STATISTICAL ANALYSIS PLAN

An Open-Label, Phase 1b/2 Study to Evaluate the Safety and Efficacy of Fruquintinib in Combination with Tislelizumab in Patients with Advanced Solid Tumors

Protocol Number:	2020-013-00US3
Name of Test Drug:	**Fruquintinib (HMPL-013)** **Tislelizumab (BGB-A317)**
Phase:	Phase 1b/2
Sponsor Name:	HUTCHMED Limited Building 4, 720 Cailun Road, China (Shanghai) Pilot Free Trade Zone Shanghai, China, 201203 Phone: PPD http://www.hutch-med.com
Analysis Plan Version	Version 2.0
Effective Date	29 July 2024

Compliance: The study described in this report was performed according to the principle of Good Clinical Practice (GCP).

APPROVAL SIGNATURES

AUTHOR:

PPD

Signature **Date**

PPD
Syneos Health

PPD

Signature **Date**

PPD
Syneos Health

APPROVED BY:

PPD

Signature **Date**

PPD
Syneos Health

PPD

Signature **Date**

PPD
HUTCHMED Limited

PPD

Signature **Date**

PPD
HUTCHMED Limited

PPD

Signature **Date**

PPD
HUTCHMED Limited

REVISION HISTORY

Date	Version	Description	Author
10Jun2021	0.1	Initial version	PPD
01July2021	0.2	Updated due to SR and internal Syneos review. Version sent to HMP	PPD
18Oct2021	0.3	Updated due to HMP comments and protocol amendment 2	PPD
15Dec2021	0.4	Updated due to HMP comments	PPD
04Mar2022	0.5	Updated due to HMP comments and protocol amendment 3	PPD
28Mar2022	1.0	Updated due to HMP comments and finalized	PPD
21Jul2022	1.1	Update sponsor name to HUTCHMED Limited and the relevant address information Updated MedDRA dictionary version and WHO Drug dictionary version. Added some additional hepatic criteria in section 4.4.3 Updated visit windowing table 11 in section 5.1.3. Removed in section 5.2.1 the derivation of EOS reasons as it is now reported in the CRF. Updated section 5.4.1 (Pharmacokinetic analysis) and 5.4.2 (Immunogenicity analysis). Updated Appendix 1: Study Schedule of Events Updated Appendix 5: Updated MedDRA Preferred Term List using version 25.0 Added Appendix 6 to define COVID related AEs	PPD

		Added Appendix 7 to define conversion tables for urinalysis results	
29Jul2024	2.0	Update due to HMP comments and protocol amendment 4 dated 02 February 2023 and amendment 5 dated 06 December 2023. Update prior to the Database Lock. – Updated the DLT-Evaluable Analysis Set and PK Analysis Set definitions. – Removed Appendix 5. – Considerations for assigning response category and patients without any post-baseline tumor assessment (patients who died or progressed clinically prior to the first scheduled tumor assessment) were added in Sections 4.2.1 and 4.2.2. – Details on censoring for PFS were added in Table 3. – Text in Section 6.2 was aligned with the interim analyses performed during the study conduct. – Additional details provided on presentation of PK data in Section 4.5.1 and ADA data in Section 4.5.2.	PPD

TABLE OF CONTENTS

List of Tables

LIST OF ABBREVIATIONS

Abbreviation	Term
ADA	Antidrug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ASCO	American Society for Clinical Oncology
ATC	Anatomic Therapeutic Classification
BLQ	Below the Lower Limit of Quantification
BMI	Body Mass Index
CAP	College of American Pathologists
CBR	Clinical Benefit Rate
CFB	Change from Baseline
CI	Confidence Interval
CR	Complete Response
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A	Cytochrome P450, family 3, subfamily A
DBL	Database Lock
DBP	Diastolic Blood Pressure
DCR	Disease Control Rate
DLT	Dose-limiting Toxicity
DoR	Duration of Response
DMC	Data Monitoring Committee
EC	Endometrial Cancer
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EOC	End of Cycle
EOI	End of Infusion
EOT	End of Treatment
ER/PR or ER/PGR	Estrogen Receptor/Progesterone Receptor
ICH	International Council on Harmonization
ICI	Immune Checkpoint Inhibitor
imAE	Immune-mediated AE
IO	Immuno-oncology

Abbreviation	Term
LLOQ	Lower Limit of Quantification
mCRC	Metastatic Colorectal Cancer
MedDRA	Medical Dictionary for Regulatory Activities
MSI	Microsatellite Instability
MSS	Microsatellite Stable
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Event
ORR	Objective Response Rate
OS	Overall Survival
PFS	Progression-free Survival
PD-L1	Programmed Death Ligand 1
PT	Preferred Term
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
StdDev	Standard Deviation
SMQs	Standardized MedDRA Queries
SOC	System Organ Class
SRC	Safety Review Committee
TEAE	Treatment-emergent Adverse Event
TLF	Table, Listing, Figure
TNBC	Triple Negative Breast Cancer
TPR	Timepoint Response
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) describes the planned statistical analyses and data presentations for study 2020-013-00US3. The SAP is based on the Protocol Amendment 5, dated 06 December 2023. Study measurements and assessments, planned statistical methods, and derived variables are summarized in this plan. Planned tables, figures, and listings are specified. All decisions regarding final analyses, as defined in this SAP document, have been made prior to locking the database. Any deviations from these guidelines will be documented in the clinical study report (CSR).

This is an amendment to the approved SAP (dated 21 July 2022) based on the most recent Protocol Amendment 5 dated 06 December 2023. Upon implementation of Protocol Amendment #4, enrollment to expansion cohorts A (TNBC immuno-oncology [IO]-treated in the metastatic setting), B (TNBC IO-Naïve in the metastatic setting) and C (EC IO Naïve) in this study has been permanently discontinued based upon the strategic evaluation of the clinical development of fruquintinib in the United States with HUTCHMED as the study Sponsor. For Cohort D (MSS mCRC, IO Naïve), at the time of this decision making, the enrollment was completed. This change is not based on any concern for patient safety or efficacy relative to fruquintinib and/or tislelizumab treatment. Patients who are currently enrolled in these cohorts and are deriving benefit from treatment with fruquintinib and/or tislelizumab may continue to participate in the study as per protocol. There is no planned interruption in the supply of fruquintinib or tislelizumab to clinical trial sites with active patients.

Syneos Health is to list and tabulate concentration data for fruquintinib, its metabolite M11, tislelizumab. Immunogenicity data will also be tabulated. Syneos Health are responsible for the production and quality control of all Study Data Tabulation Model (SDTM) datasets, Analysis Data Model (ADaM) datasets, and the tables, listings, and figures (TLFs) associated with these datasets. The SAP for population PK will be prepared in a separate analysis plan by another contract research organization (CRO).

2. STUDY DETAILS

2.1. Study Objectives

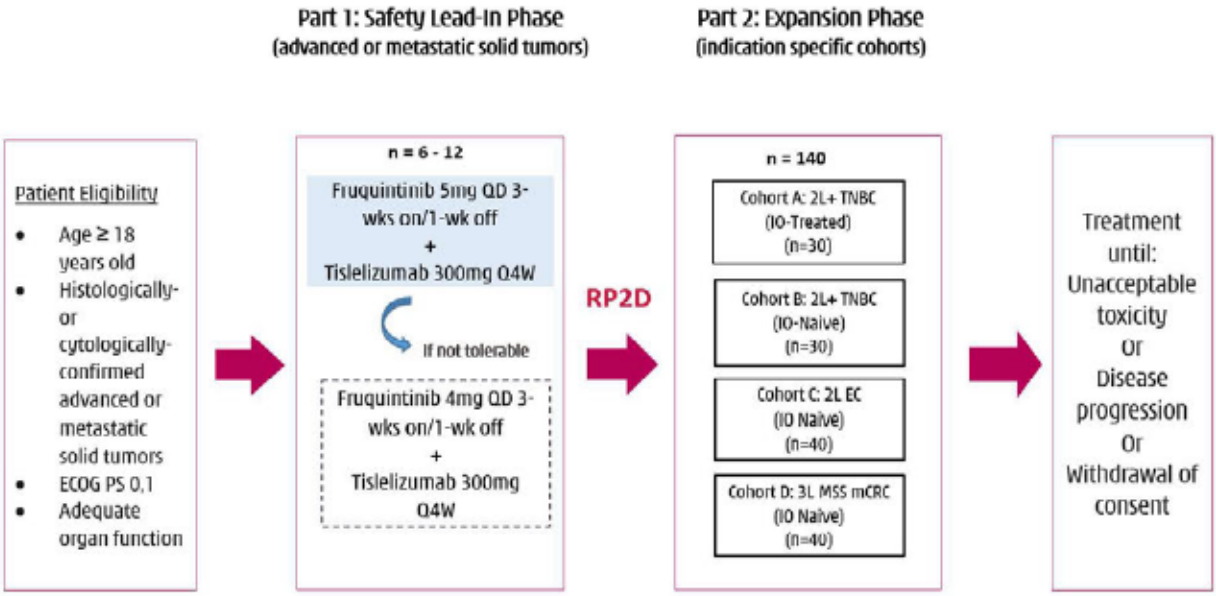
Part	Tier	Objectives	Endpoints
Part 1: Safety Lead-in Phase	Primary	To assess the safety and tolerability of fruquintinib in combination with tislelizumab in patients with advanced solid tumors	Adverse events (AEs) characterized by type, frequency, severity per The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0, timing, seriousness, relationship to study drug(s), and discontinuation of study drug(s) due to AEs
		To confirm the recommended phase 2 dose (RP2D) of fruquintinib in combination with tislelizumab	RP2D
	Secondary	To evaluate the efficacy of fruquintinib in combination with tislelizumab per investigator assessment	objective response rate (ORR) progression free survival (PFS), disease control rate (DCR), clinical benefit rate (CBR), duration of response (DoR) overall survival (OS)
		To characterize the PK profile of fruquintinib and metabolite M11 when combined with tislelizumab	Plasma concentrations of fruquintinib and M11
		To evaluate the PK and immunogenicity of fruquintinib in combination with tislelizumab	Serum concentrations of tislelizumab and incidence of anti-drug antibody (ADA) to tislelizumab
Part 2: Dose Expansion Phase	Primary	To evaluate the ORR assessed by the investigator in patients with advanced or metastatic TNBC, EC, or MSS mCRC when treated with fruquintinib in combination with tislelizumab	ORR per response evaluation criteria in solid tumors version 1.1 (RECIST v1.1)
	Secondary	To further evaluate efficacy of fruquintinib in combination with tislelizumab in patients with advanced or metastatic TNBC, EC, or MSS mCRC per investigator assessment	PFS, DCR, CBR, DoR, and OS
		To characterize the safety of fruquintinib in combination with tislelizumab	AEs characterized by type, frequency, severity per NCI CTCAE v5.0, timing, seriousness, relationship to study drug(s), and discontinuation of study drug(s) due to AEs.

Part	Tier	Objectives	Endpoints
		To assess the pharmacokinetic (PK) profile of fruquintinib and metabolite (M11) when combined with tislelizumab	Plasma concentrations and derived PK parameters of fruquintinib and M11.
		To characterize the PK and immunogenicity of fruquintinib when combined with tislelizumab	Serum concentrations of tislelizumab and incidence of ADA to tislelizumab
		To detect the expression of programmed death-ligand (PD-L1), MSS/MSI status, and other biomarkers in tumor tissues of patients, and to perform relevant efficacy analysis to provide reference for the determination of dominant population	Changes from baseline in biomarkers markers, correlation with drug exposure, and association with efficacy and safety parameters
	Exploratory	To explore potential biomarkers associated with anti-tumor effects of fruquintinib in combination with tislelizumab	Changes from baseline in tumor markers, correlation with drug exposure, and association with efficacy and safety parameters

2.2. Study Design

This is an open-label, multicenter, non-randomized, phase 1b/2 study to assess the safety and efficacy of fruquintinib in combination with tislelizumab in patients with advanced or metastatic solid tumors. This study will be conducted in 2 parts: a Safety Lead-in phase (Part 1) and a dose expansion phase (Part 2). The overall study schematic is presented in Figure 1.

Figure 1 Study Design Schema



2L=second line; 3L=third line; EC=endometrial cancer; ECOG=Eastern Cooperative Oncology Group; IO=immune-oncology; mCRC=metastatic colorectal cancer; MSS=microsatellite stable; n=total number of patients; PS=performance status; QD=once daily; Q4W=every 4 weeks; RP2D=recommended Phase 2 dose; TNBC=triple negative breast cancer.

Part 1: Safety Lead-in Phase

Approximately 6 to 12 patients with histologically or cytologically documented advanced or metastatic solid tumors of any type who have progressed on standard systemic therapy and for which no effective therapy or standard of care exists will be enrolled and assessed for DLTs during the 28-day period DLT observation period. Patients may be either immuno-oncology (IO) treated or naïve in the metastatic setting. Patients with TNBC in the Safety Lead-in must meet eligibility criteria defined in cohorts A or B, and those with EC in the Safety Lead-in must meet eligibility criteria defined in cohort C.

Part 1 of the study will begin by enrolling the first 6 patients and evaluating for DLTs during the DLT observation period. Study drug administration will begin at the full dose of

fruquintinib (5 mg daily, 3 weeks on followed by 1 week off every 4-week cycle) in combination with tislelizumab (300 mg once every 4 weeks). A lower dose level of fruquintinib (4 mg daily, 3 weeks on followed by 1 week off every 4-week cycle) will be explored as necessary depending on observed toxicity.

Only dose limiting toxicities (DLTs) during the first cycle of treatment will be assessed.

- If 0 or 1 of 6 patients experiences a DLT, the study may proceed at the current dose of both drugs.
- If 2 or more patients experience a DLT, then, following consultation with the safety review committee (SRC), the study will proceed with enrollment in the next defined lower dose (Dose Level -1), an additional 6 patients will be enrolled, and the 28-day DLT observation period will be repeated.
- If 2 or more patients experience a DLT in Dose Level -1, enrollment in the study will cease.

Part 2: Dose Expansion Phase

Approximately 140 patients will be enrolled, including approximately 60 patients with TNBC (approximately 30 patients in each cohort [A and B]) and approximately 40 patients with EC in Cohort C, and approximately 40 patients with MSS mCRC in Cohort D. Patients will be enrolled to one of the following 4 cohorts. Of note, based upon the strategic evaluation of the clinical development of fruquintinib, patient enrollment has been permanently discontinued for all cohorts in the dose expansion phase. At the time of deciding on discontinuation of enrollment, the Cohort D had completed the enrollment. Hence, the final actual total number of patients will reflect this strategic decision.

- **Cohort A** (TNBC, immuno-oncology [IO]-treated in the metastatic setting):
  Patients must have histologically or cytologically documented, advanced or metastatic TNBC as defined by American Society for Clinical Oncology (ASCO)-College of American Pathologists (CAP) guidelines. Up to 15 patients in cohort A can have ER or PR low positive disease as defined by ASCO-CAP guidelines, if the treating physician considers the patient not eligible for adjuvant endocrine therapy. TNBC is defined as ER/PR positivity of <1%, and ER/PR low positive disease is defined by ER/PR positivity of 1% to 10% (Allison 2020).

  Patients must have progressed on at least 1 line, but no more than 3 lines, of cytotoxic therapy in the locally advanced or metastatic setting. Patients must have also progressed on prior immunotherapy in the metastatic setting (Rakha 2014)Rakha 2014.

- **Cohort B** (TNBC, IO-Naïve in the metastatic setting):
  Patients must have histologically or cytologically documented, locally advanced or metastatic TNBC as defined by ASCO-CAP guidelines. Up to 15 patients in cohort B can have ER or PR low positive disease as defined by ASCO-CAP guidelines, if the treating physician considers the patient not eligible for adjuvant endocrine therapy.

TNBC is defined as ER/PR positivity of <1%, and ER/PR low positive disease is defined by ER/PR positivity of 1% to 10%.

Patients must have progressed on at least 1 line, but no more than 3 lines, of cytotoxic therapy in the locally advanced or metastatic setting. Patients must not have received prior therapy with an ICI or other immunotherapy in the metastatic setting.

- **Cohort C** (EC, IO Naïve):
  Patients must have histologically or cytologically documented, advanced or metastatic EC.

  Patients must have progressed on 1 prior, platinum-based chemotherapy regimen for EC. Participants may have received up to 1 additional line of platinum-based chemotherapy if given in the neoadjuvant or adjuvant setting and must not have received prior therapy with an ICI or other immunotherapy.

- **Cohort D** (MSS mCRC, IO Naïve):
  Patients must have histologically or cytologically confirmed, advanced or metastatic, unresectable adenocarcinoma of the colon or rectum. All other histological types are excluded.

  Patients must have failed 2 lines of standard chemotherapies, including fluorouracil, oxaliplatin, and irinotecan. Failed chemotherapies are defined as the occurrence of PD or intolerable toxicities during the treatment or after the last dose.

  Notes: a) Each line of treatment for advanced disease until PD includes one or more chemotherapy drugs used for ≥ 1 cycle; b) Previous adjuvant/neoadjuvant therapy is allowed. If relapse or metastasis occur during the adjuvant/neoadjuvant treatment period or within 6 months after the completion of the above treatment, that adjuvant/neoadjuvant therapy is considered as the failure of first line systemic chemotherapy for PD.

  Patients with RAS wild-type tumor must have received anti-VEGF and/or endothelial growth factor receptor (EGFR) antibody treatment. Patients with RAS mutation or RAS status unknown must have received anti-VEGF antibody treatment.

  Tumor tissue must have been assessed for MSS status prior to enrollment. The results should be available in the source documents and be those used to make treatment decisions for the patient. A redacted copy of the local results should accompany the archival tumor samples submitted as part of the protocol.

Overall study conduct

In all parts of the study, there is no predefined duration of treatment for each patient. That is, patients will continue receiving study drug administration until radiologically determined PD per RECIST v 1.1, unacceptable toxicity, death, or withdrawal from study.

Treatment cycles will occur consecutively without interruption, except when necessary to manage toxicities or for administrative reasons.

The dose for fruquintinib can be reduced at any time due to the intolerable toxicity following the DLT observation window in the safety lead-in phase. Once reduced, the dose cannot be re-escalated to the previous level. There is no dose reduction for tislelizumab in this study.

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

Any patient who discontinues treatment is protocol-required to return to the study site for an EOT (end of treatment) visit and safety follow-up visit.

The EOT (end of treatment) visit is conducted ≤7 days (±3 days) after the last dose when the investigator determines that the patient must permanently discontinue all study drugs.

Patients who permanently discontinue all study drugs will be asked to return to the clinic for the safety follow-up visit, which is required to be conducted 30 days (±7 days) after the EOT visit.

Every 8 weeks (±14 days) after the EOT visit, the investigator or their designee should call the patients to collect information related to survival status and their use of other anticancer treatments, including drug name, dosage, and treatment start and end dates.

The end of the study is defined as the last visit of the last patient in the study.

The SRC will review the data during Part 2 on an ongoing basis for safety.

The study scheduled assessments are presented in Appendix 1.

2.3. Determination of Sample Size

Approximately 146 to 152 patients are estimated to be enrolled in this study (approximately 6 to 12 patients in the dose escalation phase and approximately 140 patients in the dose expansion phase).

Safety Lead-In Phase

Approximately 6 to 12 patients will be enrolled into this phase of the study. The total sample size will be determined by the incidence of DLTs in the safety lead-in phase.

Dose Expansion Phase

Approximately 30 patients will be enrolled in each of the Cohorts A and B, approximately 40 patients in Cohort C, and approximately 40 patients in Cohort D in the dose expansion phase of the study. Planned patient enrollment for each cohort can provide adequate precision for the estimate of ORR at a specific time point.

Table 1 Shows the range of ORR and the corresponding 95% CIs for a sample size of 30 or 40 patients.

Table 1 Estimated ORR and 2-Sided 95% Confidence Intervals

Number of patients	Number of Responders	Estimated ORR	95% CI Lower Limit	95% CI Upper Limit
30	0	0.00	0.00	0.12
30	5	0.17	0.06	0.35
30	10	0.33	0.17	0.53
30	15	0.50	0.31	0.69
30	20	0.67	0.47	0.83
30	25	0.83	0.65	0.94
30	30	1.00	0.88	1.00
40	0	0.00	0.00	0.09
40	5	0.13	0.04	0.27
40	10	0.25	0.13	0.41
40	15	0.38	0.23	0.54
40	20	0.50	0.34	0.66
40	25	0.63	0.46	0.77
40	30	0.75	0.59	0.87
40	35	0.88	0.73	0.96
40	40	1.00	0.91	1.00

CI=confidence interval; ORR=objective response rate
95% Clopper-Pearson interval for binomial distribution

3. ANALYSIS SETS

3.1. Definition of Analysis Sets

3.1.1. Enrolled Set

The enrolled set includes all patients who have signed ICF (inform consent form).

3.1.2. Safety Analysis Set

The safety analysis set includes all enrolled patients who received at least one dose of fruquintinib or tislelizumab. The safety evaluation will be performed based on the first dose of study treatment received by a patient. This is the primary population for safety and efficacy analyses.

3.1.3. DLT-Evaluable Analysis Set

The DLT-evaluable analysis set included all patients enrolled in the Safety Lead-in portion of the study who received at least 1 dose of fruquintinib or tislelizumab and were considered DLT evaluable based on the SRC review, according to the pre-specified criteria from the protocol.

3.1.4. Response Evaluable Analysis Set

The response evaluable analysis set will include all patients who are in the safety analysis set and have a 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. Sensitivity analysis for efficacy endpoints ORR, DCR, and CBR will be conducted using this analysis set.

3.1.5. Pharmacokinetics (PK) Analysis Set

The pharmacokinetic analysis set includes all patients in the safety analysis set that have at least one quantifiable plasma concentration of fruquintinib and/or tislelizumab.

3.1.6. Antidrug Antibody (ADA) Analysis Set

The antidrug antibody analysis set includes all patients who received at least one dose of tislelizumab and have a baseline and at least one post-baseline ADA result.

3.2. Protocol Deviation

Protocol deviations including deviations that are related to COVID-19 are recorded in the Clinical Trial Management System as outlined in the latest version of the Protocol Deviation and Non-compliance Management Plan. Protocol deviations are categorized as major/minor before database lock. Certain protocol deviations are major in that they may affect the ability to assess the safety and efficacy of study drug.

4. ENDPOINTS

4.1. General Principles for Derived and Transformed Data

4.1.1. Reference Start Date and End Date and Study Day

Reference start date is defined as the first date when a non-zero dose of any study drug (i.e. fruquintinib or tislelizumab, whichever occurs first) was administrated (first administration/dose date). Day 1 is the day of the first dose of study treatment in Cycle 1.

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

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

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings.

Reference end date is defined as the last date when a non-zero dose of any study drug was administered.

4.1.2. Baseline and Change from Baseline

Baseline is defined as the last non-missing assessment prior to the first administration of any study drug (whichever occurs first), including scheduled and unscheduled visits, unless otherwise specified. For quantitative measurements:

- change from baseline (CFB) will be calculated as: CFB = Assessment value at visit X – Baseline value;
- percentage CFB (% CFB) will be calculated as % CFB = (Assessment value at each visit X – Baseline value)/Baseline value × 100.

4.1.3. Treatment Period

Unless otherwise specified, the treatment period is defined as the period from first administration date to [30 days + 7 days protocol defined window] after last administration date on treatment. For safety data, only the assessments/events collected during the treatment period will be evaluated (except for related SAE and immune-mediated AE [imAEs]).

The worst post baseline is defined as the worst assessments/events during the treatment period including both scheduled and non-scheduled visits. The last assessment on treatment measurement is defined as the latest non-missing measurement taken during the treatment period.

4.2. Efficacy Endpoints

4.2.1. Primary Endpoint

The primary efficacy endpoint for Part 2 is the objective response rate (ORR) which is defined as the proportion of patients with a confirmed best overall response (BOR) complete response (CR) or Partial Response (PR) as determined by the investigator using RECIST v1.1.

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 2009) or death; or (ii) withdrawal of consent or lost to follow-up; or (iii) receiving subsequent anti-cancer therapy (i.e. medication, not including the radiotherapy and procedure), 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 Table 2.

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 not evaluable]) will be summarized.

A patient who is in the safety analysis set but not in the response evaluable analysis set, or in response evaluable analysis set, but does not have any post-baseline tumor assessment (patients who died or progressed clinically prior to the first scheduled tumor assessment), the response category "NA" will be assigned for BOR of the patient.

Table 2 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 (8 weeks from start of treatment and allowing a 7 day visit window) on study. Otherwise, the best response will be PD.

[c] Best response will be SD if the first time point overall response if 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 patient is on study for a minimum of 49 days (counted from Cycle 1 Day 1). If the patient 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.

4.2.2. Secondary Endpoints

4.2.2.1. Progression-free Survival (PFS)

Progression-free survival (PFS) is defined as the time (months) from start of study treatment (fruquintinib or tislelizumab) until the first radiographic documentation of objective progression as assessed by the investigator using RECIST v1.1, or death from any cause.

More specifically, PFS will be determined using all the assessment data up until the last evaluable visit prior to or on the date of:

(i) disease progression as defined by RECIST Version 1.1 or death; or

(ii) withdrawal of consent or lost to follow-up; or

(iii) receipt of subsequent anti-cancer therapy (i.e. medication, not including the radiotherapy and procedure), whichever is earlier.

Patients without report of PD or death from any cause at the time of analysis are censored as described in Table 3 below.

The PFS time will always be derived based on scan dates not tumor assessment dates. RECIST assessments/scans contributing towards a particular visit may be performed on different dates. The following rules are applied:

- Date of progression is determined based on the earliest of the dates of the component that triggered the progression.
- When censoring a patient for PFS, the patient is censored at the latest of the dates contributing to a particular overall visit assessment.

Table 3 Censoring Rules for PFS

Rule	Situation	Date of Progression or Censoring	Outcome
1	PD documented from radiological assessment visits	Date of documented disease progression	Event
2	Death without PD or death before first documented PD or death after one missing radiological assessment visit	Date of death	Event
3	No baseline or post-baseline radiological assessments available	Date of start of study treatment	Censored
4	No death or PD by the time of data cut-off for final analysis	Date of last adequate radiological assessment	Censored
5	Early discontinuation (lost to follow-up or withdrawal of consent) of study without death or PD	Date of last adequate radiological assessment	Censored
6	New anti-tumor medication started prior to PD or death	Date of last adequate radiological assessment prior to or on date of initiation of new medication visit. In case of no post-baseline tumor assessments, it will be the date of first study treatment administration	Censored
7	Death or PD occurred after two or more consecutive missed radiological assessment visits	Date of last adequate radiological assessment prior to missed visits. In case of no post-baseline tumor assessments, it will be the date of first study treatment administration	Censored

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.

4.2.2.2. Disease Control Rate

Disease control rate (DCR) is defined as the proportion of patients with a BOR of CR, PR, or SD lasting for at least 7 weeks as determined by the investigator using RECIST v1.1. A patient who is in the safety analysis set but not in response evaluable analysis set, or in response

evaluable analysis set, but does not have any post-baseline tumor assessment (patients who died or progressed clinically prior to the first scheduled tumor assessment), the response category "No" will be assigned for DCR of the patient.

4.2.2.3. Clinical Benefit Rate

Clinical benefit rate (CBR) is defined as the proportion of patients with a BOR of CR, PR, or durable SD (i.e. lasting for at least 6 months) as determined by the investigator using RECIST v1.1. A patient who is in the safety analysis set but not in response evaluable analysis set, or in response evaluable analysis set, but does not have any post-baseline tumor assessment (patients who died or progressed clinically prior to the first scheduled tumor assessment), the response category "No" will be assigned for CBR of the patient.

4.2.2.4. Duration of Response

Duration of response (DoR) is defined as the time from the first occurrence of PR or CR by RECIST Version 1.1, until disease progression or death, whichever comes first.

Only those patients with confirmed objective responses of CR or PR will be included in this analysis.

Censoring will follow the rules outlined for PFS in Table 3 of Section 4.2.2.1.

For those patients with confirmed objective responses of CR or PR, DoR is calculated as (date of death or PD or last assessment – date of first occurrence of CR or PR + 1)/30.4375.

4.2.2.5. Overall Survival

Overall survival is defined as the time (months) from the start of study treatment (fruquintinib or tislelizumab) until the date of death due to any cause.

That is, OS will be calculated as (date of death or last known alive – date of start of study treatment + 1)/30.4375.

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. In the case of the imputed death date being after the end of study date and the death date and end of study date being the same month, the death date will be assigned to be the date of end of study.

Patients with no event during the study will be censored at the date last known to be alive. OS will not be censored if a patient receives subsequent anticancer treatments after discontinuation of the study drugs.

Moreover, the last known alive date will be derived for patients not known to have died at the analysis cut-off date using the latest date (including complete date and partial date with Month and Year information) among the following data:

- All assessment dates (e.g. laboratory, vital signs assessments, ECG, ECOG, performance status assessment, tumor assessment dates etc.).

- Medication dates including study medication, concomitant medications, anticancer therapies administered after study treatment discontinuation.
- Adverse events start and end date.
- Date latest known alive collected during the survival follow-up.

After sorting properly for all those available dates, if the last known alive date is a partial date with Month and Year information, day will be imputed as 15, unless this is after the cut off date in which case the cutoff date will be used as last alive date.

4.3. Exposure Endpoints

Drug exposure, including number of cycles received, total duration of exposure, cumulative dose received (mg), dose intensity, and relative dose intensity of fruquintinib and tislelizumab will be calculated as per algorithms included in **Table 4.**

The total duration of exposure (days) for fruquintinib will be calculated from the first dose date of fruquintinib in Cycle 1 to the last dose date of fruquintinib + 8 days or death date, whichever comes earlier if treatment is discontinued, or to the cut-off date if treatment is still ongoing. The total duration of exposure (days) for tislelizumab will be calculated from the first dose date of tislelizumab in Cycle 1 to the last dose date of tislelizumab + 28 days or death date, whichever comes earlier if treatment is discontinued, or to the cut-off date if treatment is still ongoing. The total duration of exposure (days) will be calculated from the first dose date of either study drug (fruquintinib or tislelizumab) in Cycle 1 to the earlier date between the last dose date of fruquintinib + 8 days and last dose date of tislelizumab + 28 days, or death date, whichever comes earlier if treatment is discontinued, or to the cut-off date if treatment is still ongoing.

Number of Cycles Received

Patients are considered to have started a cycle if they have received at least one dose of any study drug (fruquintinib or tislelizumab). In addition to the numeric summary for the number of cycles, the number of cycles will be categorized as 1, 2, 3, 4, 5, and ≥ 6.

Total Dose Administered (mg) in a Cycle for fruquintinib

In the study, fruquintinib (at a dose of 5 mg) is provided for oral administration, and in the event of dose adjustment, 1 mg fruquintinib capsules can be used.

Based on drug accountability data, the number of capsules taken for each dose level will be calculated as total dispensed – total returned in a cycle, then, the total dose administered (mg) in a cycle will be the summation as (number of 5mg capsules taken × 5 + number of 1mg capsules taken).

Table 4 Algorithms for Calculating Parameters Relevant to the Dose Exposure and Intensity

Parameter	Fruquintinib §	Tislelizumab
Dosing Schedule per Protocol	5 mg PO QD (3 weeks on/1 week off)	300 mg IV on Day 1 of a 4-weeks cycle
Number of Cycles Treatment Received	Patients will be considered to have started a cycle if they have received at least one dose of study drugs (fruquintinib or tislelizumab) in the respective cycle.	
Dose by cycle	Total dose administered (mg)	Total dose administered (mg)
Cumulative Dose (mg)	Sum of the doses administered to a patient in the duration of exposure (mg)	
Dose intensity (mg/day)	Cumulative dose (mg) / (duration of exposure) (day)	
Relative dose intensity (RDI) (%)	100 * [Dose intensity (mg/day) / (5 *21 /28 (mg)]	100 * [Dose intensity (mg/day) / (300 /28]
Relative dose (%)	100 * [Cumulative dose (mg) / (5×21× number of cycles for fruquintinib (mg)]	100 * [Cumulative dose (mg) / (300 × number of cycles for tislelizumab (mg)]
Number of Days with any recorded dose	Sum of days with recorded doses	NA
Percentage Intended Dose (PID) (%)	100 * [(number of days with any recorded doses)/duration of exposure], target PID is 75%.	NA

§ Two different doses (5 mg PO QD and 4 mg PO QD) of fruquintinib may be evaluated in Part 1. The 5 mg PO QD is expected to be the planned dose for patients in Part 2. The calculation of relevant parameters will be adjusted accordingly based on the example presented in this table.
PO = *Per os* (oral administration); QD = *Quaque die* (once daily).

In addition, the RDI (%) and RD (%) will be categorized to the groups: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%.

Study Drug Adjustment

The following endpoints to reflect study drug adjustment in the duration of exposure will be derived. Dose reduction is not allowed for tislelizumab.

- **Dosing modifications** (including both dosing interruption and dose reduction): number of patients with any dosing modification, and categorized frequency of dosing modification (0, 1, 2, 3, 4, > 4). This will be derived only for fruquintinib.
- **Dosing interruption**: number of patients with any dosing interruption and reasons for dosing interruption, and categorized frequency of dosing interruptions (0, 1, 2, > 2).

– **Dose reduction**: number of patients with any dose reduction and reasons for dose reduction, and categorized frequency of dose reduction (0, 1, 2, > 2). This will be derived only for fruquintinib.

4.4. Safety Endpoints

The safety analysis set is used to evaluate the safety variables including adverse events, clinical laboratory data, vital signs, single 12-lead ECG parameters, ECHO/MUGA parameters, physical examinations, ECOG performance status, and death. The safety data during the treatment period will be evaluated, and the treatment period is defined as the duration from the date of the first study drug administration until [30 days + 7 days protocol defined window] after the last study drug (fruquintinib or tislelizumab) administration or the date of death, whichever comes first.

4.4.1. Dose Limiting Toxicities (DLTs) or DLT-equivalent

AEs will be assessed per the DLT criteria, for patients from part 1, during the 28-day DLT assessment window in Cycle 1, which starts with the first day of administration of study drugs. Moreover, for patients from Part 1, after the 28-day DLT evaluation window of Cycle 1, an AE will also be evaluated for DLT-equivalent according to the DLT criteria. Hence, an AE will be determined whether it is a DLT/DLT-equivalent or not.

4.4.2. Adverse Events (AEs)

All AEs will be coded from verbatim text to preferred term (PTs) and grouped by system organ class (SOC) using the MedDRA (Medical Dictionary for Regulatory Activities) Version 25.0 or higher. AEs will be collected from the time of signature of informed consent throughout the treatment period. AEs will be graded by investigator according to CTCAE, Version 5.0, missing severity grade is imputed as Grade 3.

An AE is considered a TEAE based on the following definition:

1. During the treatment period from the date of the first study drug administration until 37 days after the last study drug (fruquintinib or tislelizumab) administration:
    1.1 if the onset date is on or after the start of study treatment (fruquintinib or tislelizumab); or
    1.2 if the AE has an onset date before the start of study treatment but worsened in severity;
2. After the treatment period regardless of whether or not the patient starts a new anticancer therapy, that is, at 37 days after the last dose of study drug (fruquintinib or tislelizumab) administration:
    2.1 treatment-related SAEs; or
    2.2 immune-mediated AEs (imAEs) recorded up to 90 days after the last dose of tislelizumab.

Other AE variables include drug-related AEs, AEs leading to study drug modifications (i.e. dose interruption, dose reduction, or study drug withdrawal), AEs leading to death, and SAEs.

An AE is considered treatment-related to fruquintinib or tislelizumab in the summaries if it is assessed as related to fruquintinib or tislelizumab by the investigator or if the assessment of relationship to study treatment is missing.

For AEs which are not ongoing, duration of AE (days) is defined as AE end date – AE start date +1; for ongoing AEs, the end date will be listed as 'Ongoing' and the duration of AE (days) will be approximated as '≥ date of last visit – AE start date +1'.

AEs of special interest (AESI) for fruquintinib

According to the IB Version 13.0 (dated 08 November 2021), AESI for fruquintinib are defined to include 10 categories:

- 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 5, for AESI categories (i.e. "haemorrhages", "hepatic function abnormal", "hypertension", "proteinuria", "thyroid dysfunction", "embolic and thrombotic events" "gastrointestinal perforation" and "left ventricular ejection fraction decreased"), the PTs to be included in these AESI categories are included in Appendix 3. These terms were selected by subjecting standardized MedDRA queries (SMQ) lists (narrow and/or broad scope depending on the category) for each category and had been used in the fruquintinib clinical development program for pharmacovigilance. The MedDRA terminology is subject to changes and modifications as medical knowledge develops. Thus, the terms within Table 5 and Appendix 3 could be updated/changed in the future.

Table 5 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)

AESIs Category	Search terms/strategy
Gastrointestinal perforation	MedDRA SMQ "gastrointestinal perforation" (narrow)
Left ventricular ejection fraction decreased	MedDRA SMQ "cardiac failure" (narrow)

Time to first AESI is defined as time interval from date of first administration of study drug (fruquintinib/tislelizumab) 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.

Immune-mediated AEs (imAE)

Immune mediated AEs will be identified based on the AE standardized MedDRA queries (SMQs). imAEs categories are immune-mediated AEs, serious skin adverse reactions and diabetes. The PTs to be included in these imAEs categories are included in Appendix 4.

COVID-19 Related AE

COVID-19 related AE will be identified based on the preferred term list (MedDRA version 25.0) included in Appendix 5.

4.4.3. Laboratory

Blood and urine samples for the determination of clinical chemistry, hematology, and urinalysis laboratory variables described in Table 6 will be measured.

Table 6 Laboratory Assessment

Lab Category	Lab tests
Hematology	Red blood cell count, hemoglobin, hematocrit, reticulocyte count, white blood cell count and classifications (neutrophils, lymphocytes, eosinophils, monocytes, and basophils), and platelet count
Chemistry	Albumin, blood urea nitrogen or urea, creatinine, CrCl rate, ALT, AST, alkaline phosphatase (ALP), bicarbonate, non-fasting total cholesterol, triglycerides, uric acid, lactate dehydrogenase, bilirubin/total bilirubin, Urea, sodium, potassium, magnesium, chloride, glucose, corrected calcium (for patients with hypoproteinemia), total protein, phosphorus, blood glucose, creatine phosphokinase, creatine kinase-MB (CK-MB), amylase and lipase If CK-MB fractionation is not available, troponin I and/or troponin T should be tested instead
Fasting Lipid Panel	Total cholesterol, High-density lipoprotein, Low-density lipoprotein, Triglycerides
Coagulation	Prothrombin time, INR, and aPTT

Lab Category	Lab tests
Thyroid function	Serum free tri-iodothyronine (FT3), serum free thyroxine (FT4), and thyroid stimulating hormone (TSH).
Urinalysis	Urine pH, protein, glucose, white blood cell, red blood cell

Change from baseline in laboratory test results to each assessment will be calculated.

The non-protocol specified tests (if any reported) 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.

Clinical laboratory results will be graded according to CTCAE criteria, CTCAE v5.0 criteria (see Appendix 2). Any graded abnormality that occurs following the initiation of study drug and represents at least a 1-grade increase from the baseline assessment is defined as treatment emergent. Any assessment for which CTCAE toxicity grades are not available will not be included in any analyses for which toxicity grades are required.

For the urinalysis parameters, if the test result is "-" or "negative", the investigation interpretation for the lab test will be considered to be "normal". The information of converting urinalysis parameters (i.e. WBC, RBC, and protein) results is provided in Appendix 6.

Analysis of Abnormal Hepatic Laboratory Values

The following categories of abnormal hepatic laboratory values will be evaluated for any occurrence among all post baseline assessments.

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3x upper limit of normal (ULN) and ≤ 5x ULN
- AST > 3,5,8,10, and 20x ULN, AST>5x ULN for more than 5 weeks
- ALT > 3,5,8,10, and 20x ULN, ALT > 5x ULN for more than 5 weeks
- AST and/or ALT > 3,5,8,10, and 20x ULN, >5x ULN for more than 5 weeks
- Total bilirubin elevations > 1.5x, 2x ULN
- ALP >1.5x, 2x ULN
- POTENTIAL DRUG-INDUCED LIVER INJURY (DILI): AST and/or ALT > 3x ULN and total bilirubin > 1.5x, > 2x ULN)
- AST and/or ALT >3x ULN and (total bilirubin > 2x ULN or INR > 1.5)

– Hy's Law criteria: AST and/or ALT > 3x ULN and total bilirubin ≥ 2x ULN and ALP < 2x ULN

Additionally, the last assessment on treatment, minimum, maximum values for each patient over the entire treatment period for each hematology and chemistry laboratory parameter will also be derived. The change from baseline will be calculated using these minimum and maximum values.

4.4.4. ECG

Electrocardiogram (ECG) parameters include heart rate, PR interval, RR interval, QT, QTcF and QRS intervals. Change from baseline to each post-baseline visit will be calculated and summarized by visit.

Potentially clinically significant ECG findings will be identified using the criteria which are included in Table 7.

Additionally, the last assessment on treatment, minimum and maximum values for each patient over the entire treatment period for each ECG parameter will also be derived. The change from baseline will be calculated using these minimum and maximum values.

Table 7 Potentially Clinically Significant Criteria for ECG

ECG Parameter (unit)	Criterion value
Heart Rate (bpm)	>120
	<50
PR Interval (ms)	≥ 210
RR Interval (ms)	> 1200
	< 500
QRS Interval (ms)	≥ 120
	≤ 50
QT Interval (ms)	≥ 500
	≤ 300
QTcF (msec)	> 450
	> 480
	> 500
	≤ 300
	Increase from baseline > 30
	Increase from baseline > 60
	> 450 and increase from baseline > 30
	> 450 and increase from baseline > 60
	> 480 and increase from baseline > 30

	> 480 and increase from baseline > 60
	> 500 and increase from baseline > 30
	> 500 and increase from baseline > 60

4.4.5. Vital Signs

Vital signs include systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory rate, heart rate, body temperature, weight, height, Body Mass Index (BMI) will be computed as weight (kg)/[height (m)]^2.

For vital signs, change from baseline to each post-baseline visit and timepoint will be calculated.

Potentially clinically significant findings of vital signs will also be defined based on criteria in Table 8.

Additionally, the last assessment on treatment, minimum and maximum values for each patient over the entire treatment period for each vital sign parameter will also be derived. The change from baseline will be calculated using these minimum and maximum values.

Table 8 Potentially Clinically Significant Criteria for Vital Signs

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

4.4.6. Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status is collected at screening, during the treatment period (i.e. Day 1 of each Cycle), at EOT and follow-up.

4.4.7. Echocardiogram

ECHOs will be done at Screening and every 12 weeks from C1D1 thereafter through the end of treatment visit. Assessment parameters include left ventricular ejection fraction (LVEF) and overall interpretation of cardiac function. Multiple-gated acquisition scans (MUGAs) are permitted if ECHOs cannot be performed.

4.4.8. Physical Examination

A comprehensive physical examination (PE) at Screening, it includes general appearance, eyes, ears, nose and throat, head and neck, respiratory, cardiovascular, abdomen (gastrointestinal), skin, genitourinary system, lymph nodes, musculoskeletal, neurological assessments.

Limited physical examination at scheduled visits is a subset the comprehensive physical examination as deemed appropriate by the investigator.

Abnormal clinically significant findings in PE were to be reported as AEs (post-baseline) or MHs (screening).
These data will only be available in listings.

4.5. Other Endpoints

4.5.1. Pharmacokinetic Endpoint

Blood samples will be collected for analysis of fruquintinib and metabolite M11 plasma concentrations and tislelizumab serum concentrations according to the PK schedule of events in Table 2 of the protocol.

4.5.2. Immunogenicity

Serum samples will be collected for antidrug antibody (ADA) analysis to tislelizumab according to the PK schedule of events in Table 2 of the protocol.

4.5.3. Exploratory Endpoints

Distribution of PD-L1 expression or MSS/MSI status will be examined in all patients. Other potential predictive markers including, but not limited to, TILs, TMB, cytokine expression, and gene signature profiling may be detected and analyzed.

5. ANALYSIS METHODS

5.1. General Principles

5.1.1. General Methodology

In general, all efficacy and safety will be summarized using descriptive statistics and graphs as appropriate. Continuous variables will be summarized by descriptive statistics (sample size (n), mean, standard deviation, minimum, 25% percentile (Q1), median, 75% percentile (Q3), and maximum). Categorical variables will be summarized in frequency tables (frequencies and percentages).

Time to event variable will be analyzed using Kaplan-Meier method and summarized with median, 25% and 75% percentiles with their corresponding 95% confidence intervals (CI) which are calculated from a log-log transformation based on the method by Brookmeyer 1982

. Individual data will be presented in patient listings which will be provided for all patients.

Analyses will be implemented using SAS® 9.4 or higher (SAS Institute, Cary, North Carolina, USA). The International Conference on Harmonization (ICH) numbering convention, i.e. ICH-E3, will be used for all tables and listings.

All summary tables, listings, and figures (TLFs) will be presented by cohorts as defined in Table 9. Unless otherwise specified, for Cohort A and Cohort B, the TLFs will be presented overall, by cohort, and by category of ER/PR positivity per ASCO-CAP guidelines (Allison 2020). TNBC will be defined as ER/PR positivity of <1%, and ER/PR low positive disease will be defined by ER/PR positivity of 1% to 10%. If a patient from Part 1 has the same type of cancer evaluated in Part 2, the patient from Part 1 will also be included in relevant group for analysis in Part 2.

Table 9 Treatment/Cohort Display in TLFs

Part of the study	Group	Group Description in Data Display	Subgroup
Part 1	1	Fruquintinib 5 mg + Tislelizumab	NA
	2†	Fruquintinib 4 mg + Tislelizumab	NA
Part 2 [a]	1	Cohort A BC (IO-Treated)	TNBC
			ER/PGR low positive
			Total
	2	Cohort B BC (IO-Naïve)	TNBC
			ER/PGR low positive
			Total
	3	Cohort C endometrial cancer	NA

Part of the study	Group	Group Description in Data Display	Subgroup
	4	Cohort D MSS mCRC (IO Naïve)	NA

† this cohort may not be explored in the conduct depending on observed toxicity from the dose cohort 5 mg PO QD
ER/PGR : receptor/progesterone receptor
[a] Patients with TNBC or EC enrolled in Part 1 must meet all inclusion and no exclusion criteria for the respective cohorts noted in Part 2 and will be included in relevant cohort for analysis.

For continuous data, unless otherwise specified, the mean, median, Q1, and Q3 will be presented with one more significant digit than the original values, and standard deviation will be reported with 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. The derived variables will be presented with one decimal place. Percentages will be reported with one 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 ≥ 99.5% will be presented as ">99%." Any rounding will be done after all calculations are made.

5.1.2. Handling Missing Data

In general, the observed case (OC) data for a visit will consist of the actual observations recorded for the visit. If missing, the OC data will remain missing — no missing imputation will be performed. Safety analyses will be conducted on the OC data only.

However, imputation of missing AE and concomitant medication onset and stop dates will be used to determine the status of each AE and the prior/concomitant status of each medication. The specific imputation rules are provided below, refer to Section 5.1.2.1 for the method of imputation of missing AE onset and stop date and Section 5.1.2.2 for the method of imputation of missing concomitant onset and stop dates. However, the imputed dates should not be shown in listings.

For demographic and baseline characteristics, each variable will be analyzed and/or summarized using the available data. Unless otherwise specified, patients with missing data will be excluded only from analyses for which data are not available.

5.1.2.1. Adverse Events Start/End Date

AEs with onset/end dates that are partially/completely missing will be imputed as follows.

(i) AE start date:

- If the AE onset date is completely missing, the AE start date will be imputed as the reference start date (i.e., date of first treatment).
- If the AE onset date is partial missing, then

- If both the year and the month are available and the year and the month are the corresponding year and month of the reference start date, then the AE start date will be imputed as the reference start date;
- If both the year and the month are available and the year and the month are not equal to the corresponding year and month of the reference start date, then the AE start date will be imputed as the 1st day of the month;
- If only the year is available and the available year is the corresponding year of the reference start date, then the AE start date will be imputed as the reference start date;
- If only the year is available, and the available year is not equal to the corresponding year of the reference start date, then the AE start date will be imputed as the January 1st of the year

(ii) AE end date will be imputed as below for the partial date only, the imputation rules only apply when the AE is not ongoing:

- If both the year and the month are available, AE end date will be imputed as the last day of the month;
- If only the year is available, AE end date will be imputed as the December 31st of the year.

If the imputed AE end date is after the death date for patients known to be dead at end of study or cut off date, the date of the death will be used for AE end date. If the imputed AE end date is after the last known alive date for patients alive at the end of study or cut off date, the date of last known alive date will be used for AE end date.

For AE continuing at the cut-off date, the end date will not be imputed and instead will be reported as "ongoing".

5.1.2.2. Concomitant Medication/Procedure/Surgery Start/End Date

Concomitant Medication/Procedure/Surgery with onset/end dates that are partially/completely missing will be imputed as follows.

(i) start date:

- 1st day of the month will be used to impute the start date if only the day is missing
- January 1st will be used to impute the start date if both the day and month are missing
- If the date is completely missing, then the day before the reference start date will be imputed as the start date.

(ii) end date:

- Last day of the month will be used to impute the end date if only the day is missing

- December 31st of the year will be used to impute the end date if both the day and month are missing
- If the date is completely missing, assign 'continuing' status to the end date

If the imputed end date is after the death date or last known alive date, the date of the death or last known alive date will be imputed as the concomitant medication/procedure/surgery end date.

5.1.2.3. Subsequent Anti-Cancer Therapy Date

When a partial new anti-tumor therapy start date is reported, every effort will be made to identify the precedence relationship of starting date of new anti-tumor therapy relative to the reference end date. Below rules will be used:

- If the date is completely missing, new anti-tumor therapy date will be imputed as reference end date + 1;
- If only the day is missing, 15th day will be imputed as the new anti-tumor therapy date;
- If both the day and the month are missing, then July 1st will be imputed as the new anti-tumor therapy;

If the imputed date is earlier than reference end date, then it will be replaced with reference end date + 1, if the imputed date is later than the date of death or last known alive date, it will be replaced with the date of death or last known alive date.

5.1.2.4. Primary Diagnosis Date and Metastatic Disease Diagnosis Date

When a partial date of primary diagnosis or a partial date of first metastatic disease diagnosis is reported, the below imputation rules will be used:

- If the date is completely missing, no imputation will be conducted;
- If only the day is missing, 15th day will be assigned;
- If both the day and the month are missing, then July 1st will be assigned.

Check that the imputed date is not superior or equal to the informed consent date.

5.1.3. Visit Windowing

It is expected that there will be a variation between patients in the actual number of study days from the start of administration of study drug within each cycle defined as Day 1, to the dates that the scheduled visits occur. To handle this, for tables and figures where data are grouped by visit, assessments will be categorized using visit windows based on study days (relative to the Day 1 of each cycle). The visit-window mapping is described in Table 10. Visit-based summaries will be based on the windowed visits. All data, whether or not within the visit windows, will be presented in patient's listings. Describe the visit windowing practice for the analysis of safety and efficacy variable, it is recommended to keep in mind the principle that there are no gaps between two adjacent visit windows.

For windowed visits during the treatment cycles, if more than one visit occurs during a visit window, the visit closest to the scheduled day will be assigned to the windowed visit. If two visits are equidistant from the scheduled day, the later visit will be assigned to the windowed visit. If there are multiple assessments on the same day, the worst case will be used.

For a patient who prematurely discontinues the study, the premature visit will be slotted accordingly. The window for end of treatment visit will be "last dose date of last cycle + 4 days to last dose date of last cycle + 10 days" and the window for safety follow-up visit will be “Last dose date of last cycle + 11 to last dose date of last cycle + [30 days + 7 days protocol-defined window]”.

Table 10 Visit Windowing

	Cycle 1				Cycle 2		Cycle 3 and onwards	Last Cycle	End of treatment	Safety follow-up
Visit	**C1D1**	**C1D8**	**C1D15**	**C1D21 [b]**	**C2D1**	**C2D15 [b]**	**C3D1 [b]**	**CXD1**		
Scheduled Day [a]	1	8	15	21	1	15	1	1		
ECOG	Day 1				Day -3 to EOC-3		Day -3 to EOC-3	Day -3 to EOC-4	Last dose date of last cycle +4 days to last dose date of last cycle + 10	Last dose date of last cycle + 11 to last dose date of last cycle + [30 days + 7 days protocol defined window]
Vital Sign	Day 1	2 to 11	12 to 18	19 to EOC-3	Day -3 to 8	9 to EOC-3	Day -3 to EOC-3	Day -3 to EOC-4		Last dose date of last cycle + 11 to last dose date of last cycle + [30 days + 7 days protocol defined window]
Hematology		2 to 11	12 to 18	19 to EOC-3	Day -3 to 8	9 to EOC-3	Day -3 to EOC-3	Day -3 to EOC-4		
Clinical Chemistry		2 to 11	12 to 18	19 to EOC-3	Day -3 to 8	9 to EOC-3	Day -3 to EOC-3	Day -3 to EOC-4		
Blood amylase and lipase		2 to 11	12 to EOC-3		Day -3 to 8	9 to EOC-3	Day -3 to EOC-3	Day -3 to EOC-4		
Fasting lipid panel					Day -3 to 3		Day -3 to EOC-3	Day -3 to EOC-4		
Coagulation		2 to 11	12 to 18	19 to EOC-3	Day -3 to 8	9 to EOC-3	Day -3 to EOC-3	Day -3 to EOC - 4		
Thyroid function			2 to EOC-3		Day -3 to 8	9 to EOC-3	Day -3 to EOC-3	Day -3 to EOC-4		
Urinalysis				2 to EOC-3	Day -3 to 3		Day -3 to EOC-3	Day -3 to EOC-4		

	Cycle 1				Cycle 2		Cycle 3 and onwards	Last Cycle	End of treatment	Safety follow-up
Visit	**C1D1**	**C1D8**	**C1D15**	**C1D21 [b]**	**C2D1**	**C2D15 [b]**	**C3D1 [b]**	**CXD1**		
ECHO/MUGA [c]							Day -3 to EOC-3	Day -3 to EOC-4		
ECG			2 to EOC-3		Day -3 to 3		Day -3 to EOC-3	Day -3 to EOC-4		Last dose date of last cycle + 4 to last dose date of last cycle + [30 days + 7 days protocol defined window]

[a] The scheduled day is relative to Day 1 of each cycle.
[b] If the cycle becomes the last cycle, the upper bound of the window will use EOC – 4.
[c] Every 12 weeks from C1D1 (±1 week) until progression of disease.
Note: The end date of a cycle (EOC) is defined as one day earlier than the date of Day 1 study drug administration of its next cycle. For the last cycle (where no subsequent cycle is given), the end of cycle will be defined as Day 7 relative to the last dose of the cycle.
EOC = end of cycle.

5.1.4. Adjustment of Covariates

Not applicable

5.2. Analysis Methods

5.2.1. Patient Disposition

Summary of study disposition will be provided by cohort as defined in Table 9 for the following:

- Number of patients who signed the informed consent
- Number of screen failures
- Reason for screen failure
- Number of patients who did not receive study treatment
- Number of patients who received study treatment
- Patients still on study treatment, if applicable
- Reason for study treatment discontinuation
- Number of patients going into survival follow-up
- Number and percentage of patients who discontinue the study
- Reason for discontinuation of the study

A separate table will be presented to show the patients included in each analysis set and summary reasons for exclusion from an analysis set.
Patient disposition and analysis sets will be also listed.

5.2.2. Protocol Deviation

Protocol deviations (including COVID-19 related protocol deviations) will be summarized descriptively for patients with at least one major protocol deviation by cohort. A patient can have multiple major and/or minor deviations and will be counted once per major and/or minor deviation. The protocol deviation summary is based on the safety analysis set.

In addition, all protocol deviations including deviations that are related to COVID-19 will be provided in a by-patient listing.

5.2.3. Demographic and Other Baseline Characteristics

The following demographic and other baseline characteristics will be summarized by cohort as defined in Table 9 on the safety analysis set:

- Age (years) at screening, age groups (18-65, ≥ 65 years),
- Gender, childbearing potential (female only)
- Race
- Ethnicity
- Baseline height (cm)

- Baseline weight (kg)
- Baseline BMI (kg/m^2) calculated as baseline weight (kg)/ [baseline height (m)]^2, BMI category (<18.5, ≥18.5 and <24, ≥24 kg/m^2)
- Baseline ECOG status.

5.2.4. Disease Characteristics

Oncology history will be summarized descriptively by cohort as defined in Table 9 for the safety analysis set for the following:

- Type of cancer at first diagnosis
- Cancer Stage at First Diagnosis (Stage 1, Stage 2, Stage 3, Stage 4)
- Primary Tumor Location at First Diagnosis
- EC Histological Classification
- TNBC Histological Classification (Invasive Ductal Carcinoma, Other)
- Non-TNBC/Non-EC Histological Classification
- Time since first diagnosis cancer (months): it is calculated as (date of first study treatment administration – date of first diagnosis of disease + 1)/30.4375.
- Time since diagnosis of metastatic disease (months): it is calculated as (date of first study treatment administration – date of diagnosis of metastasis disease + 1)/30.4375.
- Prior oncology treatments (prior anti-cancer medication, prior anti-cancer radiotherapy, prior anti-cancer procedures)

5.2.5. Medical History

The conditions/diseases from medical history are those conditions/diseases that stopped prior to the study entry. Medical history will be coded to SOC and PT using MedDRA version 25.0 or higher.

The number and percentage of patients with any past medical/surgical history within each SOC and PT will be provided by cohort on the safety analysis set.

A patient will only be counted once within a particular SOC (PT) even if he/she has multiple conditions/diseases in the same SOC (PT).

Each summary will be ordered by descending order of incidence of SOC according to total column and PT within each SOC. If the frequencies tie, an alphabetic order will be applied.

5.2.6. Prior and Subsequent Anti-Cancer Therapy

Prior and subsequent anti-cancer therapy, including medication, radiotherapy, and procedure or surgery, will be summarized descriptively by cohort and overall for the safety analysis set.

5.2.6.1. Prior and Subsequent Anti-Cancer Medication

Prior anti-cancer medications are defined as those taken by the patient prior to the administration of study drug. Subsequent anti-cancer medications are defined as those taken by the patient after the discontinuation of the study drug.

Prior and subsequent anti-cancer medications will be coded to Anatomical Therapeutic Classification (ATC) therapeutic group (i.e., ATC Level 2) and PT using the World Health Organization Drug Dictionary (WHO-DD) version Mar 2022 or later.

The prior anti-cancer medications will be summarized by presenting the number and percentage of patients by PT and ATC. Patients taking the same medication multiple times will only be counted once for that PT or ATC. Each summary will be ordered by descending order of incidence of ATC according to total column and PT within each ATC. If the frequencies tie, an alphabetic order will be applied.

Similarly, the subsequent anti-cancer medications will be summarized.

All prior and subsequent anti-cancer medications will be presented in patient listing.

5.2.6.2. Prior and Subsequent Anti-Cancer Radiotherapy

Prior anti-cancer radiotherapy is defined as those taken by the patient prior to the administration of study drug.

Subsequent anti-cancer radiotherapy is defined as those taken by the patient after the discontinuation of the study drug.

The number and percentage of patients with at least one prior anti-cancer radiotherapy will be summarized.

All prior and subsequent anti-cancer radiotherapy will be presented in patient listing.

5.2.6.3. Prior and Subsequent Anti-Cancer Procedure or Surgery

Prior anti-cancer procedure or surgery are defined as those taken by the patient prior to the administration of study drug.

Subsequent anti-cancer procedures or surgery are defined as those taken by the patient after the discontinuation of the study drug.

Prior and subsequent anti-cancer procedures or surgery will be coded to SOC and PT using MedDRA version 25.0 or higher.

The prior anti-cancer procedure or surgery will be summarized by presenting the number and percentage of patients by PT and SOC. Patients taking the same medication multiple times will only be counted once for that PT or SOC.

Each summary will be ordered by descending order of incidence of SOC to total column and PT within each SOC. If the frequencies tie, an alphabetic order will be applied.

Similarly, the subsequent anti-cancer procedure or surgery will be summarized.

All prior and subsequent anti-cancer procedures or surgery will be presented in a patient listing.

5.2.7. Prior and Concomitant Medications

Prior and concomitant medications (CMs) will be coded to Anatomical Therapeutic Classification (ATC) therapeutic group (i.e. ATC Level 2) and PT using the WHO-DD version Mar 2022 or higher.

Medications taken and stopped prior to the first dose of study treatment are denoted "Prior". Medications taken prior to the first dose of study treatment and continuing beyond the first dose of study treatment or those medications started on or after the first dose of study treatment but no later than 37 days after the last dose are denoted "Concomitant".

Medication with start date/time being partially or completely missing will be assumed to be concomitant if it cannot be definitely shown that the medication was not received during the treatment period.

The prior medications will be summarized by presenting the number and percentage of patients by PT and ATC. Patients taking the same medication multiple times will only be counted once for that PT or ATC. Each summary will be ordered by descending order of incidence of ATC according to total column and PT within each ATC. If the frequencies tie, an alphabetic order will be applied.

Similarly, the concomitant medications will be summarized.

All prior and concomitant medications will be presented in patient listing.

5.2.8. Concomitant Procedure

Medical or surgical procedures that started after the first dose date but no later than 37 days after the last dose date are denoted "Concomitant".
Concomitant medical or surgical procedures will be classified using the MedDRA version 25.0 or higher.

The concomitant medical or surgical procedures will be summarized by presenting the number and percentage of patients by PT and SOC. Patients having the same medical or surgical procedure multiple times will only be counted once for that PT or SOC. Each summary will be ordered by descending order of incidence of SOC according to total column and PT within each SOC. If the frequencies tie, an alphabetic order will be applied.

All concomitant medical or surgical procedures will be presented in the patient listing.

5.2.9. Efficacy Analyses

The safety analysis set will be used for all efficacy analysis unless otherwise specified. No formal hypothesis testing is planned for this study. Two-sided 95% confidence intervals (CIs) will be calculated in the applicable summary, unless otherwise specified.

5.2.9.1. Primary Efficacy Analyses

The number and percentage of patients in each category of derived BOR (CR, PR, Unconfirmed CR, Unconfirmed PR, SD, PD, NE, or NA) will be summarized for the safety analysis set. ORR and $ORR_{UNCONFIRMED}$ will be summarized by cohort as defined in Table 9 .

The 95% CIs of ORR and $ORR_{UNCONFIRMED}$ will be calculated using the Clopper-Pearson method for each cohort.

Tumor evaluation data will be presented in listings.

5.2.9.2. Secondary Efficacy Analyses

For the time to event endpoints, such as PFS, OS, and DoR, the median, 25% and 75% percentile of time-to-event will be estimated using Kaplan-Meier method with their corresponding 95% CI. For PFS and OS, additionally, estimates will be provided for the survival probability along with their 95% CIs which are calculated using linear transformation (Brookmeyer 1982

at selected landmarks, for example, at 3, 6, 9, 12, and 18 months. The Kaplan-Meier plots will be produced for PFS and OS. The duration of follow-up will be calculated descriptively using the Kaplan-Meier method.

In order to assess duration of follow-up for PFS and OS, Kaplan Meier estimates will be calculated in the same way as in their analysis, while using different censoring rule which reverses censoring indicator instead, i.e., patients who have event will be censored at the date of event. Patients who are censored will be assigned as "event".

The DCR and CBR will be analyzed in a similar way as ORR described in Section 5.2.9.1.

5.2.9.3. Sensitivity Analysis for Efficacy Endpoint

A sensitivity analysis for ORR, DCR, CBR and DoR will be conducted using the response evaluable analysis set. The analysis techniques follow those described in Section 5.2.9.1.

5.2.10. Exposure of Study Treatment

Exposure of study treatment described in Section 4.3 (duration of exposure, number of cycles of treatment received, cumulative dose, dose intensity and relative dose intensity for each study drug,) will be summarized by cohort as defined in Table 9.

Number of cycles received will be categorized as (1, 2, 3, 4, 5, 6, >6, and the number and percentage of patients for each category will be summarized.

The following summary for dose modification will be summarized separately for each drug (fruquintinib and tislelizumab) by cohort. Dose reduction/increase is not allowed with tislelizumab.

- Number of patients with any dose modification with fruquintinib (including both drug interruption and dose reduction, and frequency of dose modification: 0, 1, 2, 3, 4, 5, 6, >6

- Number of patients with any drug interrupted with fruquintinib or tislelizumab (number of patients experienced drug interruption and reasons for drug interruption, and frequency of drug interruptions: 0, 1, ≥ 2)
- Number of patients with any dose reduced with fruquintinib (Number of patients with any dose reduction and reasons for dose reduction; and frequency of dose reduction: 0, 1, ≥ 2).

5.2.11. Safety Analyses

Safety data during the treatment period will be summarized. The treatment period is defined as the duration from the date of the first study drug administration (fruquintinib and tislelizumab) until 37 days after the last study drug administration.

5.2.11.1. Dose-Limiting Toxicity (DLT)

All DLT analysis will be only performed for Part 1 based on the DLT evaluable analysis set.

In addition to summarizing the number of patients and percentage of DLTs, DLTs will be summarized by SOC, PT, and highest CTCAE grade.

DLTs will be listed.

5.2.11.2. Adverse Events

An overall summary of the number and percentage of patients along with the number of adverse events for cohort will be provided for the following categories of AEs:

Group	Summary scope
All TEAEs	– CTCAE Grade ≥3 AEs – Fruquintinib-related AEs – Tislelizumab-related AEs – AEs Leading to Dose Reduction of Fruquintinib – AEs Leading to Dose Interruption of Fruquintinib – AEs Leading to Dose Interruption of Tislelizumab – AEs Leading to Treatment Discontinuation of Fruquintinib – AEs Leading to Treatment Discontinuation of Tislelizumab – Treatment-related AEs Leading to Dose Reduction of Fruquintinib – Treatment-related AEs Leading to Dose Interruption of Fruquintinib – Treatment-related AEs Leading to Dose Interruption of Tislelizumab – Treatment-related AEs Leading to Treatment Discontinuation of Fruquintinib – Treatment-related AEs Leading to Treatment Discontinuation of Tislelizumab – AEs Leading to Death
Serious TEAEs	– CTCAE Grade ≥3 SAEs – Fruquintinib-related SAEs – Tislelizumab -related SAEs

Group	Summary scope
	– SAEs Leading to Dose Reduction of Fruquintinib – SAEs Leading to Dose Interruption of Fruquintinib – SAEs Leading to Dose Interruption of Tislelizumab – SAEs Leading to Treatment Discontinuation of Fruquintinib – SAEs Leading to Treatment Discontinuation of Tislelizumab – Fruquintinib -related SAEs Leading to Dose Reduction of Fruquintinib – Fruquintinib -related SAEs Leading to Dose Interruption of Fruquintinib – Tislelizumab-related SAEs Leading to Dose Interruption of Tislelizumab – Fruquintinib-related SAEs Leading to Treatment Discontinuation of Fruquintinib – Tislelizumab-related SAEs Leading to Treatment Discontinuation of Tislelizumab – SAEs Leading to Death
Treatment-emergent AESIs for Fruquintinib	– CTCAE Grade ≥3 AESIs – Fruquintinib-related AESIs – AESIs for Fruquintinib Leading to Dose Reduction of Fruquintinib – AESIs for Fruquintinib Leading to Dose Interruption of Fruquintinib – AESIs for Fruquintinib Leading to Dose Interruption of Tislelizumab – AESIs for Fruquintinib Leading to Treatment Discontinuation of Fruquintinib – AESIs for Fruquintinib Leading to Treatment Discontinuation of Tislelizumab – Fruquintinib -related AESIs for Fruquintinib Leading to Dose Reduction of Fruquintinib – Fruquintinib -related AESIs for Fruquintinib Leading to Dose Interruption of Fruquintinib – Fruquintinib-related AESIs for Fruquintinib Leading to Treatment Discontinuation of Fruquintinib – AESIs for Fruquintinib Leading to Death
Treatment-related imAEs to Tislelizumab	– CTCAE Grade ≥3 imAEs – imAEs for Tislelizumab Leading to Dose Reduction of Fruquintinib – imAEs for Tislelizumab Leading to Dose Interruption of Fruquintinib – imAEs for Tislelizumab Leading to Dose Interruption of Tislelizumab – imAEs for Tislelizumab Leading to Treatment Discontinuation of Fruquintinib – imAEs for Tislelizumab Leading to Treatment Discontinuation of Tislelizumab – Tislelizumab-related imAEs for Tislelizumab Leading to Dose Interruption of Tislelizumab

Group	Summary scope
	– Tislelizumab-related imAEs for Tislelizumab Leading to Treatment Discontinuation of Tislelizumab – imAEs for Tislelizumab Leading to Death
COVID-19-related TEAEs	– CTCAE Grade ≥ 3

The number and percent of patients experiencing a TEAE within each of the categories and sub-categories listed in Table above will be also summarized by SOC, PT, and highest CTCAE grade for each cohort. If a patient reports a TEAE more than once within that SOC/PT, the AE with the highest severity will be used in the corresponding severity summaries.

The summary will be sorted in descending order of frequency of SOC according to the sum of the column. Within the SOC, sorted by descending frequency of PT according to the sum of the column.

Time (days) to onset of the first treatment-emergent AESI will be descriptively summarized for each cohort.

All AEs, including AEs that started prior to the study drug, will be presented in patient listings. In addition, separate listings of all SAEs, AESIs, imAEs, AEs leading to death, drug-related AEs, AEs leading to dose reduction, AEs leading to dose interruption, and AEs leading to study drug discontinuation will be provided.

5.2.11.3. Death

Number of deaths, primary cause of death and whether autopsy was performed are summarized descriptively for each cohort. Similarly, deaths which occur during the treatment period will also be tabulated.

Data for deaths will be provided as a patient list in which the on-treatment deaths will be flagged.

5.2.11.4. Laboratory Evaluations

For hematology and clinical chemistry labs, the observed values and change from baseline will be summarized by visit using descriptive statistics.

Toxicities for clinical labs will be characterized according to CTCAE, v5.0 (Appendix 2), and the frequency and percentage of patients with each CTCAE grade for each visit during the treatment period will be described. Moreover, any occurrence of Grade 3 or Grade 4 during the overall treatment period will be summarized, and shift in grade from baseline to the worst post-baseline value will be summarized. Both the scheduled and unscheduled assessments will be used to identify the worst post-baseline values.

A summary table will be also provided for abnormal hepatic laboratory values by cohort. Abnormal hepatic laboratory values are based on the pre-specified thresholds (section 4.4.3).

Listings of all laboratory data with normal reference ranges, and CTCAE grades (when possible) will be provided.

5.2.11.5. ECG

Descriptive statistics will be presented for each ECG parameter for the observed values and change from baseline to post baseline by visit.

A listing of all ECG data will be provided.

The criteria for potentially clinically significant findings are defined in Table 7. The frequency and percentage of patients with any potentially clinically significant findings during the treatment period will be presented. The supportive data will be provided in patient data listings.

5.2.11.6. Vital Signs

For vital sign parameters (SBP, DBP, heart rate, temperature, and weight) the observed values and change from baseline will be summarized using descriptive statistics at each visit during the treatment period.

Additionally, the frequency and percentage of patients with any potentially clinically significant findings (defined in Table 8) during the overall treatment period will be presented. A listing of all vital sign data will be provided.

Moreover, the minimum, maximum, and their corresponding change from baseline vital sign values will be summarized descriptively overall treatment period.

5.2.11.7. Performance Status

The frequency and percentage of patients for each ECOG score level will be summarized by visit. Shift in grade from baseline to the maximum post-baseline score will be summarized.

A listing of ECOG scores for all patients will be provided.

5.2.11.8. Echocardiogram

Descriptive statistics for ECHO/MUGA will be summarized by visit. A by-patient listing of ECHO/MUGA values at each time point will be presented.

5.2.11.9. Physical Examination

A listing of physical examination data for all patients will be provided.

5.3. Subgroup Analyses

Not applicable.

5.4. Other Analyses

5.4.1. Pharmacokinetic Analysis

The PK analysis is used for listing and summaries of data specified in this section.

5.4.1.1. Handling of Missing Data

Missing concentration data for all patients who are administered scheduled study treatments is considered as non-informative missing and will not be imputed. No concentration estimates will be provided for missing sample values.

5.4.1.2. Handling of Dose Reduction or Interruption.

Any concentration data taken at or after the time of a dose reduced or interrupted of fruquintinib, or a dose interrupted of tislelizumab will be listed with a flag but excluded from summary statistics.

5.4.1.3. Handling of below the lower limit of quantification (BLQ) Data

PK concentration summary, the following rules apply:

- PK concentrations below the lower limit of quantification (BLQ) will be set to zero.

The following rules will apply for listing and presenting individual PK data:

- All concentrations are presented in original units and to the same decimal place as reported by Bioanalytical lab, e.g., ng/mL;
- Listing of PK sampling times including nominal and actual time elapsed from reference dose with the deviation from the nominal time and measured concentrations of the drug.
- If actual time is missing, time will be reported as NR (not recorded) and actual time will be reported as NC (not calculated). For fruquintinib, reference dose will be the fruquintinib dose on the **day** of fruquintinib PK sample collection. For tislelizumab, reference dose will be the tislelizumab dose during the same **cycle** of tislelizumab PK sample collection or last tislelizumab dose for EOT samples.

5.4.1.4. Summary of PK concentration Data

Concentration data of fruquintinib, metabolite M11, and tislelizumab will be listed and summarized. Descriptive statistics will include number of patients [n], arithmetic mean, standard deviation, coefficient of variation [CV%], median, minimum, and maximum as appropriate.

The conventions presented in Table below are used for the presentation of the descriptive statistics of PK concentrations.

Variable	Summarized with:
Minimum, Maximum	3 significant digits or as needed based on actual measured values
Mean (arithmetic), Median	3 significant digits
StdDev	3 significant digits
CV%	1 decimal point

5.4.1.5. Handling of the Difference between the Scheduled (nominal time) and the Actual Sampling Times (actual time)

For all sampling times, the actual sampling times relative to dosing will be calculated as the difference between the actual clock time of sampling and the actual clock time of dosing on the day of PK visit. For the visit when no dose administration is scheduled (e.g., no tislelizumab administration on C1D8 and C1D15), the actual sampling times will be calculated as the difference between the actual clock time of sampling and the actual clock time of the most recent dose administered prior to the visit (e.g., C1D1). If the actual time of sampling is missing, it will be reported as NR (not recorded) in the listing, the nominal time will be used for summary statistics.

5.4.2. Immunogenicity Analysis

The Antidrug Antibody (ADA) analysis set are patients that have one baseline ADA measurement and at least one post-baseline ADA measurement.

The incidences of positive ADAs and neutralizing ADAs to tislelizumab will be reported for evaluable patients. When available, titer will be reported. The immunogenicity results will be summarized using descriptive statistics by the number and percentage of patients who develop detectable ADAs to tislelizumab according to the following attributes and endpoints.

ADA attributes:

- **Treatment-boosted ADA** is defined as ADA positive at baseline that was boosted to a 4-fold or higher-level following drug administration.
  In order to calculate fold change, titer values reported as '<10' will be assigned a numerical value of 1.
- **Treatment-induced ADA** is defined as ADA negative at baseline and ADA positive post-baseline.
- **Transient ADA response** is defined as treatment-induced ADA detected only at 1 time point during treatment or follow-up, excluding last time point; or detected at 2 or more time points during treatment or follow-up, where the first and last positive samples are separated by less than 16 weeks and the last time point is negative.
- **Persistent ADA response** is defined as treatment-induced ADA detected at 2 or more time points during treatment or follow-up, where the first and last ADA positive samples are separated by 16 weeks or longer; or detected only in the last time point.
- **Neutralizing ADA** is defined as ADA that inhibits or reduces pharmacological activity.

ADA response endpoints:

- ADA incidence (also known as treatment-emergent ADA) is defined as sum of treatment-induced and treatment-boosted ADA-positive patients as a proportion of the ADA evaluable population.
- ADA prevalence is defined as proportion of all patients that are ADA positive, including pre-existing ADA, at any time point.

The following rules will apply for listing and presenting individual ADA data:

- All ADA results are presented as reported by the Bioanalytical lab, e.g., negative or positive and titer value (if applicable);
- Listing of ADA sampling times including nominal and actual time elapsed from tislelizumab dose with the deviation from the nominal time and ADA results by screening, confirmatory or titer (as applicable). If actual time is missing, time will be reported as NR (not recorded) and actual time will be reported as NC (not calculated). For ADA, reference dose will be the tislelizumab dose during the same cycle of ADA sample collection or last tislelizumab dose for EOT samples.

5.4.3. Exploratory Analyses

Distribution of PD-L1 expression or MSS/MSI status will be examined in all patients. Other potential predictive markers including, but not limited to, TILs, TMB, cytokine expression, and gene signature profiling may be detected and analyzed.

Exploratory biomarker analyses will be performed in an effort to understand the association of these markers with study drug response, such as efficacy and resistance.

The biomarker data and analysis may be reported separately from the CSR.

6. PLANNED ANALYSIS

6.1. Independent Safety Data Monitoring

Safety monitoring and evaluation of the safety lead-in (Part 1) will be carried out by the Safety Review Committee (SRC). Safety will be evaluated to determine or confirm the RP2D for the combination of fruquintinib and tislelizumab.

After the RP2D has been determined in Part 1, the SRC will continue to periodically review the cumulative safety data during the conduct of Part 2.

6.2. Interim Analysis

An interim analysis from Database Lock (DBL) was conducted to support the safety data review and regulatory interaction in the fruquintinib new drug application (NDA), the data snapshot was taken on CCI [redacted] with data cutoff date on CCI [redacted]. By the time of the scheduled interim analysis, no patients were enrolled in the Part 2, therefore, the analysis was carried out only on patients from Part 1. Key study safety data collected up through the time of defined data cutoff were summarized.

6.3. Final Analysis

The final analysis will be conducted after DBL for this study. All study data collected up through the time of the final analysis will be summarized, unless otherwise specified.

7. CHANGE FROM THE PROTOCOL

A few noted changes from the protocol are summarized as follow:

- The pharmacokinetics analysis set definition has been updated compared to the protocol as some patients may have no fruquintinib samples as the appropriate blood collection tubes were not available. However, they will still have tislelizumab samples.
- Though in the protocol, it is stated that summary will only be conducted for these cohorts if there are more than 3 patients enrolled and dosed, in the actual table production, the summary information will still be presented for a cohort regardless of the number of patients enrolled for the cohort.
- The DLT- evaluable analysis set definition in the protocol is to include all patients enrolled into the safety lead-in portion of the study **who** meet at least one criteria of (i) and (ii), and both criteria (iii) and (iv) as defined as (i) received ≥85% of scheduled fruquintinib and ≥67% of scheduled tislelizumab administration during the DLT assessment window; (ii) experienced a DLT; (iii) did not receive prophylactic supportive care that confounds the evaluation of DLTs. That is, for a patient, if there is a record in concomitant medication with category being 'PRIOR AND CONCOMITANT MEDICATIONS', indication being 'PROPHYLAXIS', and the medication is taken within 28 days (⩽ 28) since the date of first study drug administration, then the patient will be considered to have received preventive treatment during the DLT period; (iv) did not take a strong inducer of enzyme CYP3A. However, these criteria have been incorporated in the SRC review and it is aligned with those patients who took at one dose of study drug fruquintinib or tislelizumab. Therefore, the DLT-evaluable analysis set will be based on the decision from the SRC review and is defined to include all patients who took at one dose of study drug fruquintinib or tislelizumab.

REFERENCE

Allison 2020

Allison KH, Hammond EH, Dowsett M, et al. Estrogen and progesterone receptor testing in breast cancer: ASCO/CAP guideline update. J Clin Oncol. 2020;38:1346-66.

Brookmeyer 1982

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

Eisenhauer 2009

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.

Rakha 2014

Rakha EA, Starczynski J, Lee AHS, Ellis IO. The updated ASCO/CAP guideline recommendations for HER2 testing in the management of invasive breast cancer: a critical review of their implications for routine practice. Histopathology. 2014;64:609–615.

APPENDIX

Appendix 1: Study Schedule of Events

Cycle/Period			C1				C2		C3+	EOT	Safety Follow-up	Survival Follow-up
Visit	**Screening**		**D1**	**D8**	**D15**	**D21**	**D1**	**D15**	**D1**	**≤7 Days After Last Dose**	**30 Days After EOT Visit**	**Every 8 Weeks After EOT Visit**
Visit Window (days)	**-28 to -1**	**-7 to -1**		**±1**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**	**±7**	**±14**
Informed consent[a]	X											
PD-L1 expression confirmation[b]	X											
MSS/MSI status confirmation[c]	X											
Medical history, disease history[d]	X											
Demographics[e]	X											
Prior and concomitant medications and concomitant procedures[f]	X		X	X	X	X	X	X	X	X	X	
Comprehensive physical examination[g]	X		X									
Limited physical examination[h]				X	X	X	X		X	X	X	
Vital signs[i]	X		X	X	X	X	X	X	X	X	X	
ECOG performance status[i]		X	X				X		X	X	X	
Laboratory evaluations:		X										
Hematology[j]		X		X	X	X	X	X	X	X		
Blood chemistry[k]		X		X	X	X	X	X	X	X		

Cycle/Period			C1				C2		C3+	EOT	Safety Follow-up	Survival Follow-up
Visit	**Screening**		**D1**	**D8**	**D15**	**D21**	**D1**	**D15**	**D1**	**≤7 Days After Last Dose**	**30 Days After EOT Visit**	**Every 8 Weeks After EOT Visit**
Visit Window (days)	**-28 to -1**	**-7 to -1**		**±1**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**	**±7**	**±14**
Blood amylase and lipase		X		X	X		X	X	X	X		
Fasting lipid panel[l]		X					X		X	X		
Coagulation indicators[m]		X		X	X	X	X	X	X	X		
Serum pregnancy test[n]		X									X	
Urine pregnancy test[n]			X				X		X	X		
Thyroid function test[o]	X				X		X	X	X			
Urinalysis[p]		X				X	X		X			
Virological screening[q]	X								X	X		
PK assessments				Refer to protocol Table 2								
Tislelizumab immunogenicity				Refer to protocol Table 2								
12-Lead ECG[r]	X				X		X		X		X	
ECHO/MUGA scan	X		Every 12 weeks from C1D1 (±1 week) until progression of disease									
Tumor evaluation/imaging[s]	Screening and every 8 weeks (±1 week) from C1D1 until disease progression									X		
Fruquintinib drug administration			PO QD, Days 1 to 21 of each cycle									
Tislelizumab drug administration[t]			X				X		X			
AEs/SAEs[u]	X		X	X	X	X	X	X	X	X	X	
Overall survival[v]												X

AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; C=cycle; CK=creatine kinase; CKMB=creatine kinase-MB; CrCl=creatinine clearance; D=day; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=eastern cooperative oncology group; eCRF=electronic case report form; EOT=end of treatment; HBV=hepatitis B virus; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; ICF=informed consent form; INR=international normalized ratio; IV=intravenous; MSI=microsatellite instability; MSS=microsatellite stability stable; MUGA=multigated acquisition; PCR=polymerase chain reaction; PD=progressive disease; PD-L1=programmed death-ligand 1; PK=pharmacokinetics; PO=orally; QD=once daily; Q3W=every 3 weeks; Q4W=every 4 weeks; QTcF=QT interval corrected by the method of Fredericia; RNA=ribonucleic acid; RP2D=recommended phase 2 dose; SAE=serious adverse event; SOP=standard operating procedure.

[a] Written informed consent must be obtained before any study-related examinations or procedures are performed. However, before informed consent is obtained, if the examinations for standard treatment are performed within 28 days before the planned C1D1, they can be used to replace the examinations during the screening period without repeating the examinations, except for examinations that need to be performed 7 days before the start of the study drug administration.

[b] PD-L1 expression as determined locally, for Cohorts A, B, and C. The results should be available in the source documents and be those used to make treatment decisions for the patient. A redacted copy of the local results should accompany the archival tumor samples submitted as part of the protocol.

[c] MSS/MSI status as determined locally, for Cohorts C and D only. The results should be available in the source documents and be those used to make treatment decisions for the patient. A redacted copy of the local results should accompany the archival tumor samples submitted as part of the protocol.

[d] Medical history and disease history data include significant clinical disease or symptom, surgical history, history of malignancy (including date of diagnosis, classification and prognosis evaluation of the study disease, and the treatment performed and the outcome; the tumor species and outcomes of any other previous malignancies), smoking history, history of alcohol consumption, history of drug abuse, and other medical-related history.

[e] Demographic information includes sex, race, and in some countries, year of birth.

[f] Concomitant medications include any prescription and over-the-counter medications started after signing of ICF. During the screening period, all drugs used for the patient within 28 days prior to the start of study drug should be recorded. In subsequent visits, the drugs used in the patient after the last record, as well as drugs 30 days after the last dose of study drug(s), should be recorded in eCRF. Subsequent new anti-tumor treatment regimens during the Safety and Survival Follow-up Periods will also be recorded.

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

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

[i] Assessments can be performed up to and including C1D1. Details for ECOG assessment can be found in Section 6.1.11 of the protocol and for vital sign collection in Section 6.1.12 of the protocol.

[j] Hematology includes red blood cell count, hemoglobin, hematocrit, absolute reticulocyte count, white blood cell count and classifications (neutrophils, lymphocytes, eosinophils, monocytes, and basophils), and platelet count. If abnormal or primitive immature cells are seen, they must also be recorded. Any additional routine blood tests during the study shall be arranged by the investigator as needed.

[k] Blood chemistry includes ALT, AST, alkaline phosphatase (ALP), bicarbonate, bilirubin/total bilirubin, lactic dehydrogenase, non-fasting total cholesterol, triglycerides, uric acid, total protein, albumin, blood urea nitrogen or urea, creatinine, CrCl rate, sodium, potassium, magnesium, chloride, corrected calcium (for patients with hypoproteinemia), phosphorus, blood glucose, creatine phosphokinase, and creatine kinase-MB (CK-MB). If CK-MB fractionation is not available, troponin I and/or troponin T should be tested instead. Serum troponins may be substituted per local guidelines if used consistently throughout the study. If tislelizumab has been permanently discontinued, CK and CK-MB testing will be done as clinically indicated.

[l] Fasting lipid panel includes total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides.

[m] Coagulation indicators include prothrombin time, aPTT, and INR.

[n] Female patients of childbearing potential (including those who have undergone tubal ligation) must undergo a serum pregnancy test ≤7 days before the first dose and record a negative result. If serum pregnancy test was drawn within 72 hours of C1D1, then urine pregnancy test is not required on C1D1. After enrollment, urine pregnancy test should be conducted on Day 1 of every treatment cycle starting from Cycle 1, and at the EOT visit. A serum pregnancy test should be performed at the Safety Follow-up Visit. If the result of urine pregnancy testing is equivocal, a serum test should be performed. Unscheduled testing via either method can be performed if there is an indication, however, any equivocal urine pregnancy tests should be repeated via serum pregnancy testing.

[o] Thyroid function tests include serum free tri-iodothyronine, serum free thyroxine, and thyroid stimulating hormone.

[p] Urinalysis includes urine pH, protein, glucose, blood and ketones; microscopic for white blood cell and red blood cell count. A 24-hour urine for quantitative protein must be collected from all patients with 1+ proteinuria.

[q] Testing will be performed by the local laboratory at screening and will include HBV/HCV serology (HBsAg and HCV antibody) and viral load assessment (HBV DNA and HCV RNA), which will be assessed only when HBsAg or HCV antibody is positive, respectively. Additionally, for patients who have detectable HBV DNA at screening, the respective viral load test will be performed every 4 cycles starting at Cycle 5 (ie, Day 1 of Cycles 5, 9, 13, etc) and at the EOT visit.

[r] ECG indicators include PR interval, QRS interval, RR interval, QT/QTcF interval and heart rate. Unscheduled ECG or other cardiac examinations can be performed if clinically indicated. All ECGs should be done prior to dosing of study drugs.

[s] If a patient discontinues study drug(s) due to reasons other than PD or death, tumor assessments should continue to be performed following the scheduled assessment plan until the start of new anticancer therapy, PD, death, lost to follow-up, or withdrawal of consent..

[t] Tislelizumab 300 mg IV will be administered on Day 1 of each 28-day cycle (once every 4 weeks). Every 3 weeks (Q3W) dosing of tislelizumab may be explored depending on the tolerability of the Q4W dosing schedule.

[u] After signing the informed consent form, all AEs including SAEs regardless of attribution will be collected until 30 days after the last dose of study drug or initiation of a new treatment therapy, whichever is earlier. After this period, investigators should report only SAEs that are considered to be related to the study drug. Immune-mediated AEs (serious or nonserious) should be reported until 90 days after the last dose of tislelizumab regardless of whether or not the patient starts a new anticancer therapy.

[v] Following EOT, patients will be followed every 8 weeks (±14 days) via telephone or in manner that follows local site SOPs.

Appendix 2: CTCAE criteria table for lab parameters

			ATOXGR			
PARAM (SI Unit)	**Hypo**	**Hyper**	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
Hemoglobin (g/L)	Anemia	Hemoglobin increased	Increase in >0 - 2 g/dL	Increase in >2 - 4 g/dL	Increase in >4 g/dL	~
			Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L	~
Platelets (10^9/L)	Platelet count decreased		<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L
Leukocytes (10^9/L)	White blood cell decreased		<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L
Neutrophils (10^9/L)	Neutrophil count decreased		<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L
Lymphocytes (10^9/L)	Lymphocyte count decreased		<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L
		Lymphocyte count increased	~	>4000/mm3 - 20,000/mm3	>20,000/mm3	~
Eosinophils (%)		Eosinophilia	>ULN and >Baseline	-	Steroids initiated	-
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

			ATOXGR			
PARAM (SI Unit)	**Hypo**	**Hyper**	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
Creatinine (umol/L)		Creatinine increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline if baseline was abnormal; >1.5 - 3.0 x ULN if baseline was normal	>3.0 x baseline- 6.0xULN if baseline was abnormal; >3.0 - 6.0 x ULN if baseline is normal	>6.0 x ULN
Creatine phosphokinase (IU/L)		CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN- 5 x ULN	>5.0 X ULN - 10.0 x ULN	>10.0 x ULN
Alkaline Phosphatase (uKat/L)		Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Aspartate Aminotransferase (uKat/L)		Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Alanine Aminotransferase (uKat/L)		Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
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

			ATOXGR			
PARAM (SI Unit)	**Hypo**	**Hyper**	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
Sodium (mmol/L)	Hyponatremia	Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
			<LLN - 130 mmol/L	125-129 mmol/L	120-124 mmol/L	<120 mmol/L
Total cholesterol (mmol/L)		Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L
Bilirubin (umol/L)		Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
Triglycerides (mmol/L)		Hypertriglyceridemia	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L
Urinary protein		Proteinuria	1+ proteinuria; urinary protein ≥ULN - <1.0 g/24 hrs	2+ and 3+ proteinuria; urinary protein 1.0- <3.5g/24hrs	4+ proteinuria; urinary protein >= 3.5g/24hrs	~

Appendix 3: MedDRA (Version 25.0) Preferred Term List for AESI Categories

AESI Category: Thyroid Dysfunction		
Anti-thyroid antibody	Malignant exophthalmos	Thyroid stimulating hormone deficiency
Anti-thyroid antibody decreased	Marine Lenhart syndrome	Thyroid stimulating immunoglobulin increased
Anti-thyroid antibody increased	Multifocal fibrosclerosis	Thyroid therapy
Anti-thyroid antibody positive	Myxoedema	Thyroid tuberculosis
Antithyroid arthritis syndrome	Myxoedema coma	Thyroidectomy
Atrophic thyroiditis	Orbital decompression	Thyroiditis
Autoimmune hypothyroidism	Photon radiation therapy to thyroid	Thyroiditis acute
Autoimmune thyroid disorder	Polyglandular autoimmune syndrome type II	Thyroiditis chronic
Autoimmune thyroiditis	Polyglandular autoimmune syndrome type III	Thyroiditis fibrous chronic
Basedow's disease	Post procedural hypothyroidism	Thyroiditis subacute
Biopsy thyroid gland abnormal	Primary hyperthyroidism	Thyrotoxic cardiomyopathy
Blood thyroid stimulating hormone abnormal	Primary hypothyroidism	Thyrotoxic crisis
Blood thyroid stimulating hormone decreased	Protein bound iodine decreased	Thyrotoxic myopathy
Blood thyroid stimulating hormone increased	Protein bound iodine increased	Thyrotoxic periodic paralysis
Butanol-extractable iodine decreased	Radioactive iodine therapy	Thyroxin binding globulin abnormal
Butanol-extractable iodine increased	Radiotherapy to thyroid	Thyroxin binding globulin decreased
Central hypothyroidism	Reverse tri-iodothyronine decreased	Thyroxin binding globulin increased
Congenital hypothyroidism	Reverse tri-iodothyronine increased	Thyroxine abnormal
Congenital thyroid disorder	Secondary hyperthyroidism	Thyroxine decreased
Endocrine ophthalmopathy	Silent thyroiditis	Thyroxine free abnormal
Euthyroid sick syndrome	Thyreostatic therapy	Thyroxine free decreased
Exophthalmos	Thyroglobulin absent	Thyroxine free increased
Free thyroxine index abnormal	Thyroglobulin decreased	Thyroxine increased
Free thyroxine index decreased	Thyroglobulin increased	Thyroxine therapy
Free thyroxine index increased	Thyroglobulin present	Toxic goitre
Gamma radiation therapy to thyroid	Thyroid atrophy	Toxic nodular goitre
Generalised resistance to thyroid hormone	Thyroid autotransplantation	Transient hypothyroxinaemia of prematurity
Goitre	Thyroid dermatopathy	Tri-iodothyronine abnormal
Hashimoto's encephalopathy	Thyroid disorder	Tri-iodothyronine decreased
Hashitoxicosis	Thyroid dysfunction in pregnancy	Tri-iodothyronine free abnormal
Hyperthyroidism	Thyroid electron radiation therapy	Tri-iodothyronine free decreased
Hypothyroidic goitre	Thyroid function test abnormal	Tri-iodothyronine free increased
Hypothyroidism	Thyroid gland scan abnormal	Tri-iodothyronine free normal
Immune-mediated hyperthyroidism	Thyroid hemiagenesis	Tri-iodothyronine increased
Immune-mediated hypothyroidism	Thyroid hormone replacement therapy	Tri-iodothyronine uptake abnormal

Immune-mediated thyroiditis	Thyroid hormones decreased	Tri-iodothyronine uptake decreased
Inappropriate thyroid stimulating hormone secretion	Thyroid hormones increased	Tri-iodothyronine uptake increased
Infectious thyroiditis	Thyroid operation	Ultrasound thyroid abnormal
Iodine uptake abnormal	Thyroid pain	X-ray therapy to thyroid
Iodine uptake decreased	Thyroid releasing hormone challenge test abnormal	
Iodine uptake increased	Thyroid size decreased	
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	Hypertension neonatal	Metabolic syndrome
Blood pressure ambulatory increased	Hypertensive angiopathy	Neurogenic hypertension
Blood pressure diastolic increased	Hypertensive cardiomegaly	Orthostatic hypertension
Blood pressure inadequately controlled	Hypertensive cardiomyopathy	Page kidney
Blood pressure increased	Hypertensive cerebrovascular disease	Postoperative hypertension
Blood pressure management	Hypertensive crisis	Pre-eclampsia
Blood pressure orthostatic increased	Hypertensive emergency	Prehypertension
Blood pressure systolic increased	Hypertensive encephalopathy	Procedural hypertension
Catecholamine crisis	Hypertensive end-organ damage	Renal hypertension
Dialysis induced hypertension	Hypertensive heart disease	Renal sympathetic nerve ablation
Diastolic hypertension	Hypertensive nephropathy	Renovascular hypertension
Eclampsia	Hypertensive urgency	Retinopathy hypertensive
Endocrine hypertension	Labile hypertension	Secondary aldosteronism
Essential hypertension	Malignant hypertension	Secondary hypertension
Gestational hypertension	Malignant hypertensive heart disease	Superimposed pre-eclampsia
HELLP syndrome	Malignant renal hypertension	Supine hypertension
Hyperaldosteronism	Maternal hypertension affecting foetus	Systolic hypertension
Hypertension	Mean arterial pressure increased	Withdrawal hypertension
AESI Category: Haemorrhages		
Abdominal wall haematoma	Haemophilic pseudotumour	Peritoneal haematoma
Abdominal wall haemorrhage	Haemoptysis	Periventricular haemorrhage neonatal

Abnormal uterine bleeding	Haemorrhage	Petechiae
Abnormal withdrawal bleeding	Haemorrhage coronary artery	Pharyngeal contusion
Achenbach syndrome	Haemorrhage foetal	Pharyngeal haematoma
Acute haemorrhagic leukoencephalitis	Haemorrhage in pregnancy	Pharyngeal haemorrhage
Acute haemorrhagic ulcerative colitis	Haemorrhage intracranial	Pituitary apoplexy
Administration site bruise	Haemorrhage neonatal	Pituitary haemorrhage
Administration site haematoma	Haemorrhage subcutaneous	Placenta praevia haemorrhage
Administration site haemorrhage	Haemorrhage subepidermal	Plasmin increased
Adrenal haematoma	Haemorrhage urinary tract	Polymenorrhagia
Adrenal haemorrhage	Haemorrhagic adrenal infarction	Post abortion haemorrhage
Anal fissure haemorrhage	Haemorrhagic arteriovenous malformation	Post procedural contusion
Anal haemorrhage	Haemorrhagic ascites	Post procedural haematoma
Anal ulcer haemorrhage	Haemorrhagic breast cyst	Post procedural haematuria
Anastomotic haemorrhage	Haemorrhagic cerebellar infarction	Post procedural haemorrhage
Anastomotic ulcer haemorrhage	Haemorrhagic cerebral infarction	Post transfusion purpura
Aneurysm ruptured	Haemorrhagic cyst	Post-traumatic punctate intraepidermal haemorrhage
Angina bullosa haemorrhagica	Haemorrhagic diathesis	Postmenopausal haemorrhage
Anorectal varices haemorrhage	Haemorrhagic disease of newborn	Postpartum haemorrhage
Anticoagulant-related nephropathy	Haemorrhagic disorder	Prekallikrein increased
Antiplatelet reversal therapy	Haemorrhagic erosive gastritis	Premature separation of placenta
Aortic aneurysm rupture	Haemorrhagic gastroenteritis	Procedural haemorrhage
Aortic dissection rupture	Haemorrhagic hepatic cyst	Proctitis haemorrhagic
Aortic intramural haematoma	Haemorrhagic infarction	Prostatic haemorrhage
Aortic perforation	Haemorrhagic necrotic pancreatitis	Pulmonary alveolar haemorrhage
Aortic rupture	Haemorrhagic occlusive retinal vasculitis	Pulmonary contusion
Aponeurosis contusion	Haemorrhagic ovarian cyst	Pulmonary haematoma
Application site bruise	Haemorrhagic stroke	Pulmonary haemorrhage
Application site haematoma	Haemorrhagic thyroid cyst	Pulmonary haemorrhage neonatal
Application site haemorrhage	Haemorrhagic transformation stroke	Puncture site bruise
Application site purpura	Haemorrhagic tumour necrosis	Puncture site haematoma
Arterial haemorrhage	Haemorrhagic urticaria	Puncture site haemorrhage
Arterial intramural haematoma	Haemorrhagic vasculitis	Purpura
Arterial perforation	Haemorrhoidal haemorrhage	Purpura fulminans
Arterial rupture	Haemostasis	Purpura neonatal
Arteriovenous fistula site haematoma	Haemothorax	Purpura non-thrombocytopenic
Arteriovenous fistula site haemorrhage	Heavy menstrual bleeding	Purpura senile
Arteriovenous graft site haematoma	Henoch-Schonlein purpura	Putamen haemorrhage

Arteriovenous graft site haemorrhage	Hepatic artery haemorrhage	Radiation associated haemorrhage
Astringent therapy	Hepatic haemangioma rupture	Rectal haemorrhage
Atrial rupture	Hepatic haematoma	Rectal ulcer haemorrhage
Auricular haematoma	Hepatic haemorrhage	Renal artery perforation
Basal ganglia haematoma	Hereditary haemorrhagic telangiectasia	Renal cyst haemorrhage
Basal ganglia haemorrhage	Hyperfibrinolysis	Renal haematoma
Basilar artery perforation	Hypergammaglobulinaemic purpura of Waldenstrom	Renal haemorrhage
Bladder tamponade	Hyphaema	Respiratory tract haemorrhage
Bleeding varicose vein	Iliac artery perforation	Respiratory tract haemorrhage neonatal
Blood blister	Iliac artery rupture	Retinal aneurysm rupture
Blood loss anaemia	Iliac vein perforation	Retinal haemorrhage
Blood urine	Immune thrombocytopenia	Retinopathy haemorrhagic
Blood urine present	Implant site bruising	Retroperitoneal haematoma
Bloody discharge	Implant site haematoma	Retroperitoneal haemorrhage
Bloody peritoneal effluent	Implant site haemorrhage	Retroplacental haematoma
Bone contusion	Incision site haematoma	Ruptured cerebral aneurysm
Bone marrow haemorrhage	Incision site haemorrhage	Scleral haematoma
Brain contusion	Increased tendency to bruise	Scleral haemorrhage
Brain stem haematoma	Induced abortion haemorrhage	Scrotal haematocoele
Brain stem haemorrhage	Inferior vena cava perforation	Scrotal haematoma
Brain stem microhaemorrhage	Infusion site bruising	Scrotal haemorrhage
Breast haematoma	Infusion site haematoma	Shock haemorrhagic
Breast haemorrhage	Infusion site haemorrhage	Skin haemorrhage
Broad ligament haematoma	Injection site bruising	Skin neoplasm bleeding
Bronchial haemorrhage	Injection site haematoma	Skin ulcer haemorrhage
Bronchial varices haemorrhage	Injection site haemorrhage	Small intestinal haemorrhage
Bullous haemorrhagic dermatosis	Instillation site bruise	Small intestinal ulcer haemorrhage
Bursal haematoma	Instillation site haematoma	Soft tissue haemorrhage
Cardiac contusion	Instillation site haemorrhage	Spermatic cord haemorrhage
Carotid aneurysm rupture	Intermenstrual bleeding	Spinal cord haematoma
Carotid artery perforation	Internal haemorrhage	Spinal cord haemorrhage
Catheter site bruise	Intestinal haematoma	Spinal epidural haematoma
Catheter site haematoma	Intestinal haemorrhage	Spinal epidural haemorrhage
Catheter site haemorrhage	Intestinal varices haemorrhage	Spinal subarachnoid haemorrhage
Central nervous system haemorrhage	Intra-abdominal haematoma	Spinal subdural haematoma
Cephalhaematoma	Intra-abdominal haemorrhage	Spinal subdural haemorrhage
Cerebellar haematoma	Intracerebral haematoma evacuation	Spleen contusion

Cerebellar haemorrhage	Intracranial haematoma	Splenic artery perforation
Cerebellar microhaemorrhage	Intracranial haemorrhage neonatal	Splenic haematoma
Cerebral aneurysm perforation	Intracranial tumour haemorrhage	Splenic haemorrhage
Cerebral aneurysm ruptured syphilitic	Intraocular haematoma	Splenic varices haemorrhage
Cerebral arteriovenous malformation haemorrhagic	Intrapartum haemorrhage	Splinter haemorrhages
Cerebral artery perforation	Intratumoural haematoma	Spontaneous haematoma
Cerebral cyst haemorrhage	Intraventricular haemorrhage	Spontaneous haemorrhage
Cerebral haematoma	Intraventricular haemorrhage neonatal	Stoma site haemorrhage
Cerebral haemorrhage	Iris haemorrhage	Stomatitis haemorrhagic
Cerebral haemorrhage foetal	Joint microhaemorrhage	Subarachnoid haematoma
Cerebral haemorrhage neonatal	Jugular vein haemorrhage	Subarachnoid haemorrhage
Cerebral microhaemorrhage	Kidney contusion	Subarachnoid haemorrhage neonatal
Cervix haematoma uterine	Lacrimal haemorrhage	Subcapsular hepatic haematoma
Cervix haemorrhage uterine	Large intestinal haemorrhage	Subcapsular renal haematoma
Chest wall haematoma	Large intestinal ulcer haemorrhage	Subcapsular splenic haematoma
Choroidal haematoma	Laryngeal haematoma	Subchorionic haematoma
Choroidal haemorrhage	Laryngeal haemorrhage	Subchorionic haemorrhage
Chronic gastrointestinal bleeding	Lip haematoma	Subclavian artery perforation
Chronic pigmented purpura	Lip haemorrhage	Subclavian vein perforation
Ciliary body haemorrhage	Liver contusion	Subcutaneous haematoma
Coital bleeding	Lower gastrointestinal haemorrhage	Subdural haematoma
Colonic haematoma	Lower limb artery perforation	Subdural haematoma evacuation
Conjunctival haemorrhage	Lymph node haemorrhage	Subdural haemorrhage
Contusion	Mallory-Weiss syndrome	Subdural haemorrhage neonatal
Corneal bleeding	Mediastinal haematoma	Subendocardial haemorrhage
Cullen's sign	Mediastinal haemorrhage	Subgaleal haematoma
Cystitis haemorrhagic	Medical device site bruise	Subgaleal haemorrhage
Deep dissecting haematoma	Medical device site haematoma	Subretinal haematoma
Diarrhoea haemorrhagic	Medical device site haemorrhage	Superior vena cava perforation
Disseminated intravascular coagulation	Melaena	Testicular haemorrhage
Diverticulitis intestinal haemorrhagic	Melaena neonatal	Thalamus haemorrhage
Diverticulum intestinal haemorrhagic	Meningorrhagia	Third stage postpartum haemorrhage
Duodenal ulcer haemorrhage	Menometrorrhagia	Thoracic haemorrhage
Duodenitis haemorrhagic	Mesenteric haematoma	Thrombocytopenic purpura
Ear haemorrhage	Mesenteric haemorrhage	Thrombomodulin increased
Ecchymosis	Mouth haemorrhage	Thrombotic thrombocytopenic purpura
Encephalitis haemorrhagic	Mucocutaneous haemorrhage	Thyroid haemorrhage
Enterocolitis haemorrhagic	Mucosal haemorrhage	Tongue haematoma

Epidural haemorrhage	Muscle contusion	Tongue haemorrhage
Epistaxis	Muscle haemorrhage	Tonsillar haemorrhage
Exsanguination	Myocardial haemorrhage	Tooth pulp haemorrhage
Extra-axial haemorrhage	Myocardial rupture	Tooth socket haemorrhage
Extradural haematoma	Naevus haemorrhage	Tracheal haemorrhage
Extradural haematoma evacuation	Nail bed bleeding	Traumatic haematoma
Extravasation blood	Nasal septum haematoma	Traumatic haemorrhage
Eye contusion	Neonatal gastrointestinal haemorrhage	Traumatic haemothorax
Eye haematoma	Nephritis haemorrhagic	Traumatic intracranial haematoma
Eye haemorrhage	Nipple exudate bloody	Traumatic intracranial haemorrhage
Eyelid bleeding	Occult blood positive	Tumour haemorrhage
Eyelid contusion	Ocular retrobulbar haemorrhage	Ulcer haemorrhage
Eyelid haematoma	Oesophageal haemorrhage	Umbilical cord haemorrhage
Femoral artery perforation	Oesophageal intramural haematoma	Umbilical haematoma
Femoral vein perforation	Oesophageal ulcer haemorrhage	Umbilical haemorrhage
Foetal-maternal haemorrhage	Oesophageal varices haemorrhage	Upper gastrointestinal haemorrhage
Fothergill sign positive	Oesophagitis haemorrhagic	Ureteric haemorrhage
Gallbladder haematoma	Omental haemorrhage	Urethral haemorrhage
Gastric haemorrhage	Optic disc haemorrhage	Urinary bladder haematoma
Gastric occult blood positive	Optic nerve sheath haemorrhage	Urinary bladder haemorrhage
Gastric ulcer haemorrhage	Oral blood blister	Urinary occult blood
Gastric ulcer haemorrhage, obstructive	Oral contusion	Urinary occult blood positive
Gastric varices haemorrhage	Oral mucosa haematoma	Urogenital haemorrhage
Gastritis alcoholic haemorrhagic	Oral purpura	Uterine haematoma
Gastritis haemorrhagic	Orbital haematoma	Uterine haemorrhage
Gastroduodenal haemorrhage	Orbital haemorrhage	Vaccination site bruising
Gastrointestinal anastomotic haemorrhage	Osteorrhagia	Vaccination site haematoma
Gastrointestinal haemorrhage	Ovarian haematoma	Vaccination site haemorrhage
Gastrointestinal polyp haemorrhage	Ovarian haemorrhage	Vaginal haematoma
Gastrointestinal ulcer haemorrhage	Palpable purpura	Vaginal haemorrhage
Gastrointestinal vascular malformation haemorrhagic	Pancreatic haemorrhage	Varicose vein ruptured
Genital contusion	Pancreatic pseudocyst haemorrhage	Vascular access site bruising
Genital haemorrhage	Pancreatitis haemorrhagic	Vascular access site haematoma
Gingival bleeding	Papillary muscle haemorrhage	Vascular access site haemorrhage
Graft haemorrhage	Paranasal sinus haematoma	Vascular access site rupture
Grey Turner's sign	Paranasal sinus haemorrhage	Vascular anastomotic haemorrhage
Haemangioma rupture	Parathyroid haemorrhage	Vascular graft haemorrhage

Haemarthrosis	Parotid gland haemorrhage	Vascular pseudoaneurysm ruptured
Haematemesis	Pelvic haematoma	Vascular purpura
Haematochezia	Pelvic haematoma obstetric	Vascular rupture
Haematocoele	Pelvic haemorrhage	Vein rupture
Haematoma	Penile contusion	Venous haemorrhage
Haematoma evacuation	Penile haematoma	Venous perforation
Haematoma infection	Penile haemorrhage	Ventricle rupture
Haematoma muscle	Peptic ulcer haemorrhage	Vertebral artery perforation
Haematosalpinx	Pericardial haemorrhage	Vessel puncture site bruise
Haematospermia	Perineal haematoma	Vessel puncture site haematoma
Haematotympanum	Periorbital haematoma	Vessel puncture site haemorrhage
Haematuria	Periorbital haemorrhage	Vitreous haematoma
Haematuria traumatic	Periosteal haematoma	Vitreous haemorrhage
Haemobilia	Peripartum haemorrhage	Vulval haematoma
Haemoperitoneum	Peripheral artery aneurysm rupture	Vulval haematoma evacuation
Haemophilic arthropathy	Peripheral artery haematoma	Vulval haemorrhage
	Peripheral exudative haemorrhagic chorioretinopathy	Withdrawal bleed
		Wound haematoma
		Wound haemorrhage
AESI Category: Gastrointestinal perforation		
Abdominal abscess	Enterocutaneous fistula	Mesenteric abscess
Abdominal hernia perforation	Enterovesical fistula	Neonatal intestinal perforation
Abdominal wall abscess	Fistula of small intestine	Oesophageal abscess
Abscess intestinal	Focal peritonitis	Oesophageal fistula
Acquired tracheo-oesophageal fistula	Gastric fistula	Pancreatic fistula repair
Anal abscess	Gastric fistula repair	Peptic ulcer perforation
Anal fistula	Gastric perforation	Peptic ulcer perforation, obstructive
Anal fistula infection	Gastric ulcer perforation	Peptic ulcer repair
Anal fistula repair	Gastric ulcer perforation, obstructive	Perforated ulcer
Anastomotic ulcer perforation	Gastrointestinal anastomotic leak	Perineal abscess
Anovulvar fistula	Gastrointestinal fistula	Perirectal abscess
Aorto-oesophageal fistula	Gastrointestinal fistula repair	Peritoneal abscess
Aortoenteric fistula	Gastrointestinal perforation	Peritoneocutaneous fistula
Appendiceal abscess	Gastrointestinal ulcer perforation	Peritonitis
Appendicitis perforated	Gastropleural fistula	Peritonitis bacterial
Arterioenteric fistula	Gastrosplenic fistula	Pneumoperitoneum

Atrio-oesophageal fistula	Ileal perforation	Pneumoretroperitoneum
Chemical peritonitis	Ileal ulcer perforation	Procedural intestinal perforation
Colo-urethral fistula	Incisional hernia perforation	Rectal abscess
Colon fistula repair	Inguinal hernia perforation	Rectal fistula repair
Colonic abscess	Intestinal fistula	Rectal perforation
Colonic fistula	Intestinal fistula infection	Rectoprostatic fistula
Diverticular fistula	Intestinal fistula repair	Rectourethral fistula
Diverticular perforation	Intestinal perforation	Retroperitoneal abscess
Diverticulitis intestinal perforated	Intestinal ulcer perforation	Small intestinal perforation
Douglas' abscess	Jejunal perforation	Small intestinal ulcer perforation
Duodenal perforation	Jejunal ulcer perforation	Spontaneous bacterial peritonitis
Duodenal rupture	Large intestinal ulcer perforation	Umbilical hernia perforation
Duodenal ulcer perforation	Large intestine perforation	Upper gastrointestinal perforation
Duodenal ulcer perforation, obstructive	Lower gastrointestinal perforation	
Duodenal ulcer repair		
Enterocolonic fistula		
AESI Category: Embolic and thrombotic events		
Acute aortic syndrome	Embolism venous	Prosthetic cardiac valve thrombosis
Acute coronary syndrome	Endarterectomy	Prosthetic vessel implantation
Acute myocardial infarction	Eye infarction	Pseudo-occlusion of internal carotid artery
Administration site thrombosis	Femoral artery embolism	Pulmonary artery occlusion
Adrenal thrombosis	Fluorescence angiogram abnormal	Pulmonary artery therapeutic procedure
Amaurosis	Foetal cerebrovascular disorder	Pulmonary artery thrombosis
Amaurosis fugax	Foetal vascular malperfusion	Pulmonary embolism
Aneurysm thrombosis	Gastric infarction	Pulmonary endarterectomy
Angiogram abnormal	Graft thrombosis	Pulmonary infarction
Angiogram cerebral abnormal	Haemorrhagic adrenal infarction	Pulmonary microemboli
Angiogram peripheral abnormal	Haemorrhagic cerebral infarction	Pulmonary thrombosis
Angioplasty	Haemorrhagic infarction	Pulmonary tumour thrombotic microangiopathy
Antiphospholipid syndrome	Haemorrhagic stroke	Pulmonary vein occlusion
Aortic bypass	Haemorrhagic transformation stroke	Pulmonary veno-occlusive disease
Aortic embolus	Haemorrhoids thrombosed	Pulmonary venous thrombosis
Aortic surgery	Hemiparesis	Quadriparesis
Aortic thrombosis	Hemiplegia	Quadriplegia
Aortogram abnormal	Heparin-induced thrombocytopenia	Renal artery angioplasty
Application site thrombosis	Hepatic artery embolism	Renal artery occlusion
Arterectomy	Hepatic artery occlusion	Renal artery thrombosis

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

Budd-Chiari syndrome	Medical device site thrombosis	Subclavian artery occlusion
Capsular warning syndrome	Mesenteric arterial occlusion	Subclavian artery thrombosis
Cardiac ventricular thrombosis	Mesenteric arteriosclerosis	Subclavian vein occlusion
Carotid angioplasty	Mesenteric artery embolism	Subclavian vein thrombosis
Carotid arterial embolus	Mesenteric artery stenosis	Superficial vein thrombosis
Carotid artery bypass	Mesenteric artery stent insertion	Superior sagittal sinus thrombosis
Carotid artery occlusion	Mesenteric artery thrombosis	Superior vena cava occlusion
Carotid artery stent insertion	Mesenteric vascular insufficiency	Superior vena cava syndrome
Carotid artery thrombosis	Mesenteric vascular occlusion	Surgical vascular shunt
Carotid endarterectomy	Mesenteric vein thrombosis	Testicular infarction
Catheter directed thrombolysis	Mesenteric venous occlusion	Thalamic infarction
Catheter site thrombosis	Metabolic stroke	Thrombectomy
Catheterisation venous	Microembolism	Thromboangiitis obliterans
Cavernous sinus thrombosis	Monoparesis	Thromboembolectomy
Central venous catheterisation	Monoplegia	Thrombolysis
Cerebellar artery occlusion	Muscle infarction	Thrombophlebitis
Cerebellar artery thrombosis	Myocardial infarction	Thrombophlebitis migrans
Cerebellar embolism	Myocardial necrosis	Thrombophlebitis neonatal
Cerebellar infarction	Obstetrical pulmonary embolism	Thrombosed varicose vein
Cerebral artery embolism	Obstructive shock	Thrombosis
Cerebral artery occlusion	Ophthalmic artery occlusion	Thrombosis corpora cavernosa
Cerebral artery stent insertion	Ophthalmic artery thrombosis	Thrombosis in device
Cerebral artery thrombosis	Ophthalmic vein thrombosis	Thrombosis mesenteric vessel
Cerebral congestion	Optic nerve infarction	Thrombosis prophylaxis
Cerebral hypoperfusion	Ovarian vein thrombosis	Thrombosis with thrombocytopenia syndrome
Cerebral infarction	Paget-Schroetter syndrome	Thrombotic cerebral infarction
Cerebral infarction foetal	Pancreatic infarction	Thrombotic microangiopathy
Cerebral ischaemia	Papillary muscle infarction	Thrombotic stroke
Cerebral microembolism	Paradoxical embolism	Thrombotic thrombocytopenic purpura
Cerebral microinfarction	Paraneoplastic thrombosis	Thyroid infarction
Cerebral septic infarct	Paraparesis	Transient ischaemic attack
Cerebral thrombosis	Paraplegia	Transverse sinus thrombosis
Cerebral vascular occlusion	Paresis	Truncus coeliacus thrombosis
Cerebral venous sinus thrombosis	Pelvic venous thrombosis	Tumour embolism
Cerebral venous thrombosis	Penile artery occlusion	Tumour thrombectomy
Cerebrospinal thrombotic tamponade	Penile vein thrombosis	Tumour thrombosis
Cerebrovascular accident	Percutaneous coronary intervention	Ultrasonic angiogram abnormal
Cerebrovascular accident prophylaxis	Peripheral arterial occlusive disease	Ultrasound Doppler abnormal

Cerebrovascular disorder	Peripheral arterial reocclusion	Umbilical cord occlusion
Cerebrovascular insufficiency	Peripheral artery angioplasty	Umbilical cord thrombosis
Cerebrovascular operation	Peripheral artery bypass	Vaccination site thrombosis
Cerebrovascular stenosis	Peripheral artery occlusion	Vascular access site thrombosis
Choroidal infarction	Peripheral artery stent insertion	Vascular device occlusion
Coeliac artery occlusion	Peripheral artery surgery	Vascular graft
Collateral circulation	Peripheral artery thrombosis	Vascular graft occlusion
Compression garment application	Peripheral embolism	Vascular graft thrombosis
Coronary angioplasty	Peripheral endarterectomy	Vascular operation
Coronary arterial stent insertion	Peripheral revascularisation	Vascular pseudoaneurysm thrombosis
Coronary artery bypass	Peripheral vein occlusion	Vascular stent insertion
Coronary artery embolism	Peripheral vein thrombosis	Vascular stent occlusion
Coronary artery occlusion	Peripheral vein thrombus extension	Vascular stent thrombosis
Coronary artery reocclusion	Phlebectomy	Vasodilation procedure
Coronary artery surgery	Pituitary infarction	Vena cava embolism
Coronary artery thrombosis	Placental infarction	Vena cava filter insertion
Coronary bypass thrombosis	Pneumatic compression therapy	Vena cava filter removal
Coronary endarterectomy	Popliteal artery entrapment syndrome	Vena cava thrombosis
Coronary revascularisation	Portal shunt procedure	Venogram abnormal
Coronary vascular graft occlusion	Portal vein cavernous transformation	Venoocclusive disease
Deep vein thrombosis	Portal vein embolism	Venoocclusive liver disease
Deep vein thrombosis postoperative	Portal vein occlusion	Venous angioplasty
Device embolisation	Portal vein thrombosis	Venous occlusion
Device occlusion	Portosplenomesenteric venous thrombosis	Venous operation
Device related thrombosis	Post procedural myocardial infarction	Venous recanalisation
Diplegia	Post procedural pulmonary embolism	Venous repair
Directional Doppler flow tests abnormal	Post procedural stroke	Venous stent insertion
Disseminated intravascular coagulation	Post thrombotic syndrome	Venous thrombosis
Disseminated intravascular coagulation in newborn	Postinfarction angina	Venous thrombosis in pregnancy
Embolia cutis medicamentosa	Postoperative thrombosis	Venous thrombosis limb
Embolic cerebellar infarction	Postpartum thrombosis	Venous thrombosis neonatal
Embolic cerebral infarction	Postpartum venous thrombosis	Vertebral artery occlusion
Embolic pneumonia	Precerebral artery embolism	Vertebral artery thrombosis
Embolic stroke	Precerebral artery occlusion	Vessel puncture site occlusion
Embolism	Precerebral artery thrombosis	Vessel puncture site thrombosis
Embolism arterial	Profundaplasty	Visceral venous thrombosis
		Visual acuity reduced transiently
		Visual midline shift syndrome

AESI Category: Hepatic function abnormal		
AST/ALT ratio abnormal	Gastric variceal injection	Hypofibrinogenaemia
Acquired antithrombin III deficiency	Gastric variceal ligation	Hypoprothrombinaemia
Acquired factor IX deficiency	Gastric varices	Hypothrombinaemia
Acquired factor V deficiency	Gastric varices haemorrhage	Hypothromboplastinaemia
Acquired factor VIII deficiency	Gastrooesophageal variceal haemorrhage prophylaxis	Icterus index increased
Acquired factor XI deficiency	Graft versus host disease in liver	Immune-mediated cholangitis
Acquired hepatocerebral degeneration	Guanase increased	Immune-mediated hepatic disorder
Acquired protein S deficiency	Haemangioma of liver	Immune-mediated hepatitis
Acute graft versus host disease in liver	Haemorrhagic hepatic cyst	International normalised ratio abnormal
Acute hepatic failure	Hepaplastin abnormal	International normalised ratio increased
Acute on chronic liver failure	Hepaplastin decreased	Intestinal varices
Acute yellow liver atrophy	Hepatectomy	Intestinal varices haemorrhage
Alanine aminotransferase abnormal	Hepatic adenoma	Ischaemic hepatitis
Alanine aminotransferase increased	Hepatic angiosarcoma	Jaundice
Allergic hepatitis	Hepatic artery flow decreased	Jaundice cholestatic
Alloimmune hepatitis	Hepatic atrophy	Jaundice hepatocellular
Ammonia abnormal	Hepatic calcification	Kayser-Fleischer ring
Ammonia increased	Hepatic cancer	Liver carcinoma ruptured
Anti factor X activity abnormal	Hepatic cancer metastatic	Liver dialysis
Anti factor X activity decreased	Hepatic cancer recurrent	Liver disorder
Anti factor X activity increased	Hepatic cancer stage I	Liver function test abnormal
Anti-liver cytosol antibody type 1 positive	Hepatic cancer stage II	Liver function test decreased
Antithrombin III decreased	Hepatic cancer stage III	Liver function test increased
Ascites	Hepatic cancer stage IV	Liver induration
Aspartate aminotransferase abnormal	Hepatic cirrhosis	Liver injury
Aspartate aminotransferase increased	Hepatic cyst	Liver operation
Asterixis	Hepatic cyst ruptured	Liver palpable
Autoimmune hepatitis	Hepatic cytolysis	Liver scan abnormal
Bacterascites	Hepatic encephalopathy	Liver tenderness
Benign hepatic neoplasm	Hepatic encephalopathy prophylaxis	Liver transplant
Benign hepatobiliary neoplasm	Hepatic enzyme abnormal	Liver-kidney microsomal antibody positive
Bile output abnormal	Hepatic enzyme decreased	Lupoid hepatic cirrhosis
Bile output decreased	Hepatic enzyme increased	Lupus hepatitis
Biliary ascites	Hepatic failure	Magnetic resonance imaging hepatobiliary abnormal

Biliary cirrhosis	Hepatic fibrosis	Magnetic resonance proton density fat fraction measurement
Biliary fibrosis	Hepatic function abnormal	Mitochondrial aspartate aminotransferase increased
Bilirubin conjugated abnormal	Hepatic haemangioma rupture	Mixed hepatocellular cholangiocarcinoma
Bilirubin conjugated increased	Hepatic hamartoma	Mixed liver injury
Bilirubin excretion disorder	Hepatic hydrothorax	Molar ratio of total branched-chain amino acid to tyrosine
Bilirubin urine present	Hepatic hypertrophy	Nodular regenerative hyperplasia
Biopsy liver abnormal	Hepatic hypoperfusion	Non-alcoholic fatty liver
Blood bilirubin abnormal	Hepatic infiltration eosinophilic	Non-alcoholic steatohepatitis
Blood bilirubin increased	Hepatic lesion	Non-cirrhotic portal hypertension
Blood bilirubin unconjugated increased	Hepatic lipoma	Ocular icterus
Blood fibrinogen abnormal	Hepatic mass	Oedema due to hepatic disease
Blood fibrinogen decreased	Hepatic necrosis	Oesophageal varices haemorrhage
Blood thrombin abnormal	Hepatic neoplasm	Omental oedema
Blood thrombin decreased	Hepatic neuroendocrine tumour	Parenteral nutrition associated liver disease
Blood thromboplastin abnormal	Hepatic pain	Perihepatic discomfort
Blood thromboplastin decreased	Hepatic sarcoma	Peripancreatic varices
Bromosulphthalein test abnormal	Hepatic sequestration	Portal fibrosis
Cardiohepatic syndrome	Hepatic steato-fibrosis	Portal hypertension
Child-Pugh-Turcotte score abnormal	Hepatic steatosis	Portal hypertensive colopathy
Child-Pugh-Turcotte score increased	Hepatic vascular resistance increased	Portal hypertensive enteropathy
Cholaemia	Hepatic venous pressure gradient abnormal	Portal hypertensive gastropathy
Cholangiosarcoma	Hepatic venous pressure gradient increased	Portal vein cavernous transformation
Cholestasis	Hepatitis	Portal vein dilatation
Cholestatic liver injury	Hepatitis acute	Portopulmonary hypertension
Cholestatic pruritus	Hepatitis cholestatic	Primary biliary cholangitis
Chronic graft versus host disease in liver	Hepatitis chronic active	Protein C decreased
Chronic hepatic failure	Hepatitis chronic persistent	Protein S abnormal
Chronic hepatitis	Hepatitis fulminant	Protein S decreased
Coagulation factor IX level abnormal	Hepatitis toxic	Prothrombin level abnormal
Coagulation factor IX level decreased	Hepatobiliary cancer	Prothrombin level decreased
Coagulation factor V level abnormal	Hepatobiliary cancer in situ	Prothrombin time abnormal
Coagulation factor V level decreased	Hepatobiliary cyst	Prothrombin time prolonged
Coagulation factor VII level abnormal	Hepatobiliary disease	Prothrombin time ratio abnormal
Coagulation factor VII level decreased	Hepatobiliary neoplasm	Prothrombin time ratio increased
Coagulation factor X level abnormal	Hepatobiliary scan abnormal	Radiation hepatitis

Coagulation factor X level decreased	Hepatoblastoma	Regenerative siderotic hepatic nodule
Coagulation factor decreased	Hepatoblastoma recurrent	Renal and liver transplant
Coma hepatic	Hepatocellular carcinoma	Retrograde portal vein flow
Computerised tomogram liver abnormal	Hepatocellular foamy cell syndrome	Reye's syndrome
Congestive hepatopathy	Hepatocellular injury	Reynold's syndrome
Cryptogenic cirrhosis	Hepatomegaly	Splenic varices
Diabetic hepatopathy	Hepatopulmonary syndrome	Splenic varices haemorrhage
Drug-induced liver injury	Hepatorenal failure	Spontaneous bacterial peritonitis
Duodenal varices	Hepatorenal syndrome	Steatohepatitis
Flood syndrome	Hepatosplenomegaly	Subacute hepatic failure
Focal nodular hyperplasia	Hepatotoxicity	Sugiura procedure
Foetor hepaticus	Hyperammonaemia	Thrombin time abnormal
Galactose elimination capacity test abnormal	Hyperbilirubinaemia	Thrombin time prolonged
Galactose elimination capacity test decreased	Hypercholia	Total bile acids increased
Gallbladder varices	Hyperfibrinolysis	Transaminases abnormal
Gamma-glutamyltransferase abnormal	Hypertransaminasaemia	Transaminases increased
Gamma-glutamyltransferase increased	Hypocoagulable state	Ultrasound liver abnormal
		Urine bilirubin increased
		Varices oesophageal
		Varicose veins of abdominal wall
		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 4: imAE by Preferred Term

imAE Category: Immune-mediated AEs		
Immune-mediated adrenal insufficiency	Immune-mediated endocrinopathy	Immune-mediated myositis
Immune-mediated adverse reaction	Immune-mediated enterocolitis	Immune-mediated nephritis
Immune-mediated arthritis	Immune-mediated gastritis	Immune-mediated neurological disorder
Immune-mediated cholangitis	Immune-mediated hepatic disorder	Immune-mediated neuropathy
Immune-mediated cholestasis	Immune-mediated hepatitis	Immune-mediated oesophagitis
Immune-mediated cystitis	Immune-mediated hyperthyroidism	Immune-mediated pancreatitis
Immune-mediated cytopenia	Immune-mediated hypophysitis	Immune-mediated renal disorder
Immune-mediated dermatitis	Immune-mediated hypothyroidism	Immune-mediated thyroiditis
Immune-mediated encephalitis	Immune-mediated lung disease	Immune-mediated uveitis
Immune-mediated encephalopathy	Immune-mediated myocarditis	
imAE Category: Skin Adverse Reactions		
Acute febrile neutrophilic dermatosis	Oculomucocutaneous syndrome	Urticaria papular
Angioedema	Pruritus	Urticaria vesiculosa
Blister	Rash	Vitiligo
Cutaneous vasculitis	Rash erythematous	Acute generalised exanthematous pustulosis
Dermatitis	Rash follicular	Urticarial vasculitis
Dermatitis allergic	Rash macular	Rash maculovesicular
Dermatitis bullous	Rash maculo-papular	Urticaria chronic
Dermatitis exfoliative	Rash papular	Mucocutaneous rash
Dermatitis exfoliative generalised	Rash pruritic	Toxic skin eruption
Drug eruption	Rash pustular	Dermatitis psoriasiform
Eczema	Rash vesicular	Epidermal necrosis
Erythema multiforme	Skin depigmentation	Mucosal exfoliation
Fixed eruption	Skin exfoliation	Exfoliative rash
Idiopathic urticaria	Skin hypopigmentation	Mucosal necrosis
Leukoderma	Skin necrosis	Drug reaction with eosinophilia and systemic symptoms
Mucocutaneous ulceration	Stevens-Johnson syndrome	Autoimmune dermatitis
Mucosal ulceration	Toxic epidermal necrolysis	Nodular rash
Oculomucocutaneous syndrome	Urticaria	
imAE Category: Diabetes		
Diabetes mellitus	Diabetic ketoacidosis	Ketosis-prone diabetes mellitus
Diabetes mellitus inadequate control	Diabetic ketoacidotic hyperglycaemic coma	Pancreatogenous diabetes
Diabetes with hyperosmolarity	Diabetic ketosis	Latent autoimmune diabetes in adults
Diabetic hyperglycaemic coma	Increased insulin requirement	Type 1 diabetes mellitus
Diabetic hyperosmolar coma	Insulin resistant diabetes	Fulminant type 1 diabetes mellitus

Appendix 5 : MedDRA (Version 25.0) Preferred Term List for COVID-19 Related AE

Asymptomatic COVID-19	Occupational exposure to SARS-CoV-2
Breakthrough COVID-19	Post-acute COVID-19 syndrome
Congenital COVID-19	SARS-CoV-2 antibody test positive
Coronavirus infection	SARS-CoV-2 carrier
Coronavirus pneumonia	SARS-CoV-2 RNA decreased
Coronavirus test positive	SARS-CoV-2 RNA fluctuation
COVID-19	SARS-CoV-2 RNA increased
COVID-19 immunisation	SARS-CoV-2 sepsis
COVID-19 pneumonia	SARS-CoV-2 test false negative
COVID-19 prophylaxis	SARS-CoV-2 test positive
COVID-19 treatment	SARS-CoV-2 viraemia
Exposure to SARS-CoV-2	Suspected COVID-19
Multisystem inflammatory syndrome	Thrombosis with thrombocytopenia syndrome
Multisystem inflammatory syndrome in adults	Vaccine derived SARS-CoV-2 infection
Multisystem inflammatory syndrome in children	

Appendix 6 : Conversion tables for urinalysis results

Blood/Leucocytes (for parameter red blood cell and white blood cell)		
Negative	0	0 cells/μL
Trace	1+	1-24 cells/μL
Small	2+	25-79 cells/μL
Medium	3+	80-199 cells/μL
Large	4+	⩾ 200 cells/μL

Proteinuria (for parameter protein)				
NCI-CTCAE Grade	Protein by urinalysis	24-hour protein quantitation	Protein by urinalysis	24-hour protein quantitation
0	0		Negative	<10 mg/dL
1	1+	<1.0g	Trace	11-99 mg/dL
2	2+	<2.0g	Small	99-299 mg/dL
2	⩾2+	<3.5 g (excluding 3.5 g)	Medium	300-999 mg/dL
3	4+	⩾3.5 g	large	>1000 mg/dL

hmp-2020-013-00us3-7015654-statistical analysis plan v2.0 Final 29Jul2024

Final Audit Report 2024-07-31

Created:	2024-07-29
By:	PPD
Status:	Signed
Transaction ID:	PPD

"hmp-2020-013-00us3-7015654-statistical analysis plan v2.0 Final 29Jul2024" History

Document created by PPD
2024-07-29 - 9:57:59 PM GMT- IP address: PPD

PPD authenticated with Adobe Acrobat Sign.
Challenge: The user completed the signing ceremony.
2024-07-29 - 10:03:41 PM GMT

Document e-signed by PPD
Signing reason: I am the author
Signature Date: 2024-07-29 - 10:03:43 PM GMT - Time Source: server- IP address: PPD

Document emailed to PPD
PPD for signature
2024-07-29 - 10:03:45 PM GMT

Email viewed by PPD
2024-07-30 - 1:53:41 PM GMT- IP address PPD

PPD authenticated with Adobe Acrobat Sign.
Challenge: The user completed the signing ceremony.
2024-07-30 - 1:56:09 PM GMT

Document e-signed by PPD
PPD
Signing reason: I am the approver
Signature Date: 2024-07-30 - 1:56:11 PM GMT - Time Source: server- IP address: PPD

Document emailed to PPD
PPD for signature

2024-07-30 - 1:56:13 PM GMT

Email viewed by PPD

2024-07-31 - 3:11:41 AM GMT- IP address PPD

PPD authenticated with Adobe Acrobat Sign.

Challenge: The user completed the signing ceremony.

2024-07-31 - 3:14:11 AM GMT

Document e-signed by PPD
PPD

Signing reason: I am the approver
Signature Date: 2024-07-31 - 3:14:14 AM GMT - Time Source: server- IP address: PPD

Agreement completed.

2024-07-31 - 3:14:14 AM GMT

hmp-2020-013-00us3-7015654-statistical analysis plan v2.0 Final 29Jul2024

Final Audit Report 2024-07-31

Created:	2024-07-31
By:	PPD
Status:	Signed
Transaction ID:	PPD

"hmp-2020-013-00us3-7015654-statistical analysis plan v2.0 Final 29Jul2024" History

Document digitally presigned by Adobe Acrobat Sign (acrobat-sign-certified@adobe.com)
2024-07-31 - 6:55:50 AM GMT- IP address: PPD

Document created by PPD
2024-07-31 - 11:33:57 AM GMT- IP address: PPD

Signer PPD entered name at signing as PPD
2024-07-31 - 11:35:12 AM GMT- IP address: PPD

PPD authenticated with Adobe Acrobat Sign.
Challenge: The user completed the signing ceremony.
2024-07-31 - 11:35:13 AM GMT

Document e-signed by PPD
Signing reason: Approved
Signature Date: 2024-07-31 - 11:35:14 AM GMT - Time Source: server- IP address: PPD

Document emailed to PPD for signature
2024-07-31 - 11:35:16 AM GMT

Email viewed by PPD
2024-07-31 - 12:00:25 PM GMT- IP address: PPD

PPD authenticated with Adobe Acrobat Sign.
Challenge: The user opened the agreement.
2024-07-31 - 12:00:52 PM GMT

PPD authenticated with Adobe Acrobat Sign.

Challenge: The user completed the signing ceremony.

2024-07-31 - 12:01:37 PM GMT

Document e-signed by PPD

Signing reason: Approved

Signature Date: 2024-07-31 - 12:01:38 PM GMT - Time Source: server- IP address: PPD

Document emailed to PPD for signature

2024-07-31 - 12:01:41 PM GMT

Email viewed by PPD

2024-07-31 - 12:03:09 PM GMT- IP address: PPD

PPD authenticated with Adobe Acrobat Sign.

Challenge: The user opened the agreement.

2024-07-31 - 12:03:39 PM GMT

Document e-signed by PPD

Signing reason: Approved

Signature Date: 2024-07-31 - 12:04:14 PM GMT - Time Source: server- IP address: PPD

Agreement completed.

2024-07-31 - 12:04:14 PM GMT

PPD authenticated with Adobe Acrobat Sign.

Challenge: The user completed the signing ceremony.

2024-07-31 - 12:04:14 PM GMT