrollment
- Disease stage at enrollment
- Histological classification at enrollment (Adenocarcinoma, Adenosquamous Carcinoma, Carcinoid, Clear Cell Carcinoma, Indeterminate, Sarcoma, Squamous (except squamous non-small cell lung cancer [NSCLC], Other)
- Prior use of VEGF-R inhibitor (yes, no)
- Prior use of VEGF inhibitor (yes, no)
- Time since last systemic anti-neoplastic therapies to first dose of study treatment (months)
- Liver metastasis (yes, no): obtained based on whether the liver organ was involved in the target and non-target lesion tumor scan assessment at the baseline.

12.1. DERIVATIONS

- Time since primary diagnosis to first dose of study treatment (months) = (Date of first dose of study treatment – Date of primary diagnosis)/ 30.4375
- Time since first metastasis diagnosis to first dose date (months) = (Date of first dose of study treatment – Date of first metastasis diagnosis)/ 30.4375
- Time since last systemic anti-neoplastic therapies to first dose of study treatment (months) = (Date of first dose of study treatment – Date of last systemic anti-neoplastic therapies)/ 30.4375

13. ONCOLOGICAL THERAPIES

13.1. PRIOR ONCOLOGICAL THERAPY

Prior oncological therapy information are recorded as following: Prior oncology medication information, Prior oncology radiotherapy information, Prior oncology surgery and procedure information.

Prior oncology medication will be coded using World Health Organization Drug Dictionary Enhanced (WHO DDE) Version SEP2020. Prior oncology surgery and procedures will be coded using MedDRA Version 23.1 or higher.

Prior oncology medications will be presented by Anatomical Therapeutic Classification (ATC)-2nd-level term (ATC level 2) and by PTs for each dose and/ or disease cohort in each phase. ATC class and PT will be sorted in descending frequency of the total number of patients with at least one condition in the corresponding category; ATCs/PTs will be presented alphabetically for ATCs/PTs of the same total frequency. In addition, number and percent of patients who have received prior oncology medication, regimen number, and category of regimen number will be summarized for prior oncology medication.

Prior oncology surgery and procedures will be presented by SOC and PT for each cohort in each phase. SOC and PT will be sorted in descending frequency of the total number of patients with at least one condition in the corresponding category, SOCs/PTs will be presented alphabetically for SOCs/PTs of the same total frequency. Corresponding listings will be provided.

13.2. SUBSEQUENT ONCOLOGY THERAPY

Subsequent oncology therapies taken after end of treatment will be collected in below forms:

- "Oncology Medication (CHEMO1)"
- "Oncology Radiotherapy"
- "Oncology Surgery and Procedure"

Subsequent oncology therapies are defined as therapies started after the last dose of study medication. The following information will be summarized and listed for subsequent therapy:

- Number of subsequent oncology medications
- Number of subsequent regimen
- Category of number of subsequent regimen

Subsequent oncology (or anti-tumor) medications will also be presented by ATC level 2 and by PTs for each dose/ disease cohort in each phase.
Subsequent anti-tumor therapy will be flagged in the listing of oncology medication/ radiotherapy/ surgery.

14. MEDICATIONS AND PROCEDURES

Medications and procedures information are recorded as following:

- Prior and concomitant medication information
- Prior and concomitant procedure information

'Prior' medications/procedures are medications/procedures which started prior to the first dose of study medication.

'Concomitant' medications/procedures except for oncology therapies are medications which ended on or after the date of first dose of study medication or were ongoing at the end of the study, and start no later than 37 days following last dose administration.

A medication may be both prior and concomitant if it meets 2 above-mentioned definitions.

14.1. PRIOR AND CONCOMITANT MEDICATION

Medications will be coded using World Health Organization Drug Dictionary Enhanced (WHO DDE), Versions SEP2020 or higher. See section 6.3.3 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior and concomitant, the medication will be classified by the worst case, i.e. concomitant.

Concomitant medications will be presented by ATC level 2 and by PTs for each dose and/ or disease cohort in each phase. ATC class and PT will be sorted in descending frequency of the total number of patients with at least one condition in the corresponding category, ATCs/PTs will be presented alphabetically for ATCs/PTs of the same total frequency.

Prior and concomitant medications will be presented in listings with flag to differentiate whether the medication is prior medication or concomitant medication.

14.2. CONCOMITANT PROCEDURES

Surgery and procedures will be coded using MedDRA Version 23.1 or higher. Concomitant procedures will be presented by SOC and PT for each dose and/ or disease cohort in each phase.

SOC and PT will be sorted in descending frequency of the total number of patients with at least one condition in the corresponding category, SOCs/PTs will be presented alphabetically for SOCs/PTs of the same total frequency.

Prior and concomitant surgery will be listed and flagged like the listing of prior and concomitant medication.

15. STUDY MEDICATION EXPOSURE

Exposure to study medication and compliance will be presented for the SAS.

The planned treatment is given at either 3mg QD or 5mg QD in the corresponding study phase and dose and/ or disease cohort. In each 28-day cycle, a patient will take medication in the first 3 weeks followed by 1 week off treatment. Study drug administration and derived exposure information will be summarized and listed.

15.1. EXPOSURE TO STUDY MEDICATION

Below variables will be summarized:

- Number of cycle(s) received: the number of cycles in which at least one dose of Fruquintinib or placebo is taken. The number of cycles could be further categorized into:
    - 1, 2, 3, 4, 5, 6 and > 6
- Total duration of exposure (days)
- Cumulative dose (mg)
- Dose intensity (mg/day)
- Relative dose intensity (RDI, %): both continuous variable and categorical variable (< 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%)
- Actual duration of study treatment (days)
- Percentage intended dose (PID)
- Number of patients with any dose modification (including both drug interruption, dose increase, and dose reduction)
- Frequency of dose modification: 0, 1, 2, 3, 4, 5, 6, >6
- Number of patients experienced drug interruption
- Frequency of drug interruptions: 0, 1, ≥ 2
- Number of patients with any dose reduction
- Reduction from 5mg to 4mg
- Reduction from 4mg to 3mg
- Frequency of dose reduction: 0, 1, 2

15.2. STUDY MEDICATION COMPLIANCE

The study medication compliance is quantified with relative dose (RD, %) of study medication. RD is calculated as the cumulative dose taken divided by the planned total dose in the corresponding period, expressed as a percentage, see section 15.3 for more details. RDI (%) and RD (%) will be categorized as stated above in Section 15.1.

15.3. DERIVATIONS

- Total duration of exposure (days) is calculated from the first dose date of study drug in Cycle 1 to the last dose date of study drug + 8 days or death date, whichever comes earlier if treatment is discontinued, or to the cut-off date. if treatment is still ongoing.
- Actual duration of exposure (days) = Sum of the days with study drug administered

Algorithms for calculating parameters relevant to the dose exposure and intensity are listed in Table below:

Parameter	Description/ Formula [a]
Dosing schedule per protocol#	5 mg PO QD between Days 1 and Day 21, followed by 1-week off
Cumulative dose (mg) [b]	∑ [5 × (all dispensed 5-mg tablets – total returned 5-mg tablets - total lost 5-mg tablets in a cycle) + 1 × (all dispensed 1-mg tablets – total returned 1-mg tablets – total lost 1-mg tablets in a cycle)]
Dose intensity (mg/day)	Cumulative dose (mg) / Total duration of exposure (day)
Relative dose intensity (RDI, %) #	100 * [Dose intensity (mg/day) / (5 × 21/28, mg/day)]
Relative Dose (RD, %)#	100 * [Cumulative dose (mg) / (5 × 21 × number of cycles received (mg)]
Percentage intended dose (PID, %) [c]	100 * [(total number of days with any recorded doses) / total duration of exposure (days)]

[a]In the study, there are the other dose level of "3mg QD" used.
[b]In the study, both 1-mg and 5-mg fruquintinib are provided for oral administration. When dose adjustment is required, 1-mg fruquintinib is always used. Before calculating the cumulative dose, total number of 1-mg and 5-mg tablets taken should be counted separately.
[c]Given the dose schedule of a 4-week cycle in the protocol, 3 weeks on/ 1 week off, the reference value is 0.75.
# indicates 5 (mg) should be replaced with 3 (mg) for calculation in Cohort "3 mg QD".

16. EFFICACY OUTCOMES

Analyses of efficacy outcomes are based on EAS except PFS and OS, which are estimated based on SAS.

16.1. PRIMARY EFFICACY VARIABLE(S) & DERIVATION(S)

16.1.1. BEST OVERALL RESPONSE (BOR)

BOR will be determined using time point responses (TPRs) up until the last evaluable TPR prior to or on the date of (i) disease progression as defined by RECIST Version 1.1 (Eisenhauer et al., 2009) or death; or (ii) withdrawal of consent; or (iii) receiving subsequent anti-cancer therapy, whichever is earlier.

The timing of an overall TPR will always be derived based on scan dates not response assessment dates. For a scheduled tumor scan assessment, it is expected that there may be a variation for the actual timing of scans among target, non-target, and new lesions. In assigning a date for the overall response assessment at a visit, the earliest date collected at that visit will be used. Within a grouped timepoint, if there are multiple assessments on different dates for the same target lesions, the last assessment will be used.
A patient's BOR will be determined based on APPENDIX 3.

There are two ways of assigning BOR for a patient when the minimum interval for confirmation of CR and PR is not satisfied or if there are no confirmatory scans for CR and PR:

- Adding two more response categories as: unconfirmed CR, unconfirmed PR.
- Assigning BOR as SD, that is, both the unconfirmed CR and unconfirmed PR will be SD.

Both ways of assigning BOR will be implemented.

The number and percentage of patients in each category of derived BOR (Confirmed CR, Confirmed PR, SD, PD, or NE) will be summarized.

16.1.2. Objective Response Rate (ORR)

Objective response rate (ORR) will be calculated using two different ways:

- Scenario #1: ORR will be calculated using a strict interpretation of RECIST Version 1.1. Objective response will be derived as no/yes variable. Patients with a BOR of confirmed CR or PR will be assigned 'Yes'. Patients not having a BOR of confirmed CR or PR will be assigned 'No'. Hence, ORR is defined as the proportion of patients with objective response being "Yes".
- Scenario #2: $ORR_{UNCONFIRMED}$ will be calculated using all responses regardless of confirmation. Objective response will be derived as no/yes variable. Patients with a BOR of confirmed CR, confirmed PR, unconfirmed CR or unconfirmed PR will be assigned "Yes". All patients with other BOR values will be assigned "No". Hence, $ORR_{UNCONFIRMED}$ is defined as the proportion of patients with objective response being "Yes".

16.1.3. Duration of Response (DoR)

The DoR is defined as the time from the date of the first objective response (CR or PR which is subsequently confirmed) until the date of the documented progression or of death, whichever comes first. DoR will only be analyzed for patients whose BOR is either CR or PR. Censoring will follow the rules outlined below for PFS in Section 16.1.5.

16.1.4. Duration Control Rate (DCR)

The DCR is defined as the percentage of patients in EAS with a BOR of confirmed CR, confirmed PR or SD for 7 weeks.

16.1.5. Progression Free Survival (PFS)

The PFS is defined as the time from date of first dosing until the date of an objective disease progression as defined by RECIST Version 1.1 (Eisenhauer et al., 2009) or death due to any cause, whichever comes first. More specifically, PFS will be determined using all the assessment data up until the last evaluable visit prior to or on

the date of (i) disease progression as defined by RECIST Version 1.1 or death; or (ii) withdrawal of consent; or (iii) receiving subsequent anti-cancer therapy, whichever is earlier.

The rule of censoring/ event is summarized in Table 1.

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

RECIST assessments/scans contributing towards a particular visit may be performed on different dates. The following rules 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 patient for PFS the patient will be censored at the latest of the dates contributing to a particular overall visit assessment.

Table 1 Progression free survival

Description	**Event/ Censor**	**Date of Event/Censor**
Documented progression before starting use of new anticancer treatment and without missing two consecutive tumor assessment visits	Event	Date of first documented disease progression
Death without progression	Event	Date of death
Progression or death after two or more consecutive missed tumor assessments	Censor	Date of last adequate tumor assessment before two consecutive missed tumor assessment visits
No evaluable baseline tumor assessment	Censor	Date of first dosing of study treatment
No evaluable tumor assessment after first dose of study treatment	Censor	Date of first dosing of study treatment
New anticancer treatment started prior to documented disease progression or death on study	Censor	Date of last evaluable tumor assessment before start use of new anticancer treatment/two consecutive missed tumor assessment visits
No progression and no death before end of study or data cut-off	Censor	Date of last evaluable tumor assessment
Note: An adequate radiologic assessment is defined as an assessment where the Investigator determined radiological response is CR, PR, SD, or PD. If PD and new anti-cancer therapy occur on the same day, will assume that the progression was documented first, e.g. outcome is progression and the date is the date of the assessment of progression.		

Note: Two consecutive scheduled tumor assessments is equal to 126 days (=2* (8 weeks *7+ 7 days)) since previous evaluable RECIST 1.1 or baseline assessment if there is no post baseline tumor assessment.

16.1.6. Overall Survival (OS)

The OS (in months) refers to the time interval between the first dose date and the date of death (any cause). The last known alive date (i.e. the last follow-up date in patients on study or the date of EOS in patients withdrawn from the study) will be used as the censoring date for patients who have not died at the time of the statistical analysis. Patients lacking data beyond the first dose date will have their survival time censored at the first dose date.

16.1.7. Tumor Shrinkage

Tumor shrinkage will be estimated using data on sum of diameters of target lesion based on EAS. Percentage change in tumor size will be determined for patients with measurable disease at baseline and will be derived for each tumor assessment.

16.2. Analysis of Efficacy Variable(s)

The efficacy endpoints include ORR, DCR, DoR, PFS and OS. Efficacy data will be listed and summarized by dose cohort (only in dose escalation phase) or tumor specific cohorts (only in dose expansion phase) and disease type if applicable.

ORR, DCR, and DoR

The ORR and DCR will be summarized with percentages and 95% exact Clopper-Pearson confidence interval based on EAS.

DOR will be summarized using Kaplan-Meier method, and the descriptive statistics of median, 25% and 75% percentiles along with their 95% CIs will be calculated. It will be based on the EAS. The supportive data listings will also be provided.

PFS, OS, and Duration to Follow-Up

PFS and OS will be similarly summarized as DOR, and in addition to the quartile summary from Kaplan-Meier method, Kaplan-Meier estimates will be provided for the rates at 12, 16, 20, and 24 weeks along with their 95% CIs based on the Brookmeyer and Crowley method (1982).

In addition, duration (months) to follow-up for overall survival would be summarized by Kaplan-Meier method. Duration to follow-up refers to the time interval between date of first study drug administration and last date known to be alive for subjects who have not yet been reported to have died by the time of analysis, i.e. (date of last known to be alive – date of first study drug administration + 1)/ 30.475. Subjects who are reported to have died would be censored at death date.

Tumor Shrinkage

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 (minimum) percentage change from baseline (PCFB) in tumor size will be summarized using descriptive statistics and a waterfall plot will be presented also. Best post-baseline sum of diameter is defined as the sum of diameter with either the largest decrease or smallest increase from baseline sum of diameter at a single post-baseline evaluable tumor assessment visit before RECIST progression of disease. More details please refer to section 16.1.7.

17. SAFETY OUTCOMES

Unless otherwise specified, the overall safety evaluation period is from the first date of study drug administration to no later than 37 days after the date of last study treatment administration. All outputs for safety outcomes will be based on the SAS.

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

Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in vital signs and change in ECG. Safety data will be listed and summarized. Incidence of DLTs will be listed by dose cohort for dose escalation phase only.

17.1. DLTs

A DLT is defined as one of the following toxicities occurring during the DLT assessment window (Cycle 1) and determined by the investigator to have a reasonable possibility of being related to fruquintinib. All DLT analysis will be performed for dose escalation phase only. In addition to summarizing the proportion of patients with DLTs, the DLT categories will also be summarized as follows:

- 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 < 1.0 x 109/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;
- DLT leading to dose interruption for > 14 days due to toxicity

The individual data of DLTs will also be listed by dose and/ or disease cohort and by patient.

17.2. ADVERSE EVENTS

AEs will be coded using Medical Dictionary for Drug Regulatory Activities (MedDRA) central coding dictionary, Version 23.1 or higher.

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 37 days after the date of last study treatment. In case that the AE onset date coincide with the first dose date of study treatment, AE will be considered as TEAE if the response of question "Did the adverse event occur prior to the start of study treatment?" in AE form is "No".

See section 6.3.2 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, (i.e., the required imputed dates are missing or partial) the AE will be classified by the worst case, i.e. treatment emergent.

An overall summary of number of patients within each of the categories described in the sub-section below, will be provided.

Listings will include all the AEs being reported during the study with flag to distinguish TEAEs and Non-TEAEs. Imputed AE dates will not be presented in the listings.

17.2.1. ALL TEAEs

Incidence of TEAEs will be presented by System Organ Class (SOC) and Preferred Term (PT) and also broken down further by maximum severity for each phase, each dose and disease cohort and overall. The study drug related TEAEs will also be summarized in the similar way.

17.2.1.1. Severity

AE severity will be graded to 5 grades (Grade 1 to Grade 5) according to the national cancer institute common terminology criteria for adverse event (NCI CTCAE) V4.03.

TEAEs starting after the first dose of study medication with a missing severity will be classified as Grade 3. If a patient reports a TEAE more than once within that SOC/ PT, the AE with the worst-case severity will be used in the corresponding severity summaries. A summary table for TEAE with grade >= 3 will also be presented by dose or disease cohort.

17.2.1.2. Relationship to Study Drug

The relationship, as indicated by investigator, is classed as "Unrelated" and "Related". A study drug "related" TEAE is defined as a TEAE with response of "Yes" to the field "Possible causality to study drug?" on the "Adverse Event (AE)" form of the eCRF. TEAEs with a missing causality to study drug will be regarded as "Related" to study drug. If a patient reports the same AE more than once within that SOC/ PT, the AE with the worst case relationship to study drug will be used in the corresponding relationship summaries.

17.2.2. TEAEs Leading to Dose Interruption or Reduction

TEAEs leading to dose interruption or reduction will be identified as those TEAEs with a response of either "Drug Interrupted" or "Dose Reduced".

For TEAEs leading to dose interruption or reduction, summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared. Summaries for TEAEs leading to dose interruption or reduction by SOC and PT will be further limited to study medication-related TEAE and broken down by maximum severity.

17.2.3. TEAEs Leading to Discontinuation of Study Drug

TEAEs leading to permanent discontinuation of study drug will be identified as those TEAEs with a response of "Drug Withdrawal".

For TEAEs leading to discontinuation of study drug, summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared. Summaries for TEAEs leading to discontinuation of study drug by SOC and PT will be further broken down by maximum severity and strongest relationship to study drug.

TEAEs leading to discontinuation of study drug will also be listed.

17.2.4. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded with a response of "Yes" for the field "Is the adverse event serious?" on the "Adverse Events (AE)" form of eCRF. A summary of serious TEAEs by SOC and PT will be prepared. In addition, summaries for serious TEAEs by SOC and PT will be further broken down by maximum severity.

Listing of serious TEAE will also be provided.

17.2.5. Adverse Events Leading to Death

TEAEs leading to Death are those events with response of "Fatal. A summary of TEAEs leading to death by SOC and PT will be prepared.

TEAEs leading to death will also be listed.

17.2.6. Adverse Events Of Special Interest (AESI)

According to the IB Version 13.0 (dated 08 November 2021), treatment emergent adverse events of special interest (TEAESI) for fruquintinib are defined to include 10 categories:

- hepatic function abnormal
- haemorrhages
- hypertension
- infections
- thyroid dysfunction
- proteinuria
- dermatological toxicity
- gastrointestinal perforation

- embolic and thrombotic events
- left ventricular ejection fraction decreased

The MedDRA terms used to define AESIs categories are listed in Table 2, for AESI categories (i.e. "haemorrhages", "hepatic function abnormal", "hypertension", "proteinuria", "thyroid dysfunction", "embolic and thrombotic events" "gastrointestinal perforation" and "left ventricular ejection fraction decreased"), the PTs to be included in these AESI categories are included in Appendix 5. These terms were selected by subjecting standardized MedDRA queries (SMQ) lists (narrow and/or broad scope depending on the category) for each category and had been used in the fruquintinib clinical development program for pharmacovigilance. TEAESI will be summarized by AESI category and PTs. Incidence rates (frequencies and percentages) will be presented by treatment arm. Similar by severity and by relationship summary tables will also be provided separately.

Table 2: MedDRA Terms Used for Adverse Events of Special Interest

AESIs Category	Search terms/strategy
Dermatological toxicity	MedDRA SOC "skin and subcutaneous tissue disorders"
Hypertension	MedDRA SMQ "hypertension" (narrow)
Thyroid dysfunction	MedDRA SMQ "thyroid dysfunction" (broad)
Proteinuria	MedDRA SMQ "proteinuria" (narrow)
Hepatic function abnormal	MedDRA SMQ "drug related hepatic disorders-comprehensive search" (narrow)
Haemorrhages	MedDRA SMQ "haemorrhages" (narrow)
Infections	MedDRA SOC "infections and infestations"
Embolic and thrombotic events	MedDRA SMQ "embolic and thrombotic events" (narrow)
Gastrointestinal perforation	MedDRA SMQ "gastrointestinal perforation" (narrow)
Left ventricular ejection fraction decreased	MedDRA SMQ "cardiac failure" (narrow)

Time to first TEAESI will also be summarized by AESI category for each dose and/ or disease cohort in each study phase. Time to first TEAESI is defined as time interval from date of first administration of study treatment to the earliest onset date among TEAEs within the same AESI categories. That is, if a patient has multiple AEs occurrences under the same AESI category, the earliest AE onset date will be used as the first onset date to the AESI category.

17.3. DEATHS

Data on death will be listed, along with results of total number of patients died and cause of death summarized. Result of patients with on-study death, which is defined as the death after the first dose until 37 days after last dose, will also be tabulated. On-treatment death will be flagged.

17.4. LABORATORY EVALUATIONS

Results from the local laboratory will be included in the reporting of this study for Hematology, Serum chemistry, Coagulation, Urinalysis, 24-hours urine protein, and Thyroid function test.

Indexes collected for laboratory assessments are shown in table below:

Laboratory Test	Parameters
Hematology	red blood cell [RBC] count, hemoglobin, platelet count, white blood cell [WBC], neutrophils, lymphocytes, monocytes, eosinophils, basophils, hematocrit, reticulocyte count
Coagulation	activated partial thromboplastin time [aPTT], international normalized ratio [INR]
Serum chemistry	total protein, albumin, glucose, blood urea nitrogen [BUN], creatinine, creatinine clearance, alkaline phosphatase [ALP], lactate dehydrogenase [LDH], total bilirubin, Aspartate Aminotransferase [AST], Alanine Aminotransferase [ALT], calcium, magnesium, potassium, sodium, chloride, total cholesterol, triglycerides, uric acid, bicarbonate, phosphorus
Urinalysis	pH, glucose, protein, and blood
Thyroid function	thyroid stimulating hormone [TSH], free T3, and free T4

The non-protocol specified tests and urinalysis results will not be summarized; they will only be included in listings. Data recorded by the laboratory will be converted to the International System of Units (SI) and all presentations will use SI units. Quantitative laboratory measurements reported as "< X", i.e., below the lower limit of quantification (LLQ), or "> X", i.e., above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e., as "< X" or "> X" in the listings. Quantitative data collected between after date of ICF and up to 37 days following the last dose of study medication will be used for analysis. The following summaries will be provided for laboratory data:

- Observed value and change from baseline by visit (for quantitative measurements)
- Shift from baseline to worst post-baseline CTCAE toxicity for laboratory abnormalities
- Shift from baseline to the worst post-baseline investigators' assessment (i.e., normal, abnormal but not clinically significant [NCS], abnormal and clinically significant [CS] for quantitative measurements and categorical measurements)

Both the scheduled and unscheduled assessments will be used to identify the worst post-baseline values.

Listing of all laboratory data by patients, abnormal values identified according to normal range (low, normal and high) by programming and markedly abnormal criteria by investigators' assessment will be flagged.

17.4.1. Laboratory Specific Derivations

The SI unit conversion and CTCAE grade will be derived through programming.

17.4.2. 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 (APPENDIX 6). All grading will be based on laboratory 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 laboratory values, therefore will not appear in the grading system.
- A further category denoted Grade 0 would include all laboratory values within normal range 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 hyper and hypo directions will be presented separately, i.e., hyper for higher values of concern and hypo for lower values of concern.

Any graded abnormality that occurs following the initiation of study drug and represents at least a 1-grade change (i.e. increase or decrease) from the baseline assessment is defined as treatment emergent. The treatment-emergent laboratory abnormality defined by CTCAE will be summarized by CTCAE term, CTCAE toxicity grade, and visit. Any occurrence of grade 3 or grade 4 laboratory abnormality during the treatment period will also be summarized by visit.

17.4.3. Laboratory Reference Ranges

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

17.4.4. Potential Drug-Induced Liver Injury (DILI)

Below events will be identified via programming and summarized by categories and dose and/ or disease cohort for the SAS. Separate listings for patients with DILI, as defined below, will also be provided.

- Hy's Law: Serum AST or ALT >3 × ULN and ALP < 2x ULN and total bilirubin >2 × ULN
- POTENTIAL DRUG-INDUCED LIVER INJURY (DILI): Serum AST or ALT >3 × ULN and total bilirubin >2 × ULN
- AST:
  - > 3x ULN and ≤ 5 x ULN,
  - > 5 x ULN and ≤ 8 x ULN,
  - > 8 x ULN and ≤ 10 x ULN,
  - > 10 x ULN and ≤ 20 x ULN,
  - > 20x ULN,
  - AST>5x ULN for more than 5 weeks
- ALT:
  - > 3x ULN and ≤ 5 x ULN,
  - > 5 x ULN and ≤ 8 x ULN,
  - > 8 x ULN and ≤ 10 x ULN,
  - > 10 x ULN and ≤ 20 x ULN,
  - > 20x ULN,
  - > 5x ULN for more than 5 weeks

Lab abnormalities meeting the biochemical criteria for Hy's law is associated with a markedly increased possibility of severe DILI. These components will also be listed separately:

- ALP < 2 x ULN
- Total Bilirubin:
  - >1.5 and ≤ 2 x ULN
  - > 2 x ULN

17.5. ECG EVALUATIONS

Results of the Electrocardiogram (ECG) will be included in the reporting of this study. Overall assessment of ECG up to 37 days following the date of last dose of study medication will be included for analysis.

The following ECG parameters will be reported for this study:

- Heart Rate (bpm)
- PR Interval (msec)
- QT Interval (msec)
- QRS Interval (msec)
- RR Interval (msec)
- QTcF Interval (msec)

Overall assessment of ECG (Investigator's judgment): Normal, NCS, CS.

The following summaries will be provided for ECG data:

- Observed and change from baseline by visit
- Markedly abnormal value and change of ECG by visit
- Shift table of change from baseline to worst post-baseline ECG assessment by investigator

Listing of ECG data (Assessment date, Timepoint, HR, PR interval, QT interval, QRS interval, RR interval, QTcF interval) by patients, with results which meet the markedly abnormal criteria being flagged.

17.5.1. ECG Specific Derivations

QTcF values will be derived from the QT and RR intervals based on the formula of

$$QTcF = \frac{QT}{\sqrt[3]{RR}},$$

If QT and/or RR is missing, the QTcF will be left as missing.

17.5.2. Markedly Abnormal Criteria

Markedly abnormal criteria for ECG are listed in table below:

Parameter (unit)	Criterion value
Heart Rate (bpm)	>120
	<50
PR Interval (msec)	≥ 210
RR Interval (msec)	> 1200
	< 500
QRS Interval (msec)	≥ 120
	≤ 50
QT Interval (msec)	≥ 500
	≤ 300
QTcF (msec)	> 450

	> 480
	> 500
	≤ 300
	Increase from baseline > 30
	Increase from baseline > 60
	Decrease from baseline > 30
	Decrease from baseline > 60
	> 450 and increase from baseline > 30
	> 500 and increase from baseline > 60

17.6. VITAL SIGNS

The following Vital Signs measurements performed within 37 days after the date of last dose of study medication will be reported for this study:

- Heart rate (bpm)
- Respiratory rate (bpm)
- Body Temperature (C)
- Weight (kg)
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)

The following summaries will be provided for vital signs data:

- Observed and change from baseline by visit
- The frequency and percentage of patients with any potentially clinically significant findings defined in section 17.6.2 during the treatment period will be presented.

Listing of vital sign data will also be generated.

17.6.1. VITAL SIGNS SPECIFIC DERIVATIONS

There will be no specific derivations for vital signs.

17.6.2. VITAL SIGNS MARKEDLY ABNORMAL CRITERIA

Markedly abnormal quantitative Vital Signs measurements will be identified and classified in accordance with the following predefined criteria:

Vital Sign Parameter	Criterion value
SBP (mmHg), DBP (mmHg), Heart rate (bpm)	Increase from baseline of > 0 - ≤ 20 > 20 - ≤ 40 > 40

Vital Sign Parameter	Criterion value
	Decrease from baseline of > 0 - ≤ 20 > 20 - ≤ 40 > 40
Weight (kg)	Percentage decrease from baseline of < 5% ≥ 5 – < 10% ≥ 10 - < 20% ≥ 20% Percentage increase from baseline of < 5% ≥ 5 – < 10% ≥ 10 - < 20% ≥ 20%

17.7. PHYSICAL EXAMINATION

The physical examination results collected will be listed.

17.8. OTHER SAFETY ASSESSMENTS

17.8.1. ECOG PERFORMANCE STATUS

Summary of ECOG performance status by scheduled visit and change to worst post-baseline value will also be presented. All the ECOG performance status data will also be listed.

17.8.2. ECHOCARDIOGRAM

Baseline and change from baseline on left ventricular ejection fraction (LVEF) will be summarized by dose cohort (only in dose escalation phase) or tumor specific cohorts (only in dose expansion phase) and visit. Also, shift from baseline to worst post-baseline overall evaluation (i.e., normal, abnormal but NCS, abnormal and CS) will be summarized. Individual data will also be listed.

17.8.3. PREGNANCY TEST

Individual pregnancy information will be listed for the SAS.

17.8.4. TUMOR MARKER

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. The individual tumor marker test results will be listed for SAS.

17.8.5. IMPACT OF COVID-19

The study is conducted during the COVID-19 pandemic, additional data is collected for evaluating the impact of COVID-19. To eliminate potential hazards to patients and study staff due to the COVID-19 pandemic while ensuring patients safety and maintaining data integrity, patients are allowed remote visits during the pandemic. Data listing will be provided.

18. REFERENCES

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer. 2009; 45:228-247.

Brookmeyer R., and Crowley J. (1982). A confidence interval for the median survival time. Biometrics, 29-41.

APPENDIX 1. SCHEDULE OF EVENTS

Schedule of events is shown as below.

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	
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 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 2. PROGRAMMING CONVENTIONS FOR OUTPUTS

Output Conventions

For more details please refer to the general rules listed in the shell.

Dates & Times

Depending on data available, dates and times will take the form ddmmyyyyThh: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
Dose Escalation Phase: 3mg QD	Dose Escalation Phase: Fruquintinib 3mg QD
Dose Escalation Phase: 5mg QD	Dose Escalation Phase: Fruquintinib 5mg QD
Dose Expansion Phase (5mg QD): Cohort A	Dose Expansion Phase: Cohort A
Dose Escalation Phase: 5mg QD + Dose Expansion Phase (5mg QD): Cohort A	Dose Expansion Phase: Dose Escalation Fruquintinib 5mg QD + Cohort A
Dose Escalation Phase + Dose Expansion Phase	Dose Expansion Phase: Dose Escalation Phase + Dose Expansion Phase (Only for Patient Disposition, Demographic and Baseline Characteristics, Baseline Cancer Characteristics tables)

Treatment Group	For Listings
Dose Escalation Phase: 3mg QD	Dose Escalation Phase: Fruquintinib 3mg QD
Dose Escalation Phase: 5mg QD	Dose Escalation Phase: Fruquintinib 5mg QD
Dose Expansion Phase (5mg QD): Cohort A	Dose Expansion Phase: Cohort A

Treatment Group	For Figures
Dose Escalation Phase: 3mg QD	Dose Escalation Phase: Fruquintinib 3mg QD
Dose Escalation Phase: 5mg QD	Dose Escalation Phase: Fruquintinib 5mg QD

Treatment Group	For Figures
Dose Expansion Phase (5mg QD): Cohort A	Dose Expansion Phase: Cohort A
Dose Escalation Phase: 5mg QD and Dose Expansion Phase (5mg QD): Cohort A	Pooling Dose Escalation 5 mg and Cohort A
Dose Escalation Phase: 3mg QD + Dose Escalation Phase: 5mg QD and Dose Expansion Phase (5mg QD): Cohort A	Dose Escalation 3mg and Pooling Dose Escalation 5mg and Cohort A

Presentation of Visits

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

Long Name (default)	Short Name
Baseline	Baseline
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	C3D15
Cycle 4 Day 1	C4D1
Cycle X Day 1	CXD1
……	…….
End of Treatment	EOT

Listings

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

Assigned treatment group, unless otherwise specified

Center-Patient Number

Date (where applicable)

APPENDIX 3. BEST OVERALL RESPONSE WHEN CONFIRMATION OF CR AND PR ARE REQUIRED

First TPR	Second TPR[a]	Best overall response*^ for ORR	Best Overall Response for $ORR_{UNCONFIRMED}$
CR	CR	CR	CR
CR	PR	SD [b] or PD	Unconfirmed CR
CR	SD	SD [b] or PD	Unconfirmed CR
CR	PD	SD [b] or PD	Unconfirmed CR
CR	NE or NA	SD [c] or NE or NA	Unconfirmed CR
PR	CR	PR	Unconfirmed CR
PR	PR	PR	PR
PR	SD	SD [d]	Unconfirmed PR
PR	PD	SD [b] or PD	Unconfirmed PR
PR	NE or NA	SD [c] or NE or NA	Unconfirmed PR
NE	NE	NE	NE
NE	CR	SD	Unconfirmed CR
NE	PR	SD	Unconfirmed PR
NE	SD	SD	SD
NE or NA	PD	PD	PD
SD	PD	SD [b] or PD	SD [b] or PD
SD	CR	SD	SD
SD	PR	SD	SD
SD	SD	SD	SD
SD	NE or NA	SD [c] or NE or NA	SD [c] or NE
PD	No further evaluation	PD	PD

CR = Complete Response; NE = Not Evaluable; NA = Not Available; ORR = Objective Response Rate; PD = Progressive Disease; PR= Partial Response; SD = Stable Disease.

[a]The minimum interval for confirmation of CR and PR is 4 weeks.

[b]Best response will be SD if the first time point overall response is after 49 days on study. Otherwise, the best response will be PD.

[c]Best response will be SD if the first time point overall response after 49 days on study. Otherwise, the best response will be NE.

[d]Best response will be SD provided the criteria for PD have not been met from the first to second assessment.

* A best overall response of SD can only be made after the subject is on study for a minimum of 49 days (counted from Cycle 1 Day 1). If the subject is on study for less than 49 days, any tumor assessment indicating stable disease before this time period will have a best response of NE unless PD is identified.

^ Subsequent documentation of a CR may provide confirmation of a previously identified CR even with an intervening NE (e.g., CR NE CR). Subsequent documentation of a PR may provide confirmation of a previously identified PR even with an intervening NE or SD (e.g., PR NE PR or PR SD PR). However, only one (1) intervening NE or SD will be allowed between PRs for confirmation. Note: in the following scenario, PR SD NE PR, the second PR is not a confirmation of the first PR.

APPENDIX 4. VISIT-WINDOW MAPPING

	Cycle 1				Cycle 2-3		Cycle 4 and onwards	Post-treatment
Visit	**C1D1**	**C1D8**	**C1D15**	**C1D22**	**CxD1**	**CxD15**	**CxD1**	
Scheduled Day [a]	1	8	15	22	1	15	1	
ECOG	Day 1		2 to EOC-3		Day -3 to 3	4 to EOC-3	Day -3 to 3	Last dose date of last cycle +8 to last dose date +37
Vital Sign	Day 1	2 to 11	12 to 18	19 to EOC-3	Day -3 to 3	4 to EOC-3	Day -3 to 3	
Hematology		1 to 11	12 to 18	19 to EOC-3	Day -3 to 3	4 to EOC-3	Day -3 to 3	
Coagulation		1 to 11	12 to 18	19 to EOC-3	Day -3 to 3	4 to EOC-3	Day -3 to 3	
Clinical Chemistry		1 to 11	12 to 18	19 to EOC-3	Day -3 to 3	4 to EOC-3	Day -3 to 3	
Urinalysis		1 to 11	12 to 18	19 to EOC-3	Day -3 to 3	4 to EOC-3	Day -3 to 3	
Thyroid function		1 to 11	12 to 18	19 to EOC-3	Day -3 to 3	4 to EOC-3	Day -3 to 3	
12-Led ECG	Day 1		2 to EOC-3		Day -3 to 3		Day -3 to 3	

[a] The scheduled day is relative to the Day 1 of each cycle.

Note: The end date of a cycle (EOC) is defined as the one day earlier than the date of Day 1 study drug administration of its next cycle. For the last cycle (where no subsequent cycle if given), the end of cycle will be defined as Day 7 relative to the last dose of the cycle.

Tumor Assessment

	Cycle 2	Cycle 3	Cycle 4	8 Weeks after D1 of Cycle 4	8 * (X + 1) Weeks after D1 of Cycle 4 [b]	Post-treatment
Visit	**C2D1**	**C3D1**	**C4D1**	**8 Weeks after D1 of Cycle 4**	**8 * (X + 1) Weeks after D1 of Cycle 4 [b]**	
Scheduled Day [a]	1	1	1	57	1 + 7*8 * (X + 1)	
Tumor Assessment (Cohort A and B)	-3 to (EOC-3)	-3 to (EOC-3)	-3 to (EOC-3)	End of Cycle 4 to 85	28 * (2X + 1) + 2 to 28 * (2X + 3) + 1 [d]	Last dose date of last cycle +8 to last dose date +37
	Week 8	**Week 8 * (X + 1)**				
Visit	**Week 8**	**Week 8 * (X + 1) [b]**				
Scheduled Day [c]	57	1 + 7*8 * (X + 1)				
Tumor Assessment (Cohort C, D, and E)	Day 2 to 85	28 * (2X + 1) + 2 to 28 * (2X + 3) + 1 [d]				

[a] The scheduled day is relative to the Day 1 for Cycle 2 to Cycle 4, but the subsequent scheduled day is relative to Day 1 of Cycle 4.
[b] X is an intergern starting from 1, and will take maximum value at date of last study drug administration.
[c] Scheduled day is relative to Day 1 of Cycle 1.
[d] The last windowed visit end by the last dose date.

Note: The end date of a cycle (EOC) is defined as the one day earlier than the date of Day 1 study drug administration of its next cycle. For the last cycle (where no subsequent cycle if given), the end of cycle will be defined as Day 7 relative to the last dose of the cycle.

Echocardiogram

		Week 12 * (X + 1)	Post-treatment
Visit	**Week 12**	**Week 12 * (X + 1) [b]**	
Scheduled Day [c]	85	1 + 7*12 * (X + 1)	
Echocardiogram	Day 2 to 127	42 * (2X + 1) + 2 to 42 * (2X + 3) + 1 [c]	Last dose date of last cycle +8 to last dose date +37

[a] The scheduled day is relative to the Day 1 of Cycle 1.

[b] X is an intergern starting from 1, and will take maximum value at date of last study drug administration.

[c] The last windowed visit end by the last dose date.

APPENDIX 5. MEDDRA (VERSION 24.1) PREFERRED TERM LIST FOR AESI CATEGORIES

AESI Category: Thyroid Dysfunction		
Anti-thyroid antibody	Marine Lenhart syndrome	Thyroid size decreased
Anti-thyroid antibody decreased	Multifocal fibrosclerosis	Thyroid stimulating hormone deficiency
Anti-thyroid antibody increased	Myxoedema	Thyroid stimulating immunoglobulin increased
Anti-thyroid antibody positive	Myxoedema coma	Thyroid therapy
Antithyroid arthritis syndrome	Orbital decompression	Thyroid tuberculosis
Atrophic thyroiditis	Photon radiation therapy to thyroid	Thyroidectomy
Autoimmune hypothyroidism	Polyglandular autoimmune syndrome type II	Thyroiditis
Autoimmune thyroid disorder	Polyglandular autoimmune syndrome type III	Thyroiditis acute
Autoimmune thyroiditis	Post procedural hypothyroidism	Thyroiditis chronic
Basedow's disease	Primary hyperthyroidism	Thyroiditis fibrous chronic
Biopsy thyroid gland abnormal	Primary hypothyroidism	Thyroiditis subacute
Blood thyroid stimulating hormone abnormal	Protein bound iodine decreased	Thyrotoxic cardiomyopathy
Blood thyroid stimulating hormone decreased	Protein bound iodine increased	Thyrotoxic crisis
Blood thyroid stimulating hormone increased	Radioactive iodine therapy	Thyrotoxic myopathy
Butanol-extractable iodine decreased	Radiotherapy to thyroid	Thyrotoxic periodic paralysis
Butanol-extractable iodine increased	Reverse tri-iodothyronine decreased	Thyroxin binding globulin abnormal
Congenital hypothyroidism	Reverse tri-iodothyronine increased	Thyroxin binding globulin decreased
Congenital thyroid disorder	Secondary hyperthyroidism	Thyroxin binding globulin increased
Endocrine ophthalmopathy	Secondary hypothyroidism	Thyroxine abnormal
Euthyroid sick syndrome	Silent thyroiditis	Thyroxine decreased
Exophthalmos	Tertiary hypothyroidism	Thyroxine free abnormal
Free thyroxine index abnormal	Thyreostatic therapy	Thyroxine free decreased
Free thyroxine index decreased	Thyroglobulin absent	Thyroxine free increased
Free thyroxine index increased	Thyroglobulin decreased	Thyroxine increased
Gamma radiation therapy to thyroid	Thyroglobulin increased	Thyroxine therapy

Generalised resistance to thyroid hormone	Thyroglobulin present	Toxic goitre
Goitre	Thyroid atrophy	Toxic nodular goitre
Hashimoto's encephalopathy	Thyroid autotransplantation	Transient hypothyroxinaemia of prematurity
Hashitoxicosis	Thyroid dermatopathy	Tri-iodothyronine abnormal
Hyperthyroidism	Thyroid disorder	Tri-iodothyronine decreased
Hypothyroidic goitre	Thyroid dysfunction in pregnancy	Tri-iodothyronine free abnormal
Hypothyroidism	Thyroid electron radiation therapy	Tri-iodothyronine free decreased
Immune-mediated hyperthyroidism	Thyroid function test abnormal	Tri-iodothyronine free increased
Immune-mediated hypothyroidism	Thyroid gland scan abnormal	Tri-iodothyronine free normal
Immune-mediated thyroiditis	Thyroid hemiagenesis	Tri-iodothyronine increased
Inappropriate thyroid stimulating hormone secretion	Thyroid hormone replacement therapy	Tri-iodothyronine uptake abnormal
Infectious thyroiditis	Thyroid hormones decreased	Tri-iodothyronine uptake decreased
Iodine uptake abnormal	Thyroid hormones increased	Tri-iodothyronine uptake increased
Iodine uptake decreased	Thyroid operation	Ultrasound thyroid abnormal
Iodine uptake increased	Thyroid pain	X-ray therapy to thyroid
Malignant exophthalmos	Thyroid releasing hormone challenge test abnormal	
AESI Category: Proteinuria		
Albumin globulin ratio increased	Beta 2 microglobulin urine increased	Protein urine
Albumin urine present	Globulinuria	Protein urine present
Albuminuria	Microalbuminuria	Proteinuria
Bence Jones protein urine present	Myoglobinuria	Urine albumin/creatinine ratio increased
Bence Jones proteinuria	Orthostatic proteinuria	Urine protein/creatinine ratio abnormal
		Urine protein/creatinine ratio increased
AESI Category: Hypertension		
Accelerated hypertension	Eclampsia	Metabolic syndrome
Aldosterone urine abnormal	Ectopic aldosterone secretion	Metanephrine urine abnormal
Aldosterone urine increased	Ectopic renin secretion	Metanephrine urine increased

Angiotensin converting enzyme increased	Endocrine hypertension	Neurogenic hypertension
Angiotensin I increased	Epinephrine abnormal	Non-dipping
Angiotensin II increased	Epinephrine increased	Norepinephrine abnormal
Angiotensin II receptor type 1 antibody positive	Essential hypertension	Norepinephrine increased
Blood aldosterone abnormal	Gestational hypertension	Normetanephrine urine increased
Blood aldosterone increased	HELLP syndrome	Orthostatic hypertension
Blood catecholamines abnormal	Hyperaldosteronism	Page kidney
Blood catecholamines increased	Hypertension	Postoperative hypertension
Blood pressure abnormal	Hypertension neonatal	Pre-eclampsia
Blood pressure ambulatory abnormal	Hypertensive angiopathy	Prehypertension
Blood pressure ambulatory increased	Hypertensive cardiomegaly	Procedural hypertension
Blood pressure diastolic abnormal	Hypertensive cardiomyopathy	Pseudoaldosteronism
Blood pressure diastolic increased	Hypertensive cerebrovascular disease	Renal hypertension
Blood pressure fluctuation	Hypertensive crisis	Renal sympathetic nerve ablation
Blood pressure inadequately controlled	Hypertensive emergency	Renal vascular resistance increased
Blood pressure increased	Hypertensive encephalopathy	Renin abnormal
Blood pressure management	Hypertensive end-organ damage	Renin increased
Blood pressure orthostatic abnormal	Hypertensive heart disease	Renin-angiotensin system inhibition
Blood pressure orthostatic increased	Hypertensive nephropathy	Renovascular hypertension
Blood pressure systolic abnormal	Hypertensive urgency	Retinopathy hypertensive
Blood pressure systolic increased	Labile blood pressure	Secondary aldosteronism
Catecholamine crisis	Labile hypertension	Secondary hypertension
Catecholamines urine abnormal	Malignant hypertension	Superimposed pre-eclampsia
Catecholamines urine increased	Malignant hypertensive heart disease	Supine hypertension
Dialysis induced hypertension	Malignant renal hypertension	Systolic hypertension
Diastolic hypertension	Maternal hypertension affecting foetus	Tyramine reaction
Diuretic therapy	Mean arterial pressure increased	Withdrawal hypertension
AESI Category: Haemorrhages		

Abdominal wall haematoma	Haemophilic pseudotumour	Petechiae
Abdominal wall haemorrhage	Haemoptysis	Pharyngeal contusion
Abnormal uterine bleeding	Haemorrhage	Pharyngeal haematoma
Abnormal withdrawal bleeding	Haemorrhage coronary artery	Pharyngeal haemorrhage
Achenbach syndrome	Haemorrhage foetal	Pituitary apoplexy
Acute haemorrhagic leukoencephalitis	Haemorrhage in pregnancy	Pituitary haemorrhage
Acute haemorrhagic ulcerative colitis	Haemorrhage intracranial	Placenta praevia haemorrhage
Administration site bruise	Haemorrhage neonatal	Polymenorrhagia
Administration site haematoma	Haemorrhage subcutaneous	Post abortion haemorrhage
Administration site haemorrhage	Haemorrhage subepidermal	Post procedural contusion
Adrenal haematoma	Haemorrhage urinary tract	Post procedural haematoma
Adrenal haemorrhage	Haemorrhagic adrenal infarction	Post procedural haematuria
Anal fissure haemorrhage	Haemorrhagic arteriovenous malformation	Post procedural haemorrhage
Anal haemorrhage	Haemorrhagic ascites	Post transfusion purpura
Anal ulcer haemorrhage	Haemorrhagic breast cyst	Postmenopausal haemorrhage
Anastomotic haemorrhage	Haemorrhagic cerebellar infarction	Postpartum haemorrhage
Anastomotic ulcer haemorrhage	Haemorrhagic cerebral infarction	Post-traumatic punctate intraepidermal haemorrhage
Aneurysm ruptured	Haemorrhagic cyst	Premature separation of placenta
Angina bullosa haemorrhagica	Haemorrhagic diathesis	Procedural haemorrhage
Anorectal varices haemorrhage	Haemorrhagic disease of newborn	Proctitis haemorrhagic
Anticoagulant-related nephropathy	Haemorrhagic disorder	Prostatic haemorrhage
Antiplatelet reversal therapy	Haemorrhagic erosive gastritis	Pulmonary alveolar haemorrhage
Aortic aneurysm rupture	Haemorrhagic gastroenteritis	Pulmonary contusion
Aortic dissection rupture	Haemorrhagic hepatic cyst	Pulmonary haematoma
Aortic intramural haematoma	Haemorrhagic infarction	Pulmonary haemorrhage
Aortic perforation	Haemorrhagic necrotic pancreatitis	Pulmonary haemorrhage neonatal
Aortic rupture	Haemorrhagic occlusive retinal vasculitis	Puncture site bruise
Aponeurosis contusion	Haemorrhagic ovarian cyst	Puncture site haematoma
Application site bruise	Haemorrhagic stroke	Puncture site haemorrhage

Application site haematoma	Haemorrhagic thyroid cyst	Purpura
Application site haemorrhage	Haemorrhagic transformation stroke	Purpura fulminans
Application site purpura	Haemorrhagic tumour necrosis	Purpura neonatal
Arterial haemorrhage	Haemorrhagic urticaria	Purpura non-thrombocytopenic
Arterial intramural haematoma	Haemorrhagic vasculitis	Purpura senile
Arterial perforation	Haemorrhoidal haemorrhage	Putamen haemorrhage
Arterial rupture	Haemostasis	Radiation associated haemorrhage
Arteriovenous fistula site haematoma	Haemothorax	Rectal haemorrhage
Arteriovenous fistula site haemorrhage	Heavy menstrual bleeding	Rectal ulcer haemorrhage
Arteriovenous graft site haematoma	Henoch-Schonlein purpura	Renal artery perforation
Arteriovenous graft site haemorrhage	Hepatic haemangioma rupture	Renal cyst haemorrhage
Astringent therapy	Hepatic haematoma	Renal haematoma
Atrial rupture	Hepatic haemorrhage	Renal haemorrhage
Auricular haematoma	Hereditary haemorrhagic telangiectasia	Respiratory tract haemorrhage
Basal ganglia haematoma	Hyperfibrinolysis	Respiratory tract haemorrhage neonatal
Basal ganglia haemorrhage	Hypergammaglobulinaemic purpura of Waldenstrom	Retinal aneurysm rupture
Basilar artery perforation	Hyphaema	Retinal haemorrhage
Bladder tamponade	Iliac artery perforation	Retinopathy haemorrhagic
Bleeding varicose vein	Iliac artery rupture	Retroperitoneal haematoma
Blood blister	Iliac vein perforation	Retroperitoneal haemorrhage
Blood loss anaemia	Immune thrombocytopenia	Retroplacental haematoma
Blood urine	Implant site bruising	Ruptured cerebral aneurysm
Blood urine present	Implant site haematoma	Scleral haematoma
Bloody discharge	Implant site haemorrhage	Scleral haemorrhage
Bloody peritoneal effluent	Incision site haematoma	Scrotal haematocoele
Bone contusion	Incision site haemorrhage	Scrotal haematoma
Bone marrow haemorrhage	Increased tendency to bruise	Scrotal haemorrhage
Brain contusion	Induced abortion haemorrhage	Shock haemorrhagic
Brain stem haematoma	Inferior vena cava perforation	Skin haemorrhage

Brain stem haemorrhage	Infusion site bruising	Skin neoplasm bleeding
Brain stem microhaemorrhage	Infusion site haematoma	Skin ulcer haemorrhage
Breast haematoma	Infusion site haemorrhage	Small intestinal haemorrhage
Breast haemorrhage	Injection site bruising	Small intestinal ulcer haemorrhage
Broad ligament haematoma	Injection site haematoma	Soft tissue haemorrhage
Bronchial haemorrhage	Injection site haemorrhage	Spermatic cord haemorrhage
Bronchial varices haemorrhage	Instillation site bruise	Spinal cord haematoma
Bullous haemorrhagic dermatosis	Instillation site haematoma	Spinal cord haemorrhage
Bursal haematoma	Instillation site haemorrhage	Spinal epidural haematoma
Cardiac contusion	Intermenstrual bleeding	Spinal epidural haemorrhage
Carotid aneurysm rupture	Internal haemorrhage	Spinal subarachnoid haemorrhage
Carotid artery perforation	Intestinal haematoma	Spinal subdural haematoma
Catheter site bruise	Intestinal haemorrhage	Spinal subdural haemorrhage
Catheter site haematoma	Intestinal varices haemorrhage	Spleen contusion
Catheter site haemorrhage	Intra-abdominal haematoma	Splenic artery perforation
Central nervous system haemorrhage	Intra-abdominal haemorrhage	Splenic haematoma
Cephalhaematoma	Intracerebral haematoma evacuation	Splenic haemorrhage
Cerebellar haematoma	Intracranial haematoma	Splenic varices haemorrhage
Cerebellar haemorrhage	Intracranial tumour haemorrhage	Splinter haemorrhages
Cerebellar microhaemorrhage	Intraocular haematoma	Spontaneous haematoma
Cerebral aneurysm perforation	Intrapartum haemorrhage	Spontaneous haemorrhage
Cerebral aneurysm ruptured syphilitic	Intratumoural haematoma	Stoma site haemorrhage
Cerebral arteriovenous malformation haemorrhagic	Intraventricular haemorrhage	Stomatitis haemorrhagic
Cerebral artery perforation	Intraventricular haemorrhage neonatal	Subarachnoid haematoma
Cerebral cyst haemorrhage	Iris haemorrhage	Subarachnoid haemorrhage
Cerebral haematoma	Joint microhaemorrhage	Subarachnoid haemorrhage neonatal
Cerebral haemorrhage	Jugular vein haemorrhage	Subcapsular hepatic haematoma
Cerebral haemorrhage foetal	Kidney contusion	Subcapsular renal haematoma
Cerebral haemorrhage neonatal	Lacrimal haemorrhage	Subcapsular splenic haematoma

Cerebral microhaemorrhage	Large intestinal haemorrhage	Subchorionic haematoma
Cervix haematoma uterine	Large intestinal ulcer haemorrhage	Subchorionic haemorrhage
Cervix haemorrhage uterine	Laryngeal haematoma	Subclavian artery perforation
Chest wall haematoma	Laryngeal haemorrhage	Subclavian vein perforation
Choroidal haematoma	Lip haematoma	Subcutaneous haematoma
Choroidal haemorrhage	Lip haemorrhage	Subdural haematoma
Chronic gastrointestinal bleeding	Liver contusion	Subdural haematoma evacuation
Chronic pigmented purpura	Lower gastrointestinal haemorrhage	Subdural haemorrhage
Ciliary body haemorrhage	Lower limb artery perforation	Subdural haemorrhage neonatal
Coital bleeding	Lymph node haemorrhage	Subendocardial haemorrhage
Colonic haematoma	Mallory-Weiss syndrome	Subgaleal haematoma
Conjunctival haemorrhage	Mediastinal haematoma	Subgaleal haemorrhage
Contusion	Mediastinal haemorrhage	Subretinal haematoma
Corneal bleeding	Medical device site bruise	Superior vena cava perforation
Cullen's sign	Medical device site haematoma	Testicular haemorrhage
Cystitis haemorrhagic	Medical device site haemorrhage	Thalamus haemorrhage
Deep dissecting haematoma	Melaena	Third stage postpartum haemorrhage
Diarrhoea haemorrhagic	Melaena neonatal	Thoracic haemorrhage
Disseminated intravascular coagulation	Meningorrhagia	Thrombocytopenic purpura
Diverticulitis intestinal haemorrhagic	Menometrorrhagia	Thrombotic thrombocytopenic purpura
Diverticulum intestinal haemorrhagic	Mesenteric haematoma	Thyroid haemorrhage
Duodenal ulcer haemorrhage	Mesenteric haemorrhage	Tongue haematoma
Duodenitis haemorrhagic	Mouth haemorrhage	Tongue haemorrhage
Ear haemorrhage	Mucocutaneous haemorrhage	Tonsillar haemorrhage
Ecchymosis	Mucosal haemorrhage	Tooth pulp haemorrhage
Encephalitis haemorrhagic	Muscle contusion	Tooth socket haemorrhage
Enterocolitis haemorrhagic	Muscle haemorrhage	Tracheal haemorrhage
Epidural haemorrhage	Myocardial haemorrhage	Traumatic haematoma
Epistaxis	Myocardial rupture	Traumatic haemorrhage

Exsanguination	Naevus haemorrhage	Traumatic haemothorax
Extra-axial haemorrhage	Nail bed bleeding	Traumatic intracranial haematoma
Extradural haematoma	Nasal septum haematoma	Traumatic intracranial haemorrhage
Extradural haematoma evacuation	Neonatal gastrointestinal haemorrhage	Tumour haemorrhage
Extravasation blood	Nephritis haemorrhagic	Ulcer haemorrhage
Eye contusion	Nipple exudate bloody	Umbilical cord haemorrhage
Eye haematoma	Occult blood positive	Umbilical haematoma
Eye haemorrhage	Ocular retrobulbar haemorrhage	Umbilical haemorrhage
Eyelid bleeding	Oesophageal haemorrhage	Upper gastrointestinal haemorrhage
Eyelid contusion	Oesophageal intramural haematoma	Ureteric haemorrhage
Eyelid haematoma	Oesophageal ulcer haemorrhage	Urethral haemorrhage
Femoral artery perforation	Oesophageal varices haemorrhage	Urinary bladder haematoma
Femoral vein perforation	Oesophagitis haemorrhagic	Urinary bladder haemorrhage
Foetal-maternal haemorrhage	Omental haemorrhage	Urinary occult blood
Fothergill sign positive	Optic disc haemorrhage	Urinary occult blood positive
Gallbladder haematoma	Optic nerve sheath haemorrhage	Urogenital haemorrhage
Gastric haemorrhage	Oral blood blister	Uterine haematoma
Gastric occult blood positive	Oral contusion	Uterine haemorrhage
Gastric ulcer haemorrhage	Oral mucosa haematoma	Vaccination site bruising
Gastric ulcer haemorrhage, obstructive	Oral purpura	Vaccination site haematoma
Gastric varices haemorrhage	Orbital haematoma	Vaccination site haemorrhage
Gastritis alcoholic haemorrhagic	Orbital haemorrhage	Vaginal haematoma
Gastritis haemorrhagic	Osteorrhagia	Vaginal haemorrhage
Gastroduodenal haemorrhage	Ovarian haematoma	Varicose vein ruptured
Gastrointestinal anastomotic haemorrhage	Ovarian haemorrhage	Vascular access site bruising
Gastrointestinal haemorrhage	Palpable purpura	Vascular access site haematoma
Gastrointestinal polyp haemorrhage	Pancreatic haemorrhage	Vascular access site haemorrhage
Gastrointestinal ulcer haemorrhage	Pancreatic pseudocyst haemorrhage	Vascular access site rupture
Gastrointestinal vascular malformation haemorrhagic	Pancreatitis haemorrhagic	Vascular anastomotic haemorrhage

Genital contusion	Papillary muscle haemorrhage	Vascular graft haemorrhage
Genital haemorrhage	Paranasal sinus haematoma	Vascular pseudoaneurysm ruptured
Gingival bleeding	Paranasal sinus haemorrhage	Vascular purpura
Graft haemorrhage	Parathyroid haemorrhage	Vascular rupture
Grey Turner's sign	Parotid gland haemorrhage	Vein rupture
Haemangioma rupture	Pelvic haematoma	Venous haemorrhage
Haemarthrosis	Pelvic haematoma obstetric	Venous perforation
Haematemesis	Pelvic haemorrhage	Ventricle rupture
Haematochezia	Penile contusion	Vertebral artery perforation
Haematocoele	Penile haematoma	Vessel puncture site bruise
Haematoma	Penile haemorrhage	Vessel puncture site haematoma
Haematoma evacuation	Peptic ulcer haemorrhage	Vessel puncture site haemorrhage
Haematoma infection	Pericardial haemorrhage	Vitreous haematoma
Haematoma muscle	Perineal haematoma	Vitreous haemorrhage
Haematosalpinx	Periorbital haematoma	Vulval haematoma
Haematospermia	Periorbital haemorrhage	Vulval haematoma evacuation
Haematotympanum	Periosteal haematoma	Vulval haemorrhage
Haematuria	Peripartum haemorrhage	Withdrawal bleed
Haematuria traumatic	Peripheral artery aneurysm rupture	Wound haematoma
Haemobilia	Peripheral artery haematoma	Wound haemorrhage
Haemoperitoneum	Peripheral exudative haemorrhagic chorioretinopathy	
Haemophilic arthropathy	Peritoneal haematoma	
	Periventricular haemorrhage neonatal	
AESI Category: Gastrointestinal perforation		
Abdominal abscess	Focal peritonitis	Oesophageal perforation
Abdominal hernia perforation	Gastric fistula	Oesophageal rupture
Abdominal wall abscess	Gastric fistula repair	Oesophageal ulcer perforation
Abscess intestinal	Gastric perforation	Oesophageal-pulmonary fistula

Acquired tracheo-oesophageal fistula	Gastric ulcer perforation	Oesophagobronchial fistula
Anal abscess	Gastric ulcer perforation, obstructive	Oesophagomediastinal fistula
Anal fistula	Gastrointestinal anastomotic leak	Oesophagopleural fistula
Anal fistula infection	Gastrointestinal fistula	Pancreatic fistula
Anal fistula repair	Gastrointestinal fistula repair	Pancreatic fistula repair
Anastomotic ulcer perforation	Gastrointestinal perforation	Peptic ulcer perforation
Anovulvar fistula	Gastrointestinal ulcer perforation	Peptic ulcer perforation, obstructive
Aortoenteric fistula	Gastropleural fistula	Peptic ulcer repair
Aorto-oesophageal fistula	Gastrosplenic fistula	Perforated ulcer
Appendiceal abscess	Ileal perforation	Perineal abscess
Appendicitis perforated	Ileal ulcer perforation	Perirectal abscess
Arterioenteric fistula	Incisional hernia perforation	Peritoneal abscess
Atrio-oesophageal fistula	Inguinal hernia perforation	Peritoneocutaneous fistula
Chemical peritonitis	Intestinal fistula	Peritonitis
Colon fistula repair	Intestinal fistula infection	Peritonitis bacterial
Colonic abscess	Intestinal fistula repair	Pneumoperitoneum
Colonic fistula	Intestinal perforation	Pneumoretroperitoneum
Colo-urethral fistula	Intestinal ulcer perforation	Procedural intestinal perforation
Diverticular fistula	Jejunal perforation	Rectal abscess
Diverticular perforation	Jejunal ulcer perforation	Rectal fistula repair
Diverticulitis intestinal perforated	Large intestinal ulcer perforation	Rectal perforation
Douglas' abscess	Large intestine perforation	Rectoprostatic fistula
Duodenal perforation	Lower gastrointestinal perforation	Rectourethral fistula
Duodenal rupture	Mesenteric abscess	Retroperitoneal abscess
Duodenal ulcer perforation	Neonatal intestinal perforation	Small intestinal perforation
Duodenal ulcer perforation, obstructive	Oesophageal abscess	Small intestinal ulcer perforation
Duodenal ulcer repair	Oesophageal fistula	Spontaneous bacterial peritonitis
Enterocolonic fistula	Oesophageal fistula repair	Umbilical hernia perforation
Enterocutaneous fistula		Upper gastrointestinal perforation

Fistula of small intestine		
AESI Category: Embolic and thrombotic events		
Acute aortic syndrome	Embolism venous	Pseudo-occlusion of internal carotid artery
Acute myocardial infarction	Endarterectomy	Pulmonary artery occlusion
Administration site thrombosis	Eye infarction	Pulmonary artery therapeutic procedure
Adrenal thrombosis	Femoral artery embolism	Pulmonary artery thrombosis
Amaurosis	Fluorescence angiogram abnormal	Pulmonary embolism
Amaurosis fugax	Foetal cerebrovascular disorder	Pulmonary endarterectomy
Angiogram abnormal	Foetal vascular malperfusion	Pulmonary infarction
Angiogram cerebral abnormal	Gastric infarction	Pulmonary microemboli
Angiogram peripheral abnormal	Graft thrombosis	Pulmonary thrombosis
Angioplasty	Haemorrhagic adrenal infarction	Pulmonary tumour thrombotic microangiopathy
Antiphospholipid syndrome	Haemorrhagic cerebral infarction	Pulmonary vein occlusion
Aortic bypass	Haemorrhagic infarction	Pulmonary veno-occlusive disease
Aortic embolus	Haemorrhagic stroke	Pulmonary venous thrombosis
Aortic surgery	Haemorrhagic transformation stroke	Quadriparesis
Aortic thrombosis	Haemorrhoids thrombosed	Quadriplegia
Aortogram abnormal	Hemiparesis	Renal artery angioplasty
Application site thrombosis	Hemiplegia	Renal artery occlusion
Arterectomy	Heparin-induced thrombocytopenia	Renal artery thrombosis
Arterectomy with graft replacement	Hepatic artery embolism	Renal embolism
Arterial angioplasty	Hepatic artery occlusion	Renal infarct
Arterial bypass operation	Hepatic artery thrombosis	Renal vascular thrombosis
Arterial graft	Hepatic infarction	Renal vein embolism
Arterial occlusive disease	Hepatic vascular thrombosis	Renal vein occlusion
Arterial revascularisation	Hepatic vein embolism	Renal vein thrombosis
Arterial stent insertion	Hepatic vein occlusion	Renal-limited thrombotic microangiopathy
Arterial therapeutic procedure	Hepatic vein thrombosis	Retinal artery embolism

Arterial thrombosis	Homans' sign positive	Retinal artery occlusion
Arteriogram abnormal	Hypothenar hammer syndrome	Retinal artery thrombosis
Arteriogram carotid abnormal	Iliac artery embolism	Retinal infarction
Arteriotomy	Iliac artery occlusion	Retinal vascular thrombosis
Arteriovenous fistula occlusion	Iliac vein occlusion	Retinal vein occlusion
Arteriovenous fistula thrombosis	Implant site thrombosis	Retinal vein thrombosis
Arteriovenous graft thrombosis	Incision site vessel occlusion	Revascularisation procedure
Artificial blood vessel occlusion	Infarction	Shunt occlusion
Aseptic cavernous sinus thrombosis	Inferior vena cava syndrome	Shunt thrombosis
Atherectomy	Inferior vena caval occlusion	SI QIII TIII pattern
Atherosclerotic plaque rupture	Infusion site thrombosis	Silent myocardial infarction
Atrial appendage closure	Injection site thrombosis	Spinal artery embolism
Atrial appendage resection	Inner ear infarction	Spinal artery thrombosis
Atrial thrombosis	Instillation site thrombosis	Spinal cord infarction
Autoimmune heparin-induced thrombocytopenia	Internal capsule infarction	Spinal stroke
Axillary vein thrombosis	Intestinal infarction	Splenic artery thrombosis
Basal ganglia infarction	Intra-aortic balloon placement	Splenic embolism
Basal ganglia stroke	Intracardiac mass	Splenic infarction
Basilar artery occlusion	Intracardiac thrombus	Splenic thrombosis
Basilar artery thrombosis	Intraoperative cerebral artery occlusion	Splenic vein occlusion
Blindness transient	Ischaemic cerebral infarction	Splenic vein thrombosis
Bone infarction	Ischaemic stroke	Stoma site thrombosis
Brachiocephalic artery occlusion	Jugular vein embolism	Stress cardiomyopathy
Brachiocephalic vein occlusion	Jugular vein occlusion	Stroke in evolution
Brachiocephalic vein thrombosis	Jugular vein thrombosis	Strokectomy
Brain stem embolism	Lacunar infarction	Subclavian artery embolism
Brain stem infarction	Lambl's excrescences	Subclavian artery occlusion
Brain stem stroke	Left atrial appendage closure implant	Subclavian artery thrombosis
Brain stem thrombosis	Leriche syndrome	Subclavian vein occlusion

Budd-Chiari syndrome	Mahler sign	Subclavian vein thrombosis
Capsular warning syndrome	May-Thurner syndrome	Superficial vein thrombosis
Cardiac ventricular thrombosis	Medical device site thrombosis	Superior sagittal sinus thrombosis
Carotid angioplasty	Mesenteric arterial occlusion	Superior vena cava occlusion
Carotid arterial embolus	Mesenteric arteriosclerosis	Superior vena cava syndrome
Carotid artery bypass	Mesenteric artery embolism	Surgical vascular shunt
Carotid artery occlusion	Mesenteric artery stenosis	Testicular infarction
Carotid artery stent insertion	Mesenteric artery stent insertion	Thalamic infarction
Carotid artery thrombosis	Mesenteric artery thrombosis	Thrombectomy
Carotid endarterectomy	Mesenteric vascular insufficiency	Thromboangiitis obliterans
Catheter directed thrombolysis	Mesenteric vascular occlusion	Thromboembolectomy
Catheter site thrombosis	Mesenteric vein thrombosis	Thrombolysis
Catheterisation venous	Mesenteric venous occlusion	Thrombophlebitis
Cavernous sinus thrombosis	Microembolism	Thrombophlebitis migrans
Central venous catheterisation	Monoparesis	Thrombophlebitis neonatal
Cerebellar artery occlusion	Monoplegia	Thrombosed varicose vein
Cerebellar artery thrombosis	Muscle infarction	Thrombosis
Cerebellar embolism	Myocardial infarction	Thrombosis corpora cavernosa
Cerebellar infarction	Myocardial necrosis	Thrombosis in device
Cerebral artery embolism	Obstetrical pulmonary embolism	Thrombosis mesenteric vessel
Cerebral artery occlusion	Obstructive shock	Thrombosis prophylaxis
Cerebral artery stent insertion	Ophthalmic artery occlusion	Thrombosis with thrombocytopenia syndrome
Cerebral artery thrombosis	Ophthalmic artery thrombosis	Thrombotic cerebral infarction
Cerebral congestion	Ophthalmic vein thrombosis	Thrombotic microangiopathy
Cerebral hypoperfusion	Optic nerve infarction	Thrombotic stroke
Cerebral infarction	Ovarian vein thrombosis	Thrombotic thrombocytopenic purpura
Cerebral infarction foetal	Paget-Schroetter syndrome	Thyroid infarction
Cerebral ischaemia	Pancreatic infarction	Transient ischaemic attack
Cerebral microembolism	Papillary muscle infarction	Transverse sinus thrombosis

Cerebral microinfarction	Paradoxical embolism	Truncus coeliacus thrombosis
Cerebral septic infarct	Paraneoplastic thrombosis	Tumour embolism
Cerebral thrombosis	Paraparesis	Tumour thrombectomy
Cerebral vascular occlusion	Paraplegia	Tumour thrombosis
Cerebral venous sinus thrombosis	Paresis	Ultrasonic angiogram abnormal
Cerebral venous thrombosis	Pelvic venous thrombosis	Ultrasound Doppler abnormal
Cerebrospinal thrombotic tamponade	Penile artery occlusion	Umbilical cord occlusion
Cerebrovascular accident	Penile vein thrombosis	Umbilical cord thrombosis
Cerebrovascular accident prophylaxis	Percutaneous coronary intervention	Vaccination site thrombosis
Cerebrovascular disorder	Peripheral arterial occlusive disease	Vascular access site thrombosis
Cerebrovascular insufficiency	Peripheral arterial reocclusion	Vascular device occlusion
Cerebrovascular operation	Peripheral artery angioplasty	Vascular graft
Cerebrovascular stenosis	Peripheral artery bypass	Vascular graft occlusion
Choroidal infarction	Peripheral artery occlusion	Vascular graft thrombosis
Coeliac artery occlusion	Peripheral artery stent insertion	Vascular operation
Collateral circulation	Peripheral artery surgery	Vascular pseudoaneurysm thrombosis
Compression garment application	Peripheral artery thrombosis	Vascular stent insertion
Coronary angioplasty	Peripheral embolism	Vascular stent occlusion
Coronary arterial stent insertion	Peripheral endarterectomy	Vascular stent thrombosis
Coronary artery bypass	Peripheral revascularisation	Vasodilation procedure
Coronary artery embolism	Peripheral vein occlusion	Vena cava embolism
Coronary artery occlusion	Peripheral vein thrombus extension	Vena cava filter insertion
Coronary artery reocclusion	Phlebectomy	Vena cava filter removal
Coronary artery surgery	Pituitary infarction	Vena cava thrombosis
Coronary artery thrombosis	Placental infarction	Venogram abnormal
Coronary bypass thrombosis	Pneumatic compression therapy	Venoocclusive disease
Coronary endarterectomy	Popliteal artery entrapment syndrome	Venoocclusive liver disease
Coronary revascularisation	Portal shunt procedure	Venous angioplasty
Coronary vascular graft occlusion	Portal vein cavernous transformation	Venous occlusion

Deep vein thrombosis	Portal vein embolism	Venous operation
Deep vein thrombosis postoperative	Portal vein occlusion	Venous recanalisation
Device embolisation	Portal vein thrombosis	Venous repair
Device occlusion	Portosplenomesenteric venous thrombosis	Venous stent insertion
Device related thrombosis	Post procedural myocardial infarction	Venous thrombosis
Diplegia	Post procedural pulmonary embolism	Venous thrombosis in pregnancy
Directional Doppler flow tests abnormal	Post procedural stroke	Venous thrombosis limb
Disseminated intravascular coagulation	Post thrombotic syndrome	Venous thrombosis neonatal
Disseminated intravascular coagulation in newborn	Postinfarction angina	Vertebral artery occlusion
Embolia cutis medicamentosa	Postoperative thrombosis	Vertebral artery thrombosis
Embolic cerebellar infarction	Postpartum thrombosis	Vessel puncture site occlusion
Embolic cerebral infarction	Postpartum venous thrombosis	Vessel puncture site thrombosis
Embolic pneumonia	Precerebral artery embolism	Visceral venous thrombosis
Embolic stroke	Precerebral artery occlusion	Visual acuity reduced transiently
Embolism	Precerebral artery thrombosis	Visual midline shift syndrome
Embolism arterial	Profundaplasty	
	Prosthetic cardiac valve thrombosis	
	Prosthetic vessel implantation	
AESI Category: Hepatic function abnormal		
Acquired antithrombin III deficiency	Gastric variceal ligation	Hypothromboplastinaemia
Acquired factor IX deficiency	Gastric varices	Icterus index increased
Acquired factor V deficiency	Gastric varices haemorrhage	Immune-mediated cholangitis
Acquired factor VIII deficiency	Gastrooesophageal variceal haemorrhage prophylaxis	Immune-mediated hepatic disorder
Acquired factor XI deficiency	Graft versus host disease in liver	Immune-mediated hepatitis
Acquired hepatocerebral degeneration	Guanase increased	International normalised ratio abnormal
Acquired protein S deficiency	Haemangioma of liver	International normalised ratio increased
Acute graft versus host disease in liver	Haemorrhagic hepatic cyst	Intestinal varices
Acute hepatic failure	Hepaplastin abnormal	Intestinal varices haemorrhage

Acute on chronic liver failure	Hepaplastin decreased	Ischaemic hepatitis
Acute yellow liver atrophy	Hepatectomy	Jaundice
Alanine aminotransferase abnormal	Hepatic adenoma	Jaundice cholestatic
Alanine aminotransferase increased	Hepatic angiosarcoma	Jaundice hepatocellular
Allergic hepatitis	Hepatic artery flow decreased	Kayser-Fleischer ring
Alloimmune hepatitis	Hepatic atrophy	Liver carcinoma ruptured
Ammonia abnormal	Hepatic calcification	Liver dialysis
Ammonia increased	Hepatic cancer	Liver disorder
Anti factor X activity abnormal	Hepatic cancer metastatic	Liver function test abnormal
Anti factor X activity decreased	Hepatic cancer recurrent	Liver function test decreased
Anti factor X activity increased	Hepatic cancer stage I	Liver function test increased
Antithrombin III decreased	Hepatic cancer stage II	Liver induration
Ascites	Hepatic cancer stage III	Liver injury
Aspartate aminotransferase abnormal	Hepatic cancer stage IV	Liver operation
Aspartate aminotransferase increased	Hepatic cirrhosis	Liver palpable
AST/ALT ratio abnormal	Hepatic cyst	Liver scan abnormal
Asterixis	Hepatic cyst ruptured	Liver tenderness
Autoimmune hepatitis	Hepatic cytolysis	Liver transplant
Bacterascites	Hepatic encephalopathy	Lupoid hepatic cirrhosis
Benign hepatic neoplasm	Hepatic encephalopathy prophylaxis	Lupus hepatitis
Benign hepatobiliary neoplasm	Hepatic enzyme abnormal	Magnetic resonance imaging hepatobiliary abnormal
Bile output abnormal	Hepatic enzyme decreased	Magnetic resonance proton density fat fraction measurement
Bile output decreased	Hepatic enzyme increased	Mitochondrial aspartate aminotransferase increased
Biliary ascites	Hepatic failure	Mixed hepatocellular cholangiocarcinoma
Biliary cirrhosis	Hepatic fibrosis	Mixed liver injury
Biliary fibrosis	Hepatic function abnormal	Molar ratio of total branched-chain amino acid to tyrosine
Bilirubin conjugated abnormal	Hepatic haemangioma rupture	Nodular regenerative hyperplasia
Bilirubin conjugated increased	Hepatic hamartoma	Nonalcoholic fatty liver disease

Bilirubin excretion disorder	Hepatic hydrothorax	Non-alcoholic steatohepatitis
Bilirubin urine present	Hepatic hypertrophy	Non-cirrhotic portal hypertension
Biopsy liver abnormal	Hepatic hypoperfusion	Ocular icterus
Blood bilirubin abnormal	Hepatic infiltration eosinophilic	Oedema due to hepatic disease
Blood bilirubin increased	Hepatic lesion	Oesophageal varices haemorrhage
Blood bilirubin unconjugated increased	Hepatic lipoma	Parenteral nutrition associated liver disease
Blood fibrinogen abnormal	Hepatic mass	Perihepatic discomfort
Blood fibrinogen decreased	Hepatic necrosis	Peripancreatic varices
Blood thrombin abnormal	Hepatic neoplasm	Portal fibrosis
Blood thrombin decreased	Hepatic neuroendocrine tumour	Portal hypertension
Blood thromboplastin abnormal	Hepatic pain	Portal hypertensive colopathy
Blood thromboplastin decreased	Hepatic sequestration	Portal hypertensive enteropathy
Bromosulphthalein test abnormal	Hepatic steato-fibrosis	Portal hypertensive gastropathy
Cardiohepatic syndrome	Hepatic steatosis	Portal vein cavernous transformation
Child-Pugh-Turcotte score abnormal	Hepatic vascular resistance increased	Portal vein dilatation
Child-Pugh-Turcotte score increased	Hepatic venous pressure gradient abnormal	Portopulmonary hypertension
Cholaemia	Hepatic venous pressure gradient increased	Primary biliary cholangitis
Cholangiosarcoma	Hepatitis	Protein C decreased
Cholestasis	Hepatitis acute	Protein S abnormal
Cholestatic liver injury	Hepatitis cholestatic	Protein S decreased
Cholestatic pruritus	Hepatitis chronic active	Prothrombin level abnormal
Chronic graft versus host disease in liver	Hepatitis chronic persistent	Prothrombin level decreased
Chronic hepatic failure	Hepatitis fulminant	Prothrombin time abnormal
Chronic hepatitis	Hepatitis toxic	Prothrombin time prolonged
Coagulation factor decreased	Hepatobiliary cancer	Prothrombin time ratio abnormal
Coagulation factor IX level abnormal	Hepatobiliary cancer in situ	Prothrombin time ratio increased
Coagulation factor IX level decreased	Hepatobiliary cyst	Radiation hepatitis
Coagulation factor V level abnormal	Hepatobiliary disease	Regenerative siderotic hepatic nodule
Coagulation factor V level decreased	Hepatobiliary neoplasm	Renal and liver transplant

Coagulation factor VII level abnormal	Hepatobiliary scan abnormal	Retrograde portal vein flow
Coagulation factor VII level decreased	Hepatoblastoma	Reye's syndrome
Coagulation factor X level abnormal	Hepatoblastoma recurrent	Reynold's syndrome
Coagulation factor X level decreased	Hepatocellular carcinoma	Splenic varices
Coma hepatic	Hepatocellular foamy cell syndrome	Splenic varices haemorrhage
Computerised tomogram liver abnormal	Hepatocellular injury	Spontaneous bacterial peritonitis
Congestive hepatopathy	Hepatomegaly	Steatohepatitis
Cryptogenic cirrhosis	Hepatopulmonary syndrome	Steatohepatitis
Diabetic hepatopathy	Hepatorenal failure	Subacute hepatic failure
Drug-induced liver injury	Hepatorenal syndrome	Sugiura procedure
Duodenal varices	Hepatosplenomegaly	Thrombin time abnormal
Flood syndrome	Hepatotoxicity	Thrombin time prolonged
Focal nodular hyperplasia	Hyperammonaemia	Total bile acids increased
Foetor hepaticus	Hyperbilirubinaemia	Transaminases abnormal
Galactose elimination capacity test abnormal	Hypercholia	Transaminases increased
Galactose elimination capacity test decreased	Hyperfibrinolysis	Ultrasound liver abnormal
Gallbladder varices	Hypertransaminasaemia	Urine bilirubin increased
Gamma-glutamyltransferase abnormal	Hypocoagulable state	Varices oesophageal
Gamma-glutamyltransferase increased	Hypofibrinogenaemia	Varicose veins of abdominal wall
Gastric variceal injection	Hypothrombinaemia	White nipple sign
		X-ray hepatobiliary abnormal
AESI Category: Left ventricular ejection fraction decreased		
Acute left ventricular failure	Cardiohepatic syndrome	Hepatojugular reflux
Acute pulmonary oedema	Cardiopulmonary failure	Left ventricular failure
Acute right ventricular failure	Cardiorenal syndrome	Low cardiac output syndrome
Cardiac asthma	Chronic left ventricular failure	Neonatal cardiac failure
Cardiac failure	Chronic right ventricular failure	Obstructive shock
Cardiac failure acute	Congestive hepatopathy	Pulmonary oedema

Cardiac failure chronic	Cor pulmonale	Pulmonary oedema neonatal
Cardiac failure congestive	Cor pulmonale acute	Radiation associated cardiac failure
Cardiac failure high output	Cor pulmonale chronic	Right ventricular ejection fraction decreased
Cardiogenic shock	Ejection fraction decreased	Right ventricular failure
		Ventricular failure

APPENDIX 6. CLINICAL LABORATORY PARAMETERS CTCAE CRITERIA

PARAM (SI Unit)	Hypo	Hyper	ATOXGR			
			GRADE 1	GRADE 2	GRADE 3	GRADE 4
		Hemoglobin increased	Increase in >0 - 2 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >4 gm/dL above ULN or above baseline if baseline is above ULN	~
Hemoglobin (g/L)	Anemia		Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L	~
Platelets (10^9/L)	Platelet count decreased		<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L
Leukocytes (10^9/L)	White blood cell decreased		<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L

Neutrophils (10^9/L)	Neutrophil count decreased		<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L
	Lymphocyte count decreased		<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L
Lymphocytes (10^9/L)		Lymphocyte count increased	~	>4000/mm3 - 20,000/mm3	>20,000/mm3	~
Activated Partial Thromboplastin Time (s)		Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; bleeding	~
International Normalized Ratio		INR increased	>1.2 - 1.5	>1.5 - 2.5	>2.5	~
Albumin (g/L)	Hypoalbuminemia		<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	~
Glucose (mmol/L)	Hypoglycemia		<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L
Creatinine (umol/L)		Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN
Alkaline Phosphatase (IU/L)		Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN

Aspartate Aminotransferase (IU/L)		Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Alanine Aminotransferase (IU/L)		Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Serum Calcium (mmol/L)		Hypercalcemia	>ULN - 2.9 mmol/L	>2.9 - 3.1 mmol/L	>3.1 - 3.4 mmol/L	>3.4 mmol/L
	Hypocalcemia		<LLN - 2.0 mmol/L	<2.0 - 1.75 mmol/L	<1.75 - 1.5 mmol/L	<1.5 mmol/L
Magnesium (mmol/L)		Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	~	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L
	Hypomagnesemia		<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L
Potassium (mmol/L)		Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L
	Hypokalemia		<LLN - 3.0 mmol/L	~	<3.0 - 2.5 mmol/L	<2.5 mmol/L
Sodium (mmol/L)		Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
	Hyponatremia		<LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L
Total cholesterol (mmol/L)		Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L

Bilirubin (umol/L)		Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
Triglycerides (mmol/L)		Hypertriglyceridemia	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L
Urinary protein		Proteinuria	1+ proteinuria; urinary protein <1.0 g/24 hrs	2+ proteinura; urinary protein 1.0 - 3.4g/24hrs	urinary protein >= 3.5g/24hrs	~