Title: A Phase 2, Open-Label, Single-Arm Study of Cabozantinib in Japanese Patients With Advanced Renal Cell Carcinoma That Has Progressed After Prior VEGFR Tyrosine Kinase Inhibitor Therapy

NCT Number: NCT03339219

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# STATISTICAL ANALYSIS PLAN

## STUDY NUMBER: Cabozantinib-2001

A Phase 2, Open-Label, Single-Arm Study of Cabozantinib in Japanese Patients With Advanced Renal Cell Carcinoma That Has Progressed After Prior VEGFR Tyrosine Kinase Inhibitor Therapy

**PHASE 2**

Version**:** Final

Date**:** 29 June 2018

**Prepared by:**

PPD

Biostatistics, Takeda Development Center Japan

Based on:

Protocol Version: Amendment 2

Protocol Date: 23 March 2018

## 1.1 Approval Signatures

Electronic signatures can be found on the last page of this document.

## 2.0 TABLE OF CONTENTS

**LIST OF IN-TEXT TABLES**

## 3.0 LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | adverse event |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| AST | aspartate aminotransferase |
| BMI | body mass index |
| BUN | blood urea nitrogen |
| CBR | clinical benefit rate |
| CI | confidence interval |
| CR | complete response |
| CT | computerized tomography |
| CV | coefficient of variation |
| DBP | diastolic blood pressure |
| EBRT | external beam radiation therapy |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| EPO | erythropoietin |
| EQ-5D-5L | EuroQol Health questionnaire instrument |
| EQ VAS | EuroQol visual analogue scale |
| ESA | erythropoiesis stimulating agent |
| FAS | full analysis set |
| FKSI-19 | Functional Assessment of Cancer Therapy-Kidney Cancer Symptom Index |
| GCP | Good Clinical Practice |
| GGT | γ-glutamyl transferase (gamma-glutamyl transferase) |
| GI | gastrointestinal |
| HRQOL | health-related quality of life |
| ICF | informed consent form |
| IGRT | image-guided radiation therapy |
| IMRT | intensity-modulated radiation therapy |
| IRC | independent radiology committee |
| LDH | lactate dehydrogenase |
| LLN | lower limit of normal |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MET | hepatocyte growth factor receptor protein |
| MRI | magnetic resonance imaging |
| MSKCC | Memorial Sloan-Kettering Cancer Center |
| NCCN | National Comprehensive Cancer Network |
| ORR | objective response rate |
| OS | overall survival |

| | |
|---|---|
| PD | progressive disease |
| PD-1 | programmed death-1 |
| PD-L1/L2 | programmed death ligand 1/ ligand 2 |
| PFS | progression-free survival |
| PK | pharmacokinetic(s) |
| PPES | palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome) |
| PR | partial response |
| PS | performance status |
| PT | preferred term |
| PT/INR | prothrombin time international normalized ratio |
| PTE | pretreatment event |
| QD | once daily |
| QT | time interval in ECG reading |
| QTcF | corrected QT interval by the Fridericia formula |
| RBC | red blood cell |
| RCC | renal cell carcinoma |
| RECIST 1.1 | Response Evaluation Criteria In Solid Tumors Version 1.1 |
| RPLS | reversible posterior leukoencephalopathy syndrome |
| SBP | systolic blood pressure |
| SD | stable disease |
| SOC | system organ class |
| SRS | stereotactic radiosurgery |
| TEAEs | treatment-emergent adverse events |
| TKI | tyrosine kinase inhibitor |
| TSH | thyroid-stimulating hormone |
| ULN | upper limit of normal |
| UPCR | urine protein-to-creatinine ratio |
| VEGFR | vascular endothelial growth factor receptor |
| WBC | white blood cell |
| WHO | world health organization |
| XL184 | research name for investigational product cabozantinib |
| 2DXRT | conventional external beam radiation therapy |
| 3DCRT | 3-dimensional conformal radiation therapy |

# 4.0 OBJECTIVES

## 4.1 Primary Objective

The primary objective is to evaluate the efficacy of cabozantinib measured by IRC-assessed ORR in Japanese patients with advanced RCC that has progressed after prior VEGFR-TKI therapy.

## 4.2 Secondary Objectives

The secondary objectives are:

- To evaluate the efficacy of cabozantinib measured by IRC-assessed CBR in the patient population under study.
- To evaluate the efficacy of cabozantinib measured by IRC-assessed PFS in the patient population under study.
- To evaluate the efficacy of cabozantinib measured by OS in the patient population under study.
- To evaluate the safety of cabozantinib in the patient population under study.

## 4.3 Additional Objectives

The additional objectives are:

- To evaluate the efficacy of cabozantinib measured by investigator-assessed ORR, CBR and PFS, and by duration of radiographic response in the patient population under study.
- To characterize the plasma PK of cabozantinib in the patient population under study.
- To assess HRQOL by the NCCN-FKSI-19 and the EQ-5D-5L in the patient population under study.

## 4.4 Exploratory Objectives

CCI

[redacted]

## 4.5 Study Design

This is a phase 2, open-label, single arm study to evaluate the efficacy—as measured by ORR and other efficacy variables including CBR, PFS and OS—and safety, of cabozantinib in Japanese patients with advanced RCC that has progressed after prior VEGFR-TKI therapy.

*Screening Period*

Potential subjects will be screened to determine whether they meet the required eligibility criteria after informed consent. Qualifying screening assessments must be performed within 28 days before the first day of study drug administration (defined as Week 1 Day 1) unless otherwise specified.

*Treatment Period*

Subjects who meet all study eligibility criteria will receive cabozantinib 60 mg orally, QD in the fasted state (at least 2 hours after meal), preferably at bedtime. A patient is considered to be enrolled in the study when the first dose of cabozantinib has been administered.

Subjects will receive study treatment as long as they continue to experience clinical benefit in the opinion of the investigator or until there is unacceptable toxicity or need for subsequent systemic anticancer treatment, or until there are any other reasons for treatment discontinuation listed in the protocol. Treatment may continue after radiographic RCC progression per RECIST 1.1 as long as the investigator believes that the subject is still receiving clinical benefit from study treatment and that the potential benefit of continuing study treatment outweighs potential risks.

*Posttreatment Period*

A 30-day posttreatment followup visit for safety will occur 30 (+14) days after the last dose of study drug. Radiographic tumor assessments and HRQOL assessments will continue, regardless of whether study treatment is given, reduced, held or discontinued until the day of the last tumor imaging assessment. Subjects will be contacted every 8 weeks (±7 days) after the 30-day posttreatment followup visit to assess survival status and document receipt of subsequent anticancer therapy, and will continue until death, withdrawal of consent, or the sponsor decision to discontinue data collection.

## 5.0 ANALYSIS ENDPOINTS

*Primary Endpoint*

- ORR, per RECIST 1.1, by IRC

*Secondary Endpoints*

- CBR, per RECIST 1.1, by IRC
- PFS, per RECIST 1.1, by IRC
- Safety
  - Percentage of subjects with TEAEs
  - Percentage of subjects with Grade 3 or higher TEAEs
  - Percentage of subjects with serious TEAEs
  - Percentage of subjects with permanent discontinuation by TEAEs
  - Percentage of subjects with dose modification (dose reduction or interruption) by TEAEs
  - Percentage of subjects with clinically significant abnormal laboratory values
  - Percentage of subjects with clinically significant abnormal vital sign measurements
- OS

*Additional Endpoints*

- ORR, per RECIST 1.1, by investigator
- CBR, per RECIST 1.1, by investigator
- PFS, per RECIST 1.1, by investigator
- Duration of radiographic response
- Plasma concentrations of cabozantinib
- Changes in kidney cancer-related symptoms as assessed by the NCCN-FKSI-19
- Changes in mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and global health as assessed by the EQ-5D-5L

*Exploratory Endpoints*

CCI [redacted]

CCI

[redacted]

## 6.0 DETERMINATION OF SAMPLE SIZE

A study with 32 subjects will provide at least 80% power of binomial test to detect an ORR ≥17% when testing a null hypothesis of ORR ≤3% at 1-sided significance level of 5%.

In Study XL184-308, the ORR by IRC was 17% (95% CI: [13, 22]%) and 3% (95% CI: [2, 6]%) in cabozantinib and everolimus group, respectively. In reference to the above results, an ORR of 17% is assumed and the threshold is set at 3% in this study.

Assuming a 10% dropout rate, approximately 35 subjects will be enrolled.

# 7.0 METHODS OF ANALYSIS AND PRESENTATION

## 7.1 General Principles

### 7.1.1 Study Definitions

The following definitions and calculation formulas will be used.

- Descriptive statistics: Number of subjects, mean, standard deviation, maximum, minimum, and quartiles
- BMI ($kg/m^2$): Weight (kg) / height $(m)^2$
- MSKCC Risk Factors: Risk factors are the following:
  - Karnofsky PS <80%
  - Hemoglobin <13 g/dL for males and <11.5 g/dL for females
  - Corrected calcium >10 mg/dL
- Heng Criteria: Subjects will be categorized into three risk categories of favorable (no risk factors), intermediate (1 or 2 risk factors) or poor (3 to 6 risk factors) based on the following risk factors:
  - Karnofsky PS <80%
  - Time from initial diagnosis of RCC to initial VEGFR-TKI for RCC <1 year
  - Hemoglobin <LLN
  - Corrected calcium >10 mg/dL
  - Neutrophils/WBC >75%
  - Platelet count >ULN
- Neutrophil-Lymphocyte Ratio: ANC (/μL) / lymphocytes (/μL)
- Prior Nephrectomy: Prior nephrectomy is defined as surgeries/procedures performed prior to baseline and recorded on the eCRF as partial nephrectomy, simple nephrectomy, radical nephrectomy, or other surgeries/procedures which contain the term "nephrectomy."
- Medical History: Any disease recorded on the eCRF "Medical History/Medical Conditions" page whose status at informed consent is "Resolved."
- Concurrent Medical Conditions: Any disease recorded on the eCRF "Medical History/Medical Conditions" page whose status at informed consent is "Ongoing."
- Prior Anticancer Therapy: Anticancer therapy (including medication, radiation and surgery/procedure) that started and stopped prior to baseline.
- Concomitant Medication: Concomitant medication is defined as medication used during the period from the time of the signing of ICF through 30 days after the last dose of study drug

- Concomitant and Subsequent VEGFR-TKI Agent: Medications whose preferred name coded by WHO Drug dictionary is AXITINIB, LENVATINIB, PAZOPANIB, SORAFENIB, SUNITINIB or TIVOZANIB
- Agent Targeting PD-1, PD-L1/L2: Medications whose preferred name coded by WHO Drug dictionary is ATEZOLIZUMAB, AVELUMAB, DURVALUMAB, NIVOLUMAB or PEMBROLIZUMAB
- Concomitant and Subsequent Anticancer Chemotherapy: Medications whose preferred name coded by WHO Drug dictionary is CAPECITABINE, CARBOPLATIN, CISPLATIN, CYCLOPHOSPHAMIDE, FLUOROURACIL, GEMCITABINE, IXABEPILONE, MELPHALAN, VINBLASTINE or TEGAFUR;URACIL
- Duration of Exposure to Study Drug (weeks): (Date of decision to discontinue study drug – date of the first dose of study drug + 1) / 7 if date of decision to discontinue study drug is non-missing; otherwise (Date of data cutoff – date of the first dose of study drug + 1) / 7
- Average Daily Dose (mg): Total dose received (mg) / duration of exposure to study drug (days)
- Dose Intensity (%): 100 * average daily dose (mg) / 60 mg
- Dose Modification: Dose reduction or interruption
- CV (%): Standard deviation / mean * 100
- TEAE: An AE whose date of onset occurs on or after the start of study drug and within 30 days after the last dose of study drug
- PTE: Any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of study drug
- Toxicity Grade of 0 for Laboratory Parameters: Grade 0 will be assigned to non-missing values that do not meet the criteria for Grade 1 or higher in the direction of interest
- Treatment for Anemia: The definition of treatment for anemia is given in Appendix

### 7.1.2 Definition of Study Days

The following definitions and calculation formulas will be used.

- Study Day: The day before the first dose of the study drug will be defined as Study Day -1 and the day of the first dose will be defined as Study Day 1. When calculating Study Day relative to a reference date (i.e., date of first dose [Study Day 1]), if the date of the observation is on the same date or after the reference date, it will be calculated as: date of observation - reference date + 1; otherwise, it will be calculated as: date of observation - reference date. There is no Study Day 0. Month and year are operationally defined to be 30.4375 days and 365.25 days, respectively.

- Followup Day: The day after the last dose of study drug will be defined as Followup Day 1. When calculating Followup Day relative to a reference date (i.e., date of last dose [Followup Day 0]), it will be calculated as: date of observation - reference date.

### 7.1.3 Definition of Study Visit Windows

All evaluable data will be handled according to the following rules.

For each visit, observation obtained in the corresponding time interval will be used. If more than one observation lies within the same visit window, the observation with the closest Study Day to the scheduled Study Day will be used. If there are two observations equidistant to the scheduled Study Day, the later observation will be used.

Specifically, the last observation before the first dose of the study drug will be considered the baseline measurement.

**Table 7.a Visit Window for Endpoints Other Than Plasma Concentrations of Cabozantinib**

| Visit | Scheduled Study Day | Time Interval | |
|---|---|---|---|
| | | Study Day | Follow-up Day |
| Baseline | Study Day: 1 | <= 1 | |
| Week X Day 1 | Study Day: 7 * (X - 1) + 1 | • Week 3 – Week 9: Scheduled Study Day ±5<br>• Week 9 Beyond: Scheduled Study Day ±7 | <30 |
| 30-Day Posttreatment Followup | Followup Day: 30 | | 30 - 44 |

**Table 7.b Visit Window for Plasma Concentrations of Cabozantinib**

| Visit/Time point | Scheduled Study Day | Time Interval | |
|---|---|---|---|
| | | Study Day | Time from Previous Dose of Study Drug |
| Week 1 Day 1 Predose | Study Day: 1 | 1 | Before the First Dose |
| Week 1 Day 1 3 Hours Postdose | Study Day: 1 | 1 | 2.5 – 3.5 Hours |
| Week 3 Day 1 | Study Day: 15 | Scheduled Study Day ±2 | >7 Hours |
| Week 5 Day 1 | Study Day: 29 | Scheduled Study Day ±2 | >7 Hours |
| Week 9 Day 1 | Study Day: 57 | Scheduled Study Day ±2 | >7 Hours |

### 7.1.4 Significance Level and Confidence Coefficient

- Confidence coefficient:
  - Analyses for ORR: 90% (two-sided)
  - Analyses for other endpoints: 95% (two-sided)

### 7.1.5 Conventions for Missing Adverse Event Dates

Not applicable.

### 7.1.6 Conventions for Missing Concomitant Medication Dates

Not applicable.

### 7.1.7 Imputation of Other Incomplete Dates

- Incomplete initial diagnosis date of RCC
  - If day and month are missing, set to July 1st
  - If only day is missing, set to 15th of the month
  - If either imputation rule above results in diagnosis date >date of informed consent, set to date of informed consent – 1
- Incomplete start date of prior anticancer therapy (including date of prior surgery/procedure)
  - If month and day are missing, set to January 1st
  - If only day is missing, set to 1st day of the month
- Incomplete end date of prior anticancer therapy
  - If month and day are missing, set to December 31st
  - If only day is missing, set to last day of the month
  - If either imputation rule above results in end date >date of informed consent, set to date of informed consent – 1 (assuming the start date of the prior anticancer therapy <date of informed consent)
- Incomplete start date of concomitant and subsequent non-radiation anticancer therapy
  - If month and day are missing, set to January 1st if year of the start date of the anticancer therapy >year of the last dose of study drug; set to date of the last dose + 1 if year of the start date of the anticancer therapy = year of the last dose of study drug
  - If only day is missing, set to 1st day of the month if the resulting imputed date >date of the last dose of study drug; otherwise set to date of the last dose + 1
  - * If PD date per RECIST 1.1 is available and after the last dose of study drug, replace the date of the last dose of study drug with the PD date for the above imputation algorithm

## 7.2 Analysis Sets

- FAS:
  All subjects who received at least one dose of study drug
- Response-evaluable analysis set:
  All FAS subjects with measurable disease at baseline, and at least one postbaseline tumor assessment
- Safety analysis set:
  All subjects who received at least one dose of study drug

## 7.3 Disposition of Subjects

### 7.3.1 Study Information

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variables:

Date First Subject Signed Informed Consent Form

Date of Data Cutoff

MedDRA Version

WHO Drug Version

SAS Version Used for Creating the Datasets

Analytical Methods:

(1) Study Information

Study information shown in the analysis variables section will be provided.

### 7.3.2 Screen Failures

Analysis Set:

All Subjects Not Enrolled into the Treatment Period

Analysis Variables:

Age (years)

Gender [Male, Female]

Analytical Methods:

(1) Screen Failures

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

### 7.3.3 Subject Eligibility

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variables:

Enrollment Status

[Enrolled into the Treatment Period, Not Enrolled into the Treatment Period]

Primary Reason for Subject Not Being Enrolled

[Death, AE, Clinical Deterioration, Protocol Deviation, Study Terminated by Sponsor, Pregnancy, Withdrawal by Subject, Lost to Follow-up, Physician Decision, Screen Failure, Other]

Analytical Methods:

(1) Enrollment into the Treatment Period

Frequency distributions will be provided. When calculating percentages for the primary reasons for subject not being enrolled, the total number of not enrolled subjects will be used as the denominator.

### 7.3.4 Number of Subjects Enrolled into the Treatment Period by Site

Analysis Set:

All Subjects Enrolled into the Treatment Period

Analysis Variables:

Status of Enrollment into the Treatment Period [Enrolled]

Stratum:

Site [Site numbers will be used as categories]

Analytical Methods:

(1) Number of Subjects Enrolled into the Treatment Period by Site

Frequency distributions will be provided for each stratum.

### 7.3.5 Disposition of Subjects

Analysis Set:

All Subjects Enrolled into the Treatment Period

Analysis Variables:

Study Drug Administration Status

[Not Treated]

Reason for Not Being Treated

[Death, AE, Clinical Deterioration, Protocol Deviation, PD, Lack of Efficacy, Study Terminated by Sponsor, Pregnancy, Withdrawal by Subject, Lost to Follow-up, Physician Decision, Other]

Study Drug Administration Status

[Receiving Study Drug, Discontinued Study Drug]

Reason for Discontinuation of Study Drug

[Death, AE, Clinical Deterioration, Protocol Deviation, PD, Lack of Efficacy, Study Terminated by Sponsor, Pregnancy, Withdrawal by Subject, Lost to Follow-up, Physician Decision, Other]

Status of the Posttreatment Period

[Remaining in Posttreatment Period, Discontinued Posttreatment Period]

Reason for Discontinuation of the Posttreatment Period

[Death, Study Terminated by Sponsor, Withdrawal by Subject, Lost to Follow-up, Other]

Analytical Methods:

(1) Disposition of Subjects

Frequency distributions will be provided. When calculating percentages for the reasons for not being treated, the total number of subjects not treated by the study drug will be used as the denominator. When calculating percentages for the reasons for discontinuation, the total number of subjects who discontinued will be used as the denominator.

### 7.3.6 Protocol Deviations and Analysis Sets

*7.3.6.1 Protocol Deviations*

Analysis Set:

All Subjects Enrolled into the Treatment Period

Analysis Variables:

Significant Protocol Deviation

[Entry Criteria, Concomitant Medication, Procedure Not Performed Per Protocol, Study Medication, Withdrawal Criteria, Major GCP Violations]

Analytical Methods:

(1) Protocol Deviations

Frequency distributions will be provided for each deviation category. A subject who has several deviations will be counted once in each appropriate category. A subject who has several deviations that can be classified into the same category will be counted only once.

*7.3.6.2 Analysis Sets*

Analysis Set:

All Subjects Enrolled into the Treatment Period

Analysis Variables:

Analysis Sets

| | |
|---|---|
| Full Analysis Set | [Included] |
| Response-Evaluable Analysis Set | [Included] |
| Safety Analysis Set | [Included] |

Analytical Methods:

(1) Analysis Sets

Frequency distributions will be provided.

## 7.4 Demographic and Other Baseline Characteristics

Analysis Set:

Full Analysis Set

Analysis Variables:

Age (years) [Min<= - <65, 65<= - <=Max]

[Min<= - <75, 75<= - <=Max]

[Min<= - <65, 65<= - <75, 75<= - <85, 85<= - <=Max]

Gender [Male, Female]

Height (cm)

Weight (kg) at Baseline

[Min<= - <60, 60<= - <=80, 80<- <=Max]

BMI ($kg/m^2$) at Baseline

[Min<= - <18.5, 18.5<= - <25.0, 25.0<= - <30.0, 30.0<= - <=Max]

Time from Initial Diagnosis of RCC to Enrollment (years)

[Min<= - <1, 1<= - <=Max]

Time from Radiographic Progression after Most-Recent VEGFR-TKI to Enrollment (months)

[Min<= - <3, 3<= - <=Max]

Current Disease Stage

[Stage IV, Stage III, Unknown]

Extent of Baseline Disease per IRC

| | |
|---|---|
| Bone (CT or MRI) | [Yes] |
| Lung | [Yes] |
| Liver | [Yes] |
| Lung or Liver | [Yes] |
| Lung or Liver, and Bone (CT or MRI) | [Yes] |
| Brain | [Yes] |
| Lymph Node | [Yes] |
| Kidney | [Yes] |
| Other | [Yes] |

Number of Involved Organs per IRC at Baseline

[1, 2, 3<= <=Max]

Sum of Diameters of Target Lesions (mm) per IRC at Baseline

MSKCC Risk Factors at Baseline

[0, 1, 2 or 3]

Heng Criteria at Baseline

[Favorable, Intermediate, Poor]

Karnofsky PS (%)

[Min<= - <70, 70, 80, 90, 100]

[Min<= - <80, 80<= - <=Max]

ECOG PS at Baseline

[0, 1, 2, 3, 4]

Time from Initial Diagnosis of RCC to Initial VEGFR-TKI for RCC (years)

[Min<= - <1, 1<= - <=Max]

Hemoglobin (g/dL) at Baseline

[Min<= - <13 for Males or 11.5 for Females, 13 for Males or 11.5 for Females <= - <=Max]

[Min<= - <LLN, LLN<= - <=Max]

Corrected Calcium (mg/dL) at Baseline

[Min<= - <=10, 10<- <=Max]

Neutrophils/WBC (%) at Baseline

[Min<= - <=75, 75<- <=Max]

Platelet Count ($10^4$/μL) at Baseline

[Min<= - <=ULN, ULN<- <=Max]

LDH (U/L) at Baseline

[Min<= - <=ULN, ULN<- <=Max]

Neutrophil-Lymphocyte Ratio at Baseline

Prior Nephrectomy

[Yes, No]

Analytical Methods:

(1) Summary of Demographics and Baseline Characteristics

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

## 7.5 Medical History and Concurrent Medical Conditions

Analysis Set:

Safety Analysis Set

Analysis Variables:

Medical History

Concurrent Medical Conditions

Analytical Methods:

(1) Medical History by System Organ Class and Preferred Term

(2) Concurrent Medical Conditions by System Organ Class and Preferred Term

Frequency distributions will be provided. MedDRA dictionary will be used for coding. Summaries will be provided using SOC and PT, where SOC will be sorted alphabetically and PT will be sorted in decreasing frequency.

A subject with multiple occurrences of medical history or concurrent medical condition within a SOC will be counted only once in that SOC. A subject with multiple occurrences of medical history or concurrent medical condition within a PT will be counted only once in that PT.

## 7.6 Medication History and Concomitant Medications

Analysis Set:

Safety Analysis Set

Analysis Variables:

Prior Non-Radiation Anticancer Therapy

Concomitant Medications

Concomitant and Subsequent Non-Radiation Anticancer Therapy

Analytical Methods:

(1) Prior Non-Radiation Anticancer Therapy by Preferred Medication Name

(2) Concomitant Medications That Started Prior to and Were Ongoing at Baseline as well as Those That Started After Baseline by Preferred Medication Name

(3) Concomitant and Subsequent Non-Radiation Anticancer Therapy That Started After Baseline by Preferred Medication Name

(4) Concomitant and Subsequent Non-Radiation Anticancer Therapy That Started Prior to and Were Ongoing at Baseline as well as Those That Started After Baseline by Preferred Medication Name

Frequency distributions will be provided. WHO Drug dictionary will be used for coding. Summaries will be provided using preferred medication names and sorted in decreasing frequency based on the number of reports.

A subject who has been administered several medications with the same preferred medication name will be counted only once for that medication name.

## 7.7 Prior Surgery and Procedure

Analysis Set:

Safety Analysis Set

Analysis Variables:

| | |
|---|---|
| Prior Surgery/Procedure | [Yes, No] |
| Prior Surgery Type | |
| Partial Nephrectomy | [Yes] |
| Simple Nephrectomy | [Yes] |
| Partial or Simple Nephrectomy | [Yes] |
| Radical Nephrectomy | [Yes] |
| Other | [Yes] |
| History of Surgical/Procedural Wound Healing Complications | [Yes, No] |

Analytical Methods:

(1) Prior Surgery and Procedure

Frequency distributions will be provided.

## 7.8 Prior Non-Surgical Anticancer Therapy

Analysis Set:

Safety Analysis Set

Analysis Variables:

Number of Prior Systemic Non-Radiation Anticancer Agent

Number of Prior VEGFR-TKI Agent

[1, 2<= - <=Max]

[1, 2, 3<= - <=Max]

Type of Prior VEGFR-TKI Agent

| | |
|---|---|
| Sunitinib | [Yes] |
| Sunitinib Only | [Yes] |
| Sorafenib | [Yes] |
| Sorafenib Only | [Yes] |
| Pazopanib | [Yes] |

Pazopanib Only [Yes]

Axitinib [Yes]

Axitinib Only [Yes]

Other VEGFR-TKI Agent [Yes]

First VEGFR-TKI Treatment Duration (months)

[Min<= - <=6, 6<- <=Max]

Prior Treatment with Agent Targeting PD-1, PD-L1/L2

[Yes, No]

Prior Radiation Therapy

[Yes, No]

Number of Prior Radiation Therapy Types

Type of Prior Radiation Therapy

EBRT [Yes]

SRS [Yes]

2DXRT [Yes]

3DCRT [Yes]

IGRT [Yes]

IMRT [Yes]

Proton-Therapy [Yes]

Other [Yes]

Brachytherapy [Yes]

Radioisotope Therapy [Yes]

Analytical Methods:

(1) Prior Non-Surgical Anticancer Therapy

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

## 7.9 Concomitant and Subsequent Anticancer Therapy

Analysis Set:

Safety Analysis Set

Analysis Variables:

| | |
|---|---|
| Concomitant and Subsequent Non-Surgical Anticancer Therapy | [Yes, No] |
| Concomitant and Subsequent Non-Surgical Non-Radiation Anticancer Therapy | [Yes, No] |
| Systemic | [Yes] |
| Palliative | [Yes] |
| Salvage | [Yes] |
| Unknown | [Yes] |
| Local | [Yes] |
| Palliative | [Yes] |
| Salvage | [Yes] |
| Unknown | [Yes] |
| VEGFR-TKI Agent | [Yes] |
| Agent Targeting PD-1, PD-L1/L2 | [Yes] |
| Chemotherapy | [Yes] |
| Concomitant and Subsequent Radiation Therapy | [Yes, No] |
| Indication | |
| Disease under Study | [Yes] |
| Other | [Yes] |
| Therapy Type | |
| EBRT | [Yes] |
| SRS | [Yes] |
| 2DXRT | [Yes] |
| 3DCRT | [Yes] |
| IGRT | [Yes] |
| IMRT | [Yes] |
| Proton-Therapy | [Yes] |
| Other | [Yes] |
| Brachytherapy | [Yes] |

Radioisotope Therapy [Yes]

Site

Bone [Yes]

Soft Tissue [Yes]

Systemic [Yes]

Unknown [Yes]

Surgery that Impacted Tumor Lesions [Yes]

Analytical Methods:

(1) Concomitant and Subsequent Anticancer Therapy After Enrollment

For concomitant and subsequent anticancer therapies taken/performed during the treatment period, frequency distributions will be provided.

## 7.10 Study Drug Exposure and Compliance

Analysis Set:

Safety Analysis Set

Analysis Variables:

Duration of Exposure to Study Drug (weeks)

Average Daily Dose (mg)

Dose Intensity (%)

Analytical Methods:

(1) Study Drug Exposure and Compliance

Descriptive statistics for continuous variables will be provided.

## 7.11 Dose Modification

Analysis Set:

Safety Analysis Set

Analysis Variables:

Dose Reduction

Any Dose Reduction Due to AE [Yes, No]

Dose Level Received

60 mg [Yes]

40 mg Due to AE [Yes]

20 mg Due to AE [Yes]

Lowest Dose Level Received Due to AE (Excluding Dose Interruption) (mg)
[20, 40, 60]

Last Dose Level Received (Excluding Dose Interruption) (mg)
[20, 40, 60]

Last Dose Level Received (Including Dose Interruption) (mg)
[0, 20, 40, 60]

Total Duration of Treatment (days) at:

More than 0 mg

60 mg

40 mg

20 mg

0 mg

Time to 1st Dose Reduction Due to AE from the First Dose of Study Drug (days)

Time to 2nd Dose Reduction Due to AE from the First Dose of Study Drug (days)

Dose Interruption

Any Dose Interruption Due to AE [Yes, No]

Dose Interruption ≥7 days Due to AE [Yes]

Dose Interruption ≥14 days Due to AE [Yes]

Dose Interruption ≥21 days Due to AE [Yes]

Number of Dose Interruption Due to AE

Total Duration of Dose Interruption Due to AE (days)

Time to 1st Dose Interruption Due to AE from the First Dose of Study Drug (days)

Time to 1st Dose Interruption ≥7 days Due to AE from the First Dose of Study Drug (days)

Time to 1st Dose Interruption ≥14 days Due to AE from the First Dose of Study Drug (days)

Time to 1st Dose Interruption ≥21 days Due to AE from the First Dose of Study Drug (days)

Time to 2nd Dose Interruption Due to AE from the First Dose of Study Drug (days)

Time to 2nd Dose Interruption ≥7 days Due to AE from the First Dose of Study Drug (days)

Time to 2nd Dose Interruption ≥14 days Due to AE from the First Dose of Study Drug (days)

Time to 2nd Dose Interruption ≥21 days Due to AE from the First Dose of Study Drug (days)

Dose Modification

Any Dose Modification Due to AE [Yes, No]

Number of Dose Modification Due to AE

Time to 1st Dose Modification Due to AE from the First Dose of Study Drug (days)

Time to 2nd Dose Modification Due to AE from the First Dose of Study Drug (days)

Analytical Methods:

(1) Dose Modification

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

## 7.12 Efficacy Analysis

### 7.12.1 Primary Endpoint

Analysis Set:

FAS

Response-Evaluable Analysis Set

Analysis Variables:

ORR, per RECIST 1.1, by IRC

ORR is defined as proportion of subjects whose best overall response is CR or PR per RECIST 1.1, which is confirmed by a subsequent evaluation conducted ≥28 days later.

Only the results of tumor assessment conducted on or prior to the earlier of the date of PFS event or date of censoring for PFS by IRC, described in 7.12.2 Secondary Endpoints, will be used in order to determine the best overall response. Assessments performed <51 days after the first day of study drug administration will not be considered in the determination of best overall response unless i) PD is identified or ii) CR or PR is identified and subsequently confirmed ≥28 days later.

The response results are ranked as: confirmed CR, confirmed PR, SD, PD and not evaluable. If a subject has multiple response results, then use the best response results according to this ranking as the subject's best overall response.

Analytical Methods:

(1) Primary Analysis

The following analyses will be conducted using the FAS.

Best overall response, per RECIST 1.1, by IRC will be summarized using the categories of Confirmed CR, Confirmed PR, SD, PD, Not Evaluable and Missing. The result of Missing means that the subject has no qualifying post baseline assessment for overall response.

For ORR, per RECIST 1.1, by IRC, point estimate and the 2-sided 90% exact CI will be provided.

A waterfall plot of best percent change in target lesion size by IRC will be presented.

Time to tumor response (months), which is defined as time from the first day of study drug administration to the first confirmed CR or confirmed PR per RECIST 1.1 by IRC, will be summarized using the descriptive statistics for the subjects with confirmed CR or confirmed PR in the FAS.

(2) Secondary Analysis

The same analyses as those in the primary analysis for best overall response, per RECIST 1.1, by IRC and ORR, per RECIST 1.1, by IRC will be conducted using the response-evaluable analysis set.

### 7.12.2 Secondary Endpoints

Analysis Set:

FAS

Response-Evaluable Analysis Set

Analysis Variables:

CBR, per RECIST 1.1 by IRC

CBR is defined as proportion of subjects whose best overall response is CR, PR or SD per RECIST 1.1. CR and PR require confirmation by a subsequent evaluation conducted ≥28 days later, and assessment of SD have to be made at least 8 weeks (≥51 days) after the first day of study drug administration. CBR will be determined using the same data as those used in the determination of ORR.

PFS, per RECIST 1.1, by IRC

PFS is defined as time from the first day of study drug administration to the earlier of progressive disease per RECIST 1.1 or death due to any cause. PFS will be expressed in months, i.e. PFS = (earliest date of progression or death – date of the first day of study drug administration + 1) / 30.4375.

Only adequate tumor assessments (overall response of CR, PR, SD or PD) will be considered in the determination of progression and censoring date. General censoring rules for the analysis of PFS will be as follows:

- Subjects who have not experienced an event at the time of data cutoff will be censored at the date of the last adequate tumor assessment.
- Subjects who receive subsequent anticancer therapy (including radiation other than to bone) before experiencing an event will be censored at the date of the last adequate tumor assessment on or prior to the date of initiation of the subsequent treatment.
- Subjects who receive tumor resection surgery after enrollment before experiencing an event will be censored at the date of the last adequate tumor assessment on or prior to the date of the surgery.
- Subjects who miss 2 or more consecutive adequate scheduled tumor assessments (operationally defined as an interval of >18 weeks without an adequate assessment throughout the first 12 months and >26 weeks thereafter) immediately followed by an event will be censored at the date of the last adequate tumor assessment prior to the missing/inadequate assessments.
  - If the 2 or more consecutive missing adequate assessments are immediately followed by an adequate assessment with an overall response assignment of SD, PR, or CR, this will be deemed sufficient clinical evidence that progression did not occur during the period of missing data and the missing evaluations will be ignored.

OS

Overall survival is defined as time from the first day of study drug administration to death due to any cause. OS will be expressed in months, i.e. OS = (date of death – date of the first day of study drug administration + 1) / 30.4375.

Subjects who have not experienced an event at the time of data cutoff will be censored at the earlier of the data cutoff or the last date when the subjects are known to be alive.

Analytical Methods:

(1) CBR, per RECIST 1.1, by IRC

For CBR, per RECIST 1.1, by IRC, point estimate and the 2-sided 95% exact CI will be provided using the FAS.

Similar analysis using the response-evaluable analysis set will also be conducted.

(2) PFS, per RECIST 1.1, by IRC

The following analyses will be conducted using the FAS.

For PFS, per RECIST 1.1, by IRC, breakdown of the number of subjects who were censored and who experienced an event will be summarized. Quartiles of PFS will be estimated using the Kaplan-Meier method. Kaplan-Meier estimate of PFS proportion at 6, 12, 18 and 24 months will also be provided.

The Kaplan-Meier plot of PFS will be presented.

(3) OS

For OS, the same analyses as those for PFS will be conducted using the FAS.

### 7.12.3 Additional Endpoints

*7.12.3.1 ORR, CBR and PFS by Investigator*

Analysis Set:

FAS

Analysis Variables:

ORR, per RECIST 1.1, by Investigator

CBR, per RECIST 1.1 by Investigator

PFS, per RECIST 1.1, by Investigator

Analytical Methods:

(1) ORR, per RECIST 1.1, by Investigator

The same analyses as those for ORR, per RECIST 1.1, by IRC in 7.12.1 (1) Primary Analysis will be conducted.

(2) CBR, per RECIST 1.1 by Investigator

The same analyses as those for CBR, per RECIST 1.1, by IRC in 7.12.2 (1) CBR, per RECIST 1.1, by IRC will be conducted using the FAS.

(3) PFS, per RECIST 1.1, by Investigator

The same analyses as those for PFS, per RECIST 1.1, by IRC in 7.12.2 (2) PFS, per RECIST 1.1, by IRC will be conducted.

*7.12.3.2 Duration of Radiographic Response*

Analysis Set:

FAS

Analysis Variables:

Duration of Radiographic Response, per RECIST 1.1, by IRC

Duration of Radiographic Response, per RECIST 1.1, by Investigator

Duration of radiographic response is defined as time from the first confirmed CR or confirmed PR to the earlier of progressive disease per RECIST 1.1 or death due to any cause. Duration of radiographic response will be expressed in months, i.e. duration of radiographic response = (earliest date of progression or death – date of the first confirmed CR or confirmed PR + 1) / 30.4375.

Only adequate tumor assessments will be considered in the determination of progression and censoring date. The same censoring rules as those in the PFS analysis will be applied.

Analytical Methods:

(1) Duration of Radiographic Response, per RECIST 1.1, by IRC

(2) Duration of Radiographic Response, per RECIST 1.1, by Investigator

The same analyses as those in 7.12.2 (2) PFS, per RECIST 1.1, by IRC will be conducted for the subjects with confirmed CR or confirmed PR in the FAS.

*7.12.3.3 Concordance of Tumor Assessment Result*

Analysis Set:

FAS

Analysis Variables:

Concordance between IRC and Investigator Tumor Assessment Results

Disease Progression Status

[IRC: Yes and Investigator: Yes, IRC: Yes and Investigator: No, IRC: No and Investigator: Yes, IRC: No and Investigator: No]

[Concordant, Discordant]

Disease Progression Date

[Concordant, Discordant]

Response Status

[IRC: Yes and Investigator: Yes, IRC: Yes and Investigator: No, IRC: No and Investigator: Yes, IRC: No and Investigator: No]

[Concordant, Discordant]

Response Date

[Concordant, Discordant]

Analytical Methods:

(1) Concordance between IRC and Investigator Tumor Assessment Results

For disease progression status and response status, frequency distributions will be provided using the FAS, where response status of Yes means that a subject had at least one overall response assignment of CR or PR (confirmation is not necessary).

For disease progression date and response date, frequency distributions will be provided for the subjects in the FAS whose disease progression/response status by both IRC and investigator is Yes.

*7.12.3.4 Plasma Concentrations of Cabozantinib*

Analysis Set:

FAS

Analysis Variables:

Plasma Concentrations of Cabozantinib

Visit/Timepoint:

Week 1 Day 1 (Predose), Week 1 Day 1 (3 hr Postdose), Week 3 Day 1, Week 5 Day 1, Week 9 Day 1

Analytical Methods:

(1) Plasma Concentrations of Cabozantinib

Descriptive statistics and CV will be provided for each visit/timepoint.

The same analysis will be provided for subjects in the FAS who received cabozantinib 60 mg for at least 14 of 15 days immediately prior to the visit for Week 3 Day 1, Week 5 Day 1 and Week 9 Day 1.

*7.12.3.5 Health-Related Quality of Life Assessment*

Analysis Set:

FAS

Analysis Variables:

NCCN-FKSI-19

Total Score

Disease Related Symptoms – Physical Score

Disease Related Symptoms – Emotional Score

Treatment Side Effects Score

Function/Well-Being Score

Total score and subscale scores will be calculated in accordance with NCCN/FKSI-19 Scoring Guidelines (Version 4) if and only if more than 50% of the items for the score are non-missing

EQ-5D-5L

Mobility

[No Problem, Slight Problems, Moderate Problems, Severe Problems, Extreme Problems]

[No Problem, Slight Problems - Extreme Problems]

Self-Care

[No Problem, Slight Problems, Moderate Problems, Severe Problems, Extreme Problems]

[No Problem, Slight Problems - Extreme Problems]

Usual Activities

[No Problem, Slight Problems, Moderate Problems, Severe Problems, Extreme Problems]

[No Problem, Slight Problems - Extreme Problems]

Pain/Discomfort

[No Problem, Slight Problems, Moderate Problems, Severe Problems, Extreme Problems]

[No Problem, Slight Problems - Extreme Problems]

Anxiety/Depression

[No Problem, Slight Problems, Moderate Problems, Severe Problems, Extreme Problems]

[No Problem, Slight Problems - Extreme Problems]

EQ VAS Value for Your Health Today

EQ-5D-5L Index Value

EQ-5D-5L index values will be calculated using the value sets in Ikeda et al[1] if and only if all the 5 health state (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) are completed and non-missing

Visit:

Baseline, Week 5 Day 1, Week 9 Day 1, Every 4 weeks through Week 25, Every 8 Weeks Thereafter

Analytical Methods:

(1) Summary of Total and Subscale Scores of NCCN-FKSI-19 by Visit

Descriptive statistics and the two-sided 95% CI of the mean will be provided for each visit.

(2) Summary of Change from Baseline in Total and Subscale Scores of NCCN-FKSI-19 by Visit

Descriptive statistics and the two-sided 95% CI of the mean will be provided for each visit.

Mean changes from baseline will be plotted for each visit with standard deviation bars.

(3) Frequency Distributions for EQ-5D-5L Descriptive System

Frequency distributions will be provided for each of the 5-dimention descriptive system for each visit.

(4) Summary of EQ VAS and EQ-5D-5L Index Value by Visit

Descriptive statistics and the two-sided 95% CI of the mean will be provided for each visit.

(5) Summary of Change from Baseline in EQ VAS and EQ-5D-5L Index Value by Visit

Descriptive statistics and the two-sided 95% CI of the mean will be provided for each visit.

Mean changes from baseline will be plotted for each visit with standard deviation bars.

*7.12.3.6 Neutrophil-Lymphocyte Ratio*

Analysis Set:

FAS

Analysis Variables:

Neutrophil-Lymphocyte Ratio

ORR, per RECIST 1.1, by IRC

Subgroups:

For Baseline Neutrophil-Lymphocyte Ratio

| | |
|---|---|
| MSKCC Risk Factors at Baseline | [0, 1, 2 or 3] |
| Heng Criteria at Baseline | [Favorable, Intermediate, Poor] |

For ORR, per RECIST 1.1, by IRC

Percent Change from Baseline in Neutrophil-Lymphocyte Ratio (%) at Week 7 Day 1

[Min<= - <=-25.0, -25.0<- <25.0, 25.0<= - Max]

Visit:

Baseline, Week 3 Day 1, Week 5 Day 1, Week 7 Day 1, Week 9 Day 1, Every 4 Weeks Thereafter, 30-Day Posttreatment Followup

Analytical Methods:

(1) Summary of Neutrophil-Lymphocyte Ratio and Percent Change from Baseline by Visit

Descriptive statistics for observed values for each visit and percent changes from baseline will be provided.

(2) Relationship of Baseline Neutrophil-Lymphocyte Ratio with Other Prognostic Factors

Descriptive statistics of Baseline Neutrophil-Lymphocyte Ratio will be provided for the above each subgroup.

(3) Relationship of ORR, per RECIST 1.1, by IRC with Percent Change from Baseline in Neutrophil-Lymphocyte Ratio

Point estimate of ORR, per RECIST 1.1, by IRC and the 2-sided 90% exact CI will be provided for the above each subgroup. Subjects who progressed or died <38 days after the first day of study drug administration or who have missing percent change from baseline in neutrophil-lymphocyte ratio at Week 7 Day 1 will be excluded from this analysis.

### 7.12.4 Statistical/Analytical Issues

*7.12.4.1 Adjustments for Covariates*

Not applicable.

*7.12.4.2 Handling of Dropouts or Missing Data*

Missing test results will not be used for the analyses unless otherwise specified.

Values below the lower limit of quantification will be treated as zero when calculating the descriptive statistics. Values greater than or equal to the upper limit of quantification will be treated as the upper limit value when calculating the descriptive statistics.

*7.12.4.3 Multicenter Studies*

Not applicable.

*7.12.4.4 Multiple Comparison/Multiplicity*

Not applicable.

*7.12.4.5 Use of an "Efficacy Subset" of Subjects*

In addition to the analyses on the primary endpoint using the FAS, a secondary analysis will also be performed using the response-evaluable analysis set.

*7.12.4.6 Active-Control Studies Intended to Show Equivalence or Non-Inferiority*

Not applicable.

*7.12.4.7 Examination of Subgroups*

Analysis Set:

FAS

Analysis Variables:

ORR, per RECIST 1.1, by IRC

Subgroups:

| | |
|---|---|
| Age (years) | [Min<= - <65, 65<= - <=Max] |
| Gender | [Male, Female] |
| Time from Initial Diagnosis of RCC to Enrollment (years) | [Min<= - <1, 1<= - <=Max] |
| Time from Radiographic Progression after Most-Recent VEGFR-TKI to Enrollment (months) | [Min<= - <3, 3<= - <=Max] |
| Bone Metastases (CT or MRI) per IRC at Baseline | [Yes, No] |
| Lung Metastases per IRC at Baseline | [Yes, No] |
| Liver Metastases per IRC at Baseline | [Yes, No] |
| Lung or Liver Metastases per IRC at Baseline | [Yes, No] |
| Lung or Liver, and Bone Metastases (CT or MRI) per IRC at Baseline | [Yes, No] |
| Brain Metastases per IRC at Baseline | |

[Yes, No]

Number of Involved Organs per IRC at Baseline

[1, 2, 3<= - <=Max]

Sum of Diameters of Target Lesions (mm) per IRC at Baseline

[Min<= - <Median, Median<= - <=Max]

MSKCC Risk Factors at Baseline [0, 1, 2 or 3]

Heng Criteria at Baseline [Favorable, Intermediate, Poor]

ECOG PS at Baseline [0, 1, 2<= - <=Max]

Neutrophil-Lymphocyte Ratio at Baseline

[Min<= - <Median, Median<= - <=Max]

Prior Nephrectomy [Yes, No]

Number of Prior VEGFR-TKI Agent [1, 2<= - <=Max]

Only Prior VEGFR-TKI Sunitinib [Yes, No]

Only Prior VEGFR-TKI Pazopanib [Yes, No]

First VEGFR-TKI Treatment Duration (months)

[Min<= - <=6, 6<- <=Max]

Prior Treatment with Agent Targeting PD-1, PD-L1/L2

[Yes, No]

Analytical Methods:

(1) Subgroup Analysis for ORR, per RECIST 1.1, by IRC

Point estimate of ORR, per RECIST 1.1, by IRC and the 2-sided 90% exact CI will be provided for the above each subgroup.

## 7.13 Safety Analysis

### 7.13.1 Adverse Events

*7.13.1.1 Overview of Treatment-Emergent Adverse Events*

Analysis Set:

Safety Analysis Set

Analysis Variables:

TEAE

Categories:

| | |
|---|---|
| Relationship to Study Drug | [Related, Not Related] |
| Toxicity Grade | [Grade 1, Grade 2, Grade 3, Grade 4, Grade 5] |

Analytical Methods:

The following summaries will be provided.

(1) Overview of Treatment-Emergent Adverse Events

1) All Treatment-Emergent Adverse Events (Number of Events, Number and Percentage of Subjects)
2) Relationship of Treatment-Emergent Adverse Events to Study Drug (Number of Events, Number and Percentage of Subjects)
3) Toxicity Grade of Treatment-Emergent Adverse Events (Number of Events, Number and Percentage of Subjects)
4) Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation (Number of Events, Number and Percentage of Subjects)
5) Serious Treatment-Emergent Adverse Events (Number of Events, Number and Percentage of Subjects)
6) Relationship of Serious Treatment-Emergent Adverse Events to Study Drug (Number of Events, Number and Percentage of Subjects)
7) Serious Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation (Number of Events, Number and Percentage of Subjects)
8) Treatment-Emergent Adverse Events Resulting in Death (Number of Events, Number and Percentage of Subjects)

TEAEs will be counted according to the rules below.

<u>Number of subjects</u>

- Summaries for 2) and 6)

  A subject with occurrences of TEAE in both categories (i.e., Related and Not Related) will be counted once in the Related category.

- Summary for 3)

  A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum toxicity grade.

- Summaries other than 2), 3), and 6)

  A subject with multiple occurrences of TEAE will be counted only once.

Number of events

For each summary, the total number of events will be calculated.

*7.13.1.2 Displays of Treatment-Emergent Adverse events*

Analysis Set:

Safety Analysis Set

Analysis Variables:

TEAE

Categories:

Toxicity Grade [Grade 1, Grade 2, Grade 3, Grade 4, Grade 5]

Analytical Methods:

The following summaries will be provided using frequency distribution.

TEAEs will be coded using the MedDRA and will be summarized using SOC and PT.

SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT. SOC and PT will be sorted in decreasing frequency for tables provided by SOC only or PT only.

The definitions of the following TEAEs to monitor are given in Appendix:

GI Perforation, Fistula, Abscess, Intra-Abdominal and Pelvic Abscess, Hemorrhage (Grade ≥3), Arterial Thrombotic Events, Venous and Mixed/Unspecified Thrombotic Events, Wound Complication, Hypertension, Osteonecrosis, PPES, Proteinuria, RPLS, Diarrhea, QT Prolongation, Renal Failure, Hypothyroidism, Hepatotoxicity

(1) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Any Grade and Grade ≥3)

(2) Treatment-Emergent Adverse Events by System Organ Class

(3) Treatment-Emergent Adverse Events by Preferred Term (Any Grade and Grade ≥3)

(4) Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Any Grade and Grade ≥3)

(5) Drug-Related Treatment-Emergent Adverse Events by Preferred Term (Any Grade and Grade ≥3)

(6) Toxicity Grade of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(7) Toxicity Grade of Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(8) Grade 5 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(9) Grade 5 Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(10) Grade 5 Treatment-Emergent Adverse Events Judged Not Causally Related to Disease under Study by System Organ Class and Preferred Term

(11) Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Any Grade and Grade ≥3)

(12) Serious Treatment-Emergent Adverse Events by Preferred Term (Any Grade and Grade ≥3)

(13) Drug-Related Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Any Grade and Grade ≥3)

(14) Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term (Any Grade and Grade ≥3)

(15) Drug-Related Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term (Any Grade and Grade ≥3)

(16) Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation and Judged Not Causally Related to Disease under Study by System Organ Class and Preferred Term (Any Grade and Grade ≥3)

(17) Treatment-Emergent Adverse Events Leading to Study Drug Dose Modification by System Organ Class and Preferred Term (Any Grade and Grade ≥3)

(18) Drug-Related Treatment-Emergent Adverse Events Leading to Study Drug Dose Modification by System Organ Class and Preferred Term (Any Grade and Grade ≥3)

(19) Treatment-Emergent Adverse Events Leading to Study Drug Dose Reduction by System Organ Class and Preferred Term (Any Grade and Grade ≥3)

(20) Drug-Related Treatment-Emergent Adverse Events Leading to Study Drug Dose Reduction by System Organ Class and Preferred Term (Any Grade and Grade ≥3)

(21) Treatment-Emergent Adverse Events Leading to Study Drug Dose Interruption by System Organ Class and Preferred Term (Any Grade and Grade ≥3)

(22) Drug-Related Treatment-Emergent Adverse Events Leading to Study Drug Dose Interruption by System Organ Class and Preferred Term (Any Grade and Grade ≥3)

(23) Treatment-Emergent Adverse Events of GI Perforation by System Organ Class and Preferred Term (Any Grade and Grade ≥3)

(24) Treatment-Emergent Adverse Events of Fistula by System Organ Class and Preferred Term (Any Grade and Grade ≥3)

(25) Treatment-Emergent Adverse Events of Abscess by System Organ Class and Preferred Term (Any Grade and Grade ≥3)

(26) Treatment-Emergent Adverse Events of Intra-Abdominal and Pelvic Abscess by System Organ Class and Preferred Term (Any Grade and Grade ≥3)

(27) Grade 3 or Higher Treatment-Emergent Adverse Events of Hemorrhage by System Organ Class and Preferred Term

(28) Treatment-Emergent Arterial Thrombotic Adverse Events by System Organ Class and Preferred Term (Any Grade and Grade ≥3)

(29) Treatment-Emergent Venous and Mixed/Unspecified Thrombotic Adverse Events by System Organ Class and Preferred Term (Any Grade and Grade ≥3)

(30) Treatment-Emergent Adverse Events of Wound Complication by System Organ Class and Preferred Term (Any Grade and Grade ≥3)

(31) Treatment-Emergent Adverse Events of Hypertension by System Organ Class and Preferred Term (Any Grade and Grade ≥3)

(32) Treatment-Emergent Adverse Events of Osteonecrosis by System Organ Class and Preferred Term (Any Grade and Grade ≥3)

(33) Treatment-Emergent Adverse Events of PPES by System Organ Class and Preferred Term (Any Grade and Grade ≥3)

(34) Treatment-Emergent Adverse Events of Proteinuria by System Organ Class and Preferred Term (Any Grade and Grade ≥3)

(35) Treatment-Emergent Adverse Events of RPLS by System Organ Class and Preferred Term (Any Grade and Grade ≥3)

(36) Treatment-Emergent Adverse Events of Diarrhea by System Organ Class and Preferred Term (Any Grade and Grade ≥3)

(37) Treatment-Emergent Adverse Events of QT Prolongation by System Organ Class and Preferred Term (Any Grade and Grade ≥3)

(38) Treatment-Emergent Adverse Events of Renal Failure by System Organ Class and Preferred Term (Any Grade and Grade ≥3)

(39) Treatment-Emergent Adverse Events of Hypothyroidism by System Organ Class and Preferred Term (Any Grade and Grade ≥3)

(40) Treatment-Emergent Adverse Events of Hepatotoxicity by System Organ Class and Preferred Term (Any Grade and Grade ≥3)

The frequency distribution will be provided according to the rules below.

Number of subjects

- Summary tables other than (6) and (7)

  A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT.

- Summary tables for (6) and (7)

  A subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once for the TEAE with the maximum toxicity grade.

*7.13.1.3 Time to First Occurrence of TEAEs to Monitor*

Analysis Set:

Safety Analysis Set

Analysis Variables:

TEAEs to Monitor

GI Perforation, Fistula, Abscess, Intra-Abdominal and Pelvic Abscess, Hemorrhage (Grade ≥3), Arterial Thrombotic Events, Venous and Mixed/Unspecified Thrombotic Events, Wound Complication, Hypertension, Osteonecrosis, PPES, Proteinuria, RPLS, Diarrhea, QT Prolongation, Renal Failure, Hypothyroidism, Hepatotoxicity

Analytical Methods:

(1) Time to First Occurrence of TEAEs to Monitor

Descriptive statistics of the time from the first day of study drug administration to first occurrence will be provided for each TEAEs to monitor for subjects experienced the corresponding event in the safety analysis set.

*7.13.1.4 Death*

Analysis Set:

Safety Analysis Set

Analysis Variables:

| | |
|---|---|
| Subject Status | [Alive, Expired] |
| Deaths ≤ 30 Days after the Last Dose of Study Drug | [Yes] |
| Primary Cause of Death | [Progression of Disease under Study, Other] |

Death Causally Associated with Disease under Study

[Yes, No, Unknown]

Deaths >30 Days after the Last Dose of Study Drug

[Yes]

Primary Reason for Death [Progression of Disease under Study, Other]

Death Causally Associated with Disease under Study

[Yes, No, Unknown]

Analytical Methods:

(1) Summary of Death

Frequency distributions will be provided.

*7.13.1.5 Displays of Pretreatment Events*

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variables:

PTE

Analytical Methods:

The following summaries will be provided using frequency distribution.

PTEs will be coded using the MedDRA and will be summarized using SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency.

(1) Pretreatment Events by System Organ Class and Preferred Term

(2) Serious Pretreatment Events by System Organ Class and Preferred Term

The frequency distribution will be provided according to the rules below.

Number of subjects

A subject with multiple occurrences of PTE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of PTE within a PT will be counted only once in that PT.

### 7.13.2 Clinical Laboratory Evaluations

Analysis Set:

Safety Analysis Set

Analysis Variables:

Hematology

WBC, Neutrophils, Neutrophils/WBC, Basophils, Basophils/WBC, Eosinophils, Eosinophils/WBC, Lymphocytes, Lymphocytes/WBC, Monocytes, Monocytes/WBC, Hematocrit, Platelets, RBC, Hemoglobin, Reticulocytes

Serum Chemistry

Albumin, ALP, ALT, Amylase, AST, BUN, Corrected Calcium, Bicarbonate, Chloride, Creatinine, Creatinine Clearance, GGT, Fasted Glucose, LDH, Lipase, Magnesium, Phosphorus, Potassium, Sodium, Total Bilirubin, Conjugated Bilirubin, Unconjugated Bilirubin, Total Protein

Coagulation

PT/INR, APTT

Thyroid Function

TSH

Urine Chemistry

UPCR

Categories:

Toxicity Grade [Grade 0, Grade 1, Grade 2, Grade 3, Grade 4]

[Grade 0, Grade 1 – Grade 4]

Visit:

Hematology, Serum Chemistry

Baseline, Week 3 Day 1, Week 5 Day 1, Week 7 Day 1, Week 9 Day 1, Every 4 Weeks Thereafter, 30-Day Posttreatment Followup

Coagulation

Baseline, Week 5 Day 1, Week 9 Day 1, Every 4 Weeks Thereafter, 30-Day Posttreatment Followup

Thyroid Function

Baseline, Week 5 Day 1, Week 9 Day 1, Every 8 Weeks Thereafter, 30-Day Posttreatment Followup

Urine Chemistry

Baseline, Week 3 Day 1, Week 5 Day 1, Week 9 Day 1, Every 4 Weeks Thereafter, 30-Day Posttreatment Followup

Analytical Methods:

For each variable, summaries (1) to (2) will be provided.

For applicable variables, summaries (3) to (8) will be provided.

(1) Summary of Laboratory Test Results and Change from Baseline by Visit

Descriptive statistics for observed values for each visit and changes from baseline will be provided.

(2) Case Plots

Plots over time for each subject will be presented.

(3) Number and Percentage of Subjects with Clinically Significant Abnormal Laboratory Values

Frequency distributions of post-baseline maximum grade for laboratory abnormalities will be provided. Further details are given in Appendix.

(4) Summary of Shifts of Laboratory Test Results

Shift tables showing the number of subjects in each category of baseline grade and post-baseline maximum grade for laboratory abnormalities will be provided.

(5) Number and Percentage of Subjects with Elevated Liver Enzyme Laboratory Parameters

Overall frequency distributions of post-baseline elevated hepatic parameters will be provided. Further details are given in Appendix.

(6) Time to First Occurrence of ALT or AST >3xULN

Descriptive statistics of the time from the first day of study drug administration to first occurrence of ALT or AST >3xULN through 30 days after the date of the last dose will be provided for subjects experienced ALT or AST >3xULN in the safety analysis set.

(7) Number and Percentage of Subjects with Elevated Serum Creatinine

Overall frequency distributions of post-baseline elevated serum creatinine will be provided. Further details are given in Appendix.

(8) Summary of Thyroid Function Status

For TSH, shift tables showing the number of subjects in each category of "Low", "Normal" or "High" relative to the normal reference range provided by the central laboratory for baseline value and post-baseline minimum/maximum value obtained up to 30 days after the date of the last dose will be provided.

Frequency distributions of TSH and free T4 status will be provided using the post-baseline value obtained up to 30 days after the date of the last dose based on the following categories:

- For increased TSH:
  High TSH with Low Free T4 at any post-baseline visit
  High TSH with Normal Free T4 (not meet the above condition)
- For decreased TSH:
  Low TSH with High Free T4 at any post-baseline visit
  Low TSH with Normal Free T4 (not meet the above condition)

### 7.13.3 Vital Signs and Weight

Analysis Set:

Safety Analysis Set

Analysis Variables:

Systolic Blood Pressure

Diastolic Blood Pressure

Pulse Rate

Respiratory Rate

Temperature

Weight

Visit:

Baseline, Week 3 Day 1, Week 5 Day 1, Week 7 Day 1, Week 9 Day 1, Every 4 Weeks Thereafter, 30-Day Posttreatment Followup

Analytical Methods:

For each variable, summaries (1) and (2) will be provided.

For applicable variables, summaries (3) and (4) will be provided.

(1) Summary of Vital Signs Parameters and Change from Baseline by Visit

Descriptive statistics for observed values for each visit and changes from baseline will be provided.

(2) Case Plots

Plots over time for each subject will be presented.

(3) Number and Percentage of Subjects with Clinically Significant Abnormal Vital Sign Measurements

Frequency distributions of post-baseline clinically significant abnormal vital sign measurements will be provided. Further details are given in Appendix.

(4) Time to First Occurrence of Decrease in Weight ≥10% from Baseline

Descriptive statistics of the time from the first day of study drug administration to first occurrence of decrease in weight ≥10% through 30 days after the date of the last dose will be provided for subjects experienced the weight decrease in the safety analysis set.

### 7.13.4 12-Lead ECGs

Analysis Set:

Safety Analysis Set

Analysis Variables:

QTcF Interval

Interpretation

[Normal, Abnormal but not Clinically Significant, Abnormal and Clinically Significant]

Visit:

Baseline, Week 5 Day 1, Week 9 Day 1, Every 12 Weeks Thereafter, 30-Day Posttreatment Followup

Analytical Methods:

For QTcF interval, summaries (1) to (3) will be provided.

For 12-lead ECG interpretation, summary (4) will be provided.

(1) Summary of ECG Parameters and Change from Baseline by Visit

Descriptive statistics for observed values for each visit and changes from baseline will be provided

(2) Case Plots

Plots over time for each subject will be presented.

(3) Number and Percentage of Subjects with Clinically Significant Abnormal QTcF Measurements

Frequency distributions of post-baseline clinically significant abnormal QTcF measurements will be provided. Further details are given in Appendix.

(4) Summary of Shift of 12-lead ECG Interpretation

Shift table showing the number of subjects in each category for baseline result and the worst post-baseline result obtained up to 30 days after the date of the last dose will be provided.

### 7.13.5 Other Observations Related to Safety

*7.13.5.1 ECOG Performance Status*

Analysis Set:

Safety Analysis Set

Analysis Variables:

ECOG Performance Status

Analytical Methods:

(1) Summary of Shift of ECOG Performance Status

Shift table showing the number of subjects in each category for baseline result and the worst post-baseline result obtained up to 30 days after the date of the last dose will be provided.

(2) Number and Percentage of Subjects with Increase in ECOG PS

Frequency distributions of maximum post-baseline change in ECOG PS of ≥1 and ≥2 obtained up to 30 days after the date of the last dose will be provided.

*7.13.5.2 Transfusion*

Analysis Set:

Safety Analysis Set

Analysis Variables:

Treatment for Anemia

| | |
|---|---|
| Any Treatment for Anemia after Enrollment | [Yes, No] |
| No Prior Treatment for Anemia ≤ 28 Days before Enrollment | [Yes] |
| Any Treatment for Anemia after Enrollment | [Yes, No] |
| Any Prior Treatment for Anemia ≤ 28 Days before Enrollment | [Yes] |
| Any Treatment for Anemia after Enrollment | [Yes, No] |
| Number of Treatment for Anemia after Enrollment | |

Platelet Transfusion

| | |
|---|---|
| Any Platelet Transfusion after Enrollment | [Yes, No] |
| No Prior Platelet Transfusion ≤ 28 Days before Enrollment | [Yes] |
| Any Platelet Transfusion after Enrollment | [Yes, No] |
| Any Prior Platelet Transfusion ≤ 28 Days before Enrollment | [Yes] |

Any Platelet Transfusion after Enrollment [Yes, No]

Number of Platelet Transfusion after Enrollment

Analytical Methods:

(1) Transfusion

Frequency distributions for categorical variables will be provided. For number of treatment/transfusion after enrollment, descriptive statistics will be provided for all subjects and for subjects with any treatment/transfusion in the safety analysis set.

### 7.14 Interim Analysis

Not applicable.

### 7.15 Changes in the Statistical Analysis Plan

The analyses in the statistical analysis plan do not differ from the analyses specified in the protocol.

## 8.0 REFERENCES

[1] Ikeda, S., Shiroiwa, T., Igarashi. A., Noto, S., Fukuda, T., Saito, S. & Shimozuma, K. (2015). Developing a Japanese version of the EQ-5D-5L value set. *Journal of the National Institute of Public Health*, **64**(1), 47-55.

# 9.0 APPENDIX

## 9.1 Criteria for Clinically Significant Abnormal Values

For each parameter, all evaluable data (i.e., non-missing data) obtained up to 30 days after the date of the last dose will be classified as a clinically significant abnormal value or not. The criteria in the table below will be used.

**Table 9.a Clinically Significant Abnormal Value Criteria for Laboratory Parameters**

| Abnormality | Criteria |
|---|---|
| WBC Increased | CTCAE v4.03 |
| WBC Decreased | CTCAE v4.03 |
| ANC Decreased | CTCAE v4.03 |
| Lymphocytes Increased | CTCAE v4.03 |
| Lymphocytes Decreased | CTCAE v4.03 |
| Platelets Decreased | CTCAE v4.03 |
| Hemoglobin Increased | CTCAE v4.03 |
| Hemoglobin Decreased | CTCAE v4.03 |
| Albumin Decreased | CTCAE v4.03 |
| ALP Increased | CTCAE v4.03 |
| Amylase Increased | CTCAE v4.03 |
| ALT Increased | CTCAE v4.03 |
| AST Increased | CTCAE v4.03 |
| Corrected Calcium Increased | CTCAE v4.03 |
| Corrected Calcium Decreased | CTCAE v4.03 |
| Creatinine Increased | CTCAE v4.03 |
| GGT Increased | CTCAE v4.03 |
| Glucose Increased | CTCAE v4.03 |
| Glucose Decreased | CTCAE v4.03 |
| LDH Increased | Grade 1: ULN<- <=2xULN<br>Grade 2: 2xULN<- <=3xULN<br>Grade 3: 3xULN< |
| Lipase Increased | CTCAE v4.03 |
| Magnesium Increased | CTCAE v4.03 |
| Magnesium Decreased | CTCAE v4.03 |
| Phosphate Decreased | CTCAE v4.03 |
| Potassium Increased | CTCAE v4.03 |
| Potassium Decreased | CTCAE v4.03 |
| Sodium Increased | CTCAE v4.03 |
| Sodium Decreased | CTCAE v4.03 |
| Total Bilirubin Increased | CTCAE v4.03 |
| UPCR Increased | Grade 1: 17.0<= - <=121.0 g/mol<br>Grade 2: 121.0<- <=396.0 g/mol<br>Grade 3: 396.0 g/mol< |

**Table 9.b Clinically Significant Abnormal Value Criteria for Vital Sign Parameters**

| Abnormality | Criteria |
|---|---|
| Blood Pressure Increased<br>(Assign the worst category when a subject meets multiple criteria) | • SBP <120 mmHg and DBP <80 mmHg<br>• SBP 120<= - <=139 mmHg or DBP 80<= - <=89 mmHg<br>• SBP 140<= - <=159 mmHg or DBP 90<= - <=99 mmHg<br>• (SBP 160 mmHg<= and DBP <120 mmHg) or DBP 100<= - <=119 mmHg<br>• DBP 120 mmHg<=<br>* Need to meet the criteria at 2 or more visits (need not be consecutive) |
| Weight Decreased | Weight decreased >= 10% from baseline |

**Table 9.c Clinically Significant Abnormal Value Criteria for ECG Parameters**

| Abnormality | Criteria |
|---|---|
| QTcF Interval Prolongation<br>(based on observed value) | 500msec< |
| QTcF Interval Prolongation<br>(based on change from baseline) | 60msec< |

## 9.2 Criteria for Elevated Liver Enzyme and Elevated Serum Creatinine

All evaluable data (i.e., non-missing data) obtained up to 30 days after the date of the last dose will be used to determine whether each criteria for elevated liver enzyme or elevated serum creatinine in the table below is met or not. If there is more than one parameter that need to be considered for a criteria, parameter measurements taken on the same day will be used.

**Table 9.d Criteria for Elevated Liver Enzyme**

| Label | Criteria for Elevated Liver Enzyme | |
|---|---|---|
| | Elevated | Not Elevated |
| Tbili >2xULN | Total bilirubin is greater than twice the ULN | Total bilirubin is non-missing and less than or equal to twice the ULN |
| ALT >3xULN | ALT is greater than 3 times the ULN | ALT is non-missing and less than or equal to 3 times the ULN |
| ALT >5xULN | ALT is greater than 5 times the ULN | ALT is non-missing and less than or equal to 5 times the ULN |
| ALT >10xULN | ALT is greater than 10 times the ULN | ALT is non-missing and less than or equal to 10 times the ULN |
| ALT >20xULN | ALT is greater than 20 times the ULN | ALT is non-missing and less than or equal to 20 times the ULN |

| Label | Criteria for Elevated Liver Enzyme | |
|---|---|---|
| | **Elevated** | **Not Elevated** |
| ALT >3xULN with Tbili >2xULN | ALT is greater than 3 times the ULN and the total bilirubin is greater than twice the ULN | Either ALT is non-missing and less than or equal to 3 times the ULN, or the total bilirubin is non-missing and less than or equal to twice the ULN |
| AST >3xULN | AST is greater than 3 times the ULN | AST is non-missing and less than or equal to 3 times the ULN |
| AST >5xULN | AST is greater than 5 times the ULN | AST is non-missing and less than or equal to 5 times the ULN |
| AST >10xULN | AST is greater than 10 times the ULN | AST is non-missing and less than or equal to 10 times the ULN |
| AST >20xULN | AST is greater than 20 times the ULN | AST is non-missing and less than or equal to 20 times the ULN |
| AST >3xULN with Tbili >2xULN | AST is greater than 3 times the ULN and the total bilirubin is greater than twice the ULN | Either AST is non-missing and less than or equal to 3 times the ULN, or the total bilirubin is non-missing and less than or equal to twice the ULN |
| ALT or AST >3xULN | Either ALT or AST is greater than 3 times the ULN | Both ALT and AST are non-missing and less than or equal to 3 times the ULN |
| ALT or AST >5xULN | Either ALT or AST is greater than 5 times the ULN | Both ALT and AST are non-missing and less than or equal to 5 times the ULN |
| ALT or AST >10xULN | Either ALT or AST is greater than 10 times the ULN | Both ALT and AST are non-missing and less than or equal to 10 times the ULN |
| ALT or AST >20xULN | Either ALT or AST is greater than 20 times the ULN | Both ALT and AST are non-missing and less than or equal to 20 times the ULN |
| ALT or AST >3xULN with Tbili >2xULN and ALP <2xULN | Either ALT or AST is greater than 3 times the ULN and the total bilirubin is greater than twice the ULN and ALP is non-missing and less than twice the ULN | If any of the following conditions is met:<br>- Both ALT and AST are non-missing and less than or equal to 3 times the ULN.<br>- Total bilirubin is non-missing and less than or equal to twice the ULN.<br>- ALP is greater than or equal to twice the ULN. |
| ALT or AST >3xULN with Tbili >2xULN and ALP ≥2xULN | Either ALT or AST is greater than 3 times the ULN and the total bilirubin is greater than twice the ULN and ALP is greater than or equal to twice the ULN | If any of the following conditions is met:<br>- Both ALT and AST are non-missing and less than or equal to 3 times the ULN.<br>- Total bilirubin is non-missing and less than or equal to twice the ULN.<br>- ALP is non-missing and less than twice the ULN. |
| ALP >1.5xULN | ALP is greater than 1.5 times the ULN | ALP is non-missing and less than or equal to 1.5 times the ULN |

**Table 9.e Criteria for Elevated Serum Creatinine**

| Label | Criteria for Elevated Serum Creatinine | |
|---|---|---|
| | Elevated | Not Elevated |
| Elevated Serum Creatinine | 1) Creatinine clearance <30 mL/min or<br>2) Creatinine clearance <= 0.5 x baseline or<br>3) Serum creatinine >= 3 x ULN and >=2 x baseline | 1) Creatinine Clearance is non-missing and >= 30 mL/min and >0.5 x baseline and<br>2) Serum creatinine is non-missing and either <3x ULN or <2 x baseline |

## 9.3 Definition of Treatment for Anemia

Treatment for anemia is defined as any transfusion recorded on the eCRF "Concomitant Transfusions" page whose transfusion type is "Packed RBC" or "Whole Blood."

Treatment for anemia also includes the use of concomitant medication of ESA/EPO agents. ESA/EPO agents will be identified as the concomitant medications whose preferred name is one of the followings:

- ADENOSINE TRIPHOSPHATE, DISODIUM SALT;COCARBOXYLASE;COENZYME A;LIVER EXTRACT
- ADENOSINE;COCARBOXYLASE;COENZYME A;LIVER EXTRACT
- ALBUMIN NOS;DARBEPOETIN ALFA
- ASTRAGALUS SPP. ROOT;BLOOD, PIG;ZIZIPHUS JUJUBA FRUIT
- ASTRAGALUS SPP.;BLOOD, PIG;ZIZIPHUS JUJUBA
- BLOOD, PIG
- DARBEPOETIN ALFA
- EPOETIN ALFA
- EPOETIN BETA
- EPOETIN DELTA
- EPOETIN KAPPA
- EPOETIN LAMBDA
- EPOETIN NOS
- EPOETIN OMEGA
- EPOETIN THETA
- EPOETIN ZETA
- ERYTHROPOIESIS-STIMULATING AGENTS

- ERYTHROPOIETIN
- ERYTHROPOIETIN HUMAN
- FLAVINE ADENINE DINUCLEOTIDE DISODIUM;LIVER EXTRACT
- FLAVINE ADENINE DINUCLEOTIDE;LIVER EXTRACT
- INOSINE;LIVER EXTRACT
- LEXAPTEPID PEGOL
- LIVER EXTRACT;LIVER HYDROLYSATE
- LIVER EXTRACT;SPLEEN EXTRACT, PROTEINFREE
- LIVER FRACTION 1
- LIVER INJECTION
- LUSPATERCEPT
- METHOXY POLYETHYLENE GLYCOL-EPOETIN BETA
- MOLIDUSTAT
- PEGINESATIDE
- PEGINESATIDE ACETATE
- RECOMBINANT HUMAN THROMBOPOIETIN
- ROXADUSTAT

### 9.4 Definition of Treatment-Emergent Adverse Events to Monitor

- GI Perforation

  Abdominal hernia perforation; Appendicitis perforated; Diverticular perforation; Duodenal perforation; Duodenal ulcer perforation; Duodenal ulcer perforation, obstructive; Duodenal ulcer repair; Gastric perforation; Gastric ulcer perforation; Gastric ulcer perforation, obstructive; Gastrointestinal perforation; Gastrointestinal ulcer perforation; Ileal perforation; Ileal ulcer perforation; Intestinal perforation; Intestinal ulcer perforation; Jejunal perforation; Jejunal ulcer perforation; Large intestinal ulcer perforation; Large intestine perforation; Neonatal intestinal perforation; Oesophageal perforation; Oesophageal rupture; Oesophageal ulcer perforation; Peptic ulcer perforation; Peptic ulcer perforation, obstructive; Perforated peptic ulcer oversewing; Perforated ulcer; Peritonitis; Peritonitis bacterial; Rectal perforation; Small intestinal perforation; Small intestinal ulcer perforation

- Fistula

  Acquired tracheo-oesophageal fistula; Anal fistula; Anal fistula excision; Anal fistula infection; Anastomotic fistula; Anovulvar fistula; Aortoenteric fistula; Aorto-oesophageal

fistula; Arterioenteric fistula; Arteriovenous fistula; Arteriovenous fistula aneurysm; Arteriovenous fistula occlusion; Arteriovenous fistula operation; Arteriovenous fistula site complication; Arteriovenous fistula site infection; Arteriovenous fistula thrombosis; Biliary fistula; Biliary fistula repair; Bladder fistula repair; Bone fistula; Bronchial fistula; Bronchial fistula repair; Bronchopleural fistula; Cerebrospinal fistula; Colon fistula repair; Colonic fistula; Congenital arteriovenous fistula; Congenital aural fistula; Congenital lip fistula; Dental fistula; Diverticular fistula; Dural arteriovenous fistula; Enterocolonic fistula; Enterocutaneous fistula; Enterovesical fistula; Female genital tract fistula; Fistula; Fistula discharge; Fistula of small intestine; Fistula repair; Gallbladder fistula; Gallbladder fistula repair; Gastric fistula; Gastric fistula repair; Gastrointestinal fistula; Gastrointestinal fistula repair; Gastropleural fistula; Gastrosplenic fistula; Infected fistula; Intestinal fistula; Intestinal fistula infection; Intestinal fistula repair; Intrahepatic portal hepatic venous fistula; Labyrinthine fistula; Lacrimal fistula; Laryngeal fistula; Laryngeal fistula repair; Lymphatic fistula; Male genital tract fistula; Mammary fistula; Mammary fistula repair; Ocular fistula; Oesophageal fistula; Oesophageal fistula repair; Oesophagobronchial fistula; Oral cavity fistula; Oroantral fistula; Pancreatic fistula; Pancreatic fistula repair; Perineal fistula; Pharyngeal fistula; Pharyngeal fistula repair; Pleural fistula; Pleurocutaneous fistula; Post procedural fistula; Postauricular fistula; Pulmonary arteriovenous fistula; Pulmonary fistula; Rectal fistula repair; Rectoprostatic fistula; Rectourethral fistula; Renal pelvis fistula; Salivary gland fistula; Thyroglossal fistula; Thyroglossal fistula excision; Tracheal fistula; Tracheal fistula repair; Tracheo-oesophageal fistula; Ureteric fistula; Urethral fistula; Urethroperineal fistula; Urinary fistula; Urogenital fistula; Urogenital fistula repair; Uterine fistula; Vaginal fistula; Vaginal fistula repair; Vesical fistula; Vesicocutaneous fistula

- Abscess

  Abdominal wall abscess; Abscess; Abscess bacterial; Abscess drainage; Abscess fungal; Abscess intestinal; Abscess jaw; Abscess limb; Abscess management; Abscess neck; Abscess of external auditory meatus; Abscess of eyelid; Abscess of salivary gland; Abscess oral; Abscess rupture; Abscess soft tissue; Abscess sterile; Abscess sweat gland; Administration site abscess; Adrenal gland abscess; Amoebic brain abscess; Amoebic lung abscess; Anal abscess; Appendiceal abscess; Application site abscess; Arteriovenous graft site abscess; Bacterial abscess central nervous system; Bartholin's abscess; Biliary abscess; Bone abscess; Brain abscess; Breast abscess; Cardiac valve abscess; Catheter site abscess; Central nervous system abscess; Chest wall abscess; Clitoris abscess; Colonic abscess; Corneal abscess; Douglas' abscess; Dural abscess; Extradural abscess; Eye abscess; Fallopian tube abscess; Fungal abscess central nervous system; Gallbladder abscess; Genital abscess; Gingival abscess; Groin abscess; Implant site abscess; Incision site abscess; Infusion site abscess; Injection site abscess; Injection site abscess sterile; Instillation site abscess; Joint abscess; Liver abscess; Lung abscess; Lymph node abscess; Mastoid abscess; Mediastinal abscess; Mesenteric abscess; Muscle abscess; Mycobacterium abscessus infection; Myocardiac abscess; Nasal abscess; Ovarian abscess; Pancreatic abscess; Parametric abscess; Paraoesophageal abscess; Paraspinal abscess; Parathyroid gland abscess; Parotid abscess; Pelvic abscess; Penile abscess; Perihepatic abscess; Perineal abscess;

Perinephric abscess; Periorbital abscess; Perirectal abscess; Peritoneal abscess; Peritonsillar abscess; Periumbilical abscess; Pharyngeal abscess; Pharyngolaryngeal abscess; Postoperative abscess; Prostatic abscess; Psoas abscess; Puncture site abscess; Pyloric abscess; Rectal abscess; Rectovaginal septum abscess; Renal abscess; Retroperitoneal abscess; Scrotal abscess; Spinal cord abscess; Splenic abscess; Staphylococcal abscess; Stitch abscess; Stoma site abscess; Streptococcal abscess; Subarachnoid abscess; Subcutaneous abscess; Subdiaphragmatic abscess; Testicular abscess; Thymus abscess; Thyroid gland abscess; Tongue abscess; Tooth abscess; Transplant abscess; Tuberculous abscess central nervous system; Tubo-ovarian abscess; Urachal abscess; Ureter abscess; Urethral abscess; Urinary bladder abscess; Urinary tract abscess; Uterine abscess; Vaccination site abscess; Vaccination site abscess sterile; Vaginal abscess; Vitreous abscess; Vulval abscess; Wound abscess

- Intra-Abdominal and Pelvic Abscess

  Abdominal abscess; Abdominal wall abscess; Abscess intestinal; Adrenal gland abscess; Anal abscess; Appendiceal abscess; Biliary abscess; Clitoris abscess; Colonic abscess; Douglas' abscess; Fallopian tube abscess; Gallbladder abscess; Genital abscess; Groin abscess; Liver abscess; Mesenteric abscess; Ovarian abscess; Pancreatic abscess; Parametric abscess; Pelvic abscess; Penile abscess; Perihepatic abscess; Perineal abscess; Perinephric abscess; Perirectal abscess; Peritoneal abscess; Periumbilical abscess; Prostatic abscess; Psoas abscess; Pyloric abscess; Rectal abscess; Rectovaginal septum abscess; Renal abscess; Retroperitoneal abscess; Scrotal abscess; Splenic abscess; Stoma site abscess; Subdiaphragmatic abscess; Testicular abscess; Tubo-ovarian abscess; Urachal abscess; Ureter abscess; Urethral abscess; Urinary bladder abscess; Urinary tract abscess; Uterine abscess; Vaginal abscess; Vulval abscess

- Hemorrhage

  Abdominal wall haematoma; Abdominal wall haemorrhage; Abnormal withdrawal bleeding; Adrenal haematoma; Adrenal haemorrhage; Anal haemorrhage; Anal ulcer haemorrhage; Anastomotic haemorrhage; Anastomotic ulcer haemorrhage; Aneurysm ruptured; Anorectal varices haemorrhage; Aortic aneurysm rupture; Aortic dissection rupture; Aortic intramural haematoma; Aortic rupture; Arterial haemorrhage; Arterial rupture; Arteriovenous fistula site haematoma; Arteriovenous fistula site haemorrhage; Arteriovenous graft site haematoma; Arteriovenous graft site haemorrhage; Atrial rupture; Auricular haematoma; Basal ganglia haemorrhage; Bladder tamponade; Bleeding varicose vein; Blood blister; Blood urine; Blood urine present; Bloody discharge; Bloody peritoneal effluent; Bone marrow haemorrhage; Brain stem haematoma; Brain stem haemorrhage; Breast haematoma; Breast haemorrhage; Broad ligament haematoma; Bronchial haemorrhage; Carotid aneurysm rupture; Catheter site haemorrhage; Central nervous system haemorrhage; Cephalhaematoma; Cerebellar haematoma; Cerebellar haemorrhage; Cerebral arteriovenous malformation haemorrhagic; Cerebral haematoma; Cerebral haemorrhage; Cerebral haemorrhage foetal; Cerebral haemorrhage neonatal; Cerebral microhaemorrhage; Cervix haematoma uterine; Cervix haemorrhage uterine; Choroidal haematoma; Choroidal

haemorrhage; Chronic gastrointestinal bleeding; Ciliary body haemorrhage; Colonic haematoma; Conjunctival haemorrhage; Corneal bleeding; Cullen's sign; Cystitis haemorrhagic; Deep dissecting haematoma; Diarrhoea haemorrhagic; Diverticulitis intestinal haemorrhagic; Diverticulum intestinal haemorrhagic; Duodenal ulcer haemorrhage; Duodenitis haemorrhagic; Dysfunctional uterine bleeding; Ear haemorrhage; Encephalitis haemorrhagic; Enterocolitis haemorrhagic; Epidural haemorrhage; Epistaxis; Exsanguination; Extradural haematoma; Extravasation blood; Eye contusion; Eye haemorrhage; Eyelid bleeding; Foetal-maternal haemorrhage; Gastric haemorrhage; Gastric ulcer haemorrhage; Gastric ulcer haemorrhage, obstructive; Gastric varices haemorrhage; Gastritis haemorrhagic; Gastroduodenal haemorrhage; Gastroduodenitis haemorrhagic; Gastrointestinal haemorrhage; Gastrointestinal polyp haemorrhage; Gastrointestinal ulcer haemorrhage; Gastrointestinal vascular malformation haemorrhagic; Genital haemorrhage; Gingival bleeding; Graft haemorrhage; Haemarthrosis; Haematemesis; Haematochezia; Haematoma; Haematosalpinx; Haematospermia; Haematotympanum; Haematuria; Haemobilia; Haemoptysis; Haemorrhage; Haemorrhage coronary artery; Haemorrhage foetal; Haemorrhage in pregnancy; Haemorrhage intracranial; Haemorrhage neonatal; Haemorrhage subcutaneous; Haemorrhage subepidermal; Haemorrhage urinary tract; Haemorrhagic anaemia; Haemorrhagic arteriovenous malformation; Haemorrhagic ascites; Haemorrhagic cerebral infarction; Haemorrhagic diathesis; Haemorrhagic disease of newborn; Haemorrhagic disorder; Haemorrhagic erosive gastritis; Haemorrhagic hepatic cyst; Haemorrhagic infarction; Haemorrhagic ovarian cyst; Haemorrhagic stroke; Haemorrhagic thyroid cyst; Haemorrhagic transformation stroke; Haemorrhagic tumour necrosis; Haemorrhagic urticaria; Haemorrhagic vasculitis; Haemorrhoidal haemorrhage; Haemostasis; Haemothorax; Hepatic haemangioma rupture; Hepatic haematoma; Hepatic haemorrhage; Hyphaema; Iliac artery rupture; Implant site haemorrhage; Incision site haemorrhage; Infusion site haemorrhage; Injection site haemorrhage; Instillation site haemorrhage; Intestinal haematoma; Intestinal haemorrhage; Intra-abdominal haematoma; Intra-abdominal haemorrhage; Intracerebral haematoma evacuation; Intracranial haematoma; Intracranial tumour haemorrhage; Intraocular haematoma; Intraventricular haemorrhage; Intraventricular haemorrhage neonatal; Iris haemorrhage; Lacrimal haemorrhage; Large intestinal haemorrhage; Large intestinal ulcer haemorrhage; Laryngeal haematoma; Laryngeal haemorrhage; Lip haematoma; Lip haemorrhage; Lower gastrointestinal haemorrhage; Lymph node haemorrhage; Mallory-Weiss syndrome; Mediastinal haematoma; Mediastinal haemorrhage; Melaena; Melaena neonatal; Meningorrhagia; Menometrorrhagia; Menorrhagia; Mesenteric haematoma; Mesenteric haemorrhage; Metrorrhagia; Mouth haemorrhage; Mucosal haemorrhage; Muscle haemorrhage; Myocardial haemorrhage; Myocardial rupture; Naevus haemorrhage; Neonatal gastrointestinal haemorrhage; Nephritis haemorrhagic; Ocular retrobulbar haemorrhage; Oesophageal haemorrhage; Oesophageal ulcer haemorrhage; Oesophageal varices haemorrhage; Oesophagitis haemorrhagic; Optic disc haemorrhage; Optic nerve sheath haemorrhage; Oral mucosa haematoma; Osteorrhagia; Ovarian haematoma; Ovarian haemorrhage; Pancreatic haemorrhage; Pancreatitis haemorrhagic; Papillary muscle haemorrhage; Paranasal sinus haematoma; Parathyroid haemorrhage; Parotid gland

haemorrhage; Pelvic haematoma; Pelvic haematoma obstetric; Pelvic haemorrhage; Penile haematoma; Penile haemorrhage; Peptic ulcer haemorrhage; Pericardial haemorrhage; Perineal haematoma; Periorbital haematoma; Peripartum haemorrhage; Perirenal haematoma; Peritoneal haematoma; Peritoneal haemorrhage; Pharyngeal haematoma; Pharyngeal haemorrhage; Pituitary haemorrhage; Polymenorrhagia; Post procedural haemorrhage; Postmenopausal haemorrhage; Premature separation of placenta; Procedural haemorrhage; Proctitis haemorrhagic; Prostatic haemorrhage; Pulmonary alveolar haemorrhage; Pulmonary haematoma; Pulmonary haemorrhage; Puncture site haemorrhage; Putamen haemorrhage; Radiation associated haemorrhage; Rectal haemorrhage; Rectal ulcer haemorrhage; Renal cyst haemorrhage; Renal haematoma; Renal haemorrhage; Respiratory tract haemorrhage; Respiratory tract haemorrhage neonatal; Retinal haemorrhage; Retinopathy haemorrhagic; Retroperitoneal haematoma; Retroperitoneal haemorrhage; Retroplacental haematoma; Ruptured cerebral aneurysm; Scleral haemorrhage; Scrotal haematocoele; Scrotal haematoma; Shock haemorrhagic; Skin haemorrhage; Skin ulcer haemorrhage; Small intestinal haemorrhage; Small intestinal ulcer haemorrhage; Soft tissue haemorrhage; Spermatic cord haemorrhage; Spinal cord haematoma; Spinal cord haemorrhage; Spinal epidural haematoma; Spinal epidural haemorrhage; Spinal subarachnoid haemorrhage; Spinal subdural haematoma; Spinal subdural haemorrhage; Splenic haematoma; Splenic haemorrhage; Splenic varices haemorrhage; Splinter haemorrhages; Spontaneous haematoma; Spontaneous haemorrhage; Stoma site haemorrhage; Stomatitis haemorrhagic; Subarachnoid haemorrhage; Subarachnoid haemorrhage neonatal; Subchorionic haematoma; Subcutaneous haematoma; Subdural haematoma; Subdural haematoma evacuation; Subdural haemorrhage; Subdural haemorrhage neonatal; Subgaleal haematoma; Subretinal haematoma; Testicular haemorrhage; Thalamus haemorrhage; Thoracic haemorrhage; Thrombocytopenic purpura; Thrombotic thrombocytopenic purpura; Thyroid haemorrhage; Tongue haematoma; Tongue haemorrhage; Tonsillar haemorrhage; Tooth pulp haemorrhage; Tooth socket haemorrhage; Tracheal haemorrhage; Tumour haemorrhage; Ulcer haemorrhage; Upper gastrointestinal haemorrhage; Ureteric haemorrhage; Urethral haemorrhage; Urinary bladder haemorrhage; Urogenital haemorrhage; Uterine haematoma; Uterine haemorrhage; Vaccination site haemorrhage; Vaginal haematoma; Vaginal haemorrhage; Varicose vein ruptured; Vascular pseudoaneurysm ruptured; Vascular purpura; Vascular rupture; Venous haemorrhage; Ventricle rupture; Vessel puncture site haemorrhage; Vitreous haematoma; Vitreous haemorrhage; Vulval haematoma; Vulval haematoma evacuation; Vulval haemorrhage; Wound haemorrhage

- Arterial Thrombotic Events

  Acute aortic syndrome; Acute myocardial infarction; Aortic embolus; Aortic thrombosis; Arterial occlusive disease; Arterial thrombosis; Basal ganglia infarction; Basal ganglia stroke; Basilar artery occlusion; Basilar artery thrombosis; Bone infarction; Brachiocephalic artery occlusion; Brain stem embolism; Brain stem infarction; Brain stem stroke; Brain stem thrombosis; Carotid arterial embolus; Carotid artery occlusion; Carotid artery thrombosis; Cerebellar artery occlusion; Cerebellar artery thrombosis; Cerebellar embolism; Cerebellar

infarction; Cerebral artery embolism; Cerebral artery occlusion; Cerebral artery thrombosis; Cerebral infarction; Cerebral infarction foetal; Cerebral ischaemia; Cerebral septic infarct; Cerebral thrombosis; Cerebrovascular accident; Choroidal infarction; Coeliac artery occlusion; Coronary artery embolism; Coronary artery occlusion; Coronary artery reocclusion; Coronary artery thrombosis; Coronary bypass thrombosis; Embolic cerebral infarction; Embolic stroke; Embolism arterial; Femoral artery embolism; Hepatic artery embolism; Hepatic artery occlusion; Hepatic artery thrombosis; Hepatic infarction; Iliac artery embolism; Iliac artery occlusion; Infarction; Inner ear infarction; Intestinal infarction; Ischaemic cerebral infarction; Ischaemic stroke; Lacunar infarction; Leriche syndrome; Mesenteric arterial occlusion; Mesenteric artery embolism; Mesenteric artery thrombosis; Myocardial infarction; Myocardial necrosis; Optic nerve infarction; Pancreatic infarction; Papillary muscle infarction; Penile artery occlusion; Peripheral arterial occlusive disease; Peripheral arterial reocclusion; Peripheral artery occlusion; Peripheral artery thrombosis; Peripheral embolism; Pituitary infarction; Placental infarction; Post procedural myocardial infarction; Post procedural stroke; Precerebral artery occlusion; Precerebral artery thrombosis; Renal artery occlusion; Renal artery thrombosis; Renal embolism; Renal infarct; Retinal artery embolism; Retinal artery occlusion; Retinal artery thrombosis; Retinal infarction; Retinal vascular thrombosis; Silent myocardial infarction; Spinal artery embolism; Spinal artery thrombosis; Spinal cord infarction; Splenic artery thrombosis; Splenic embolism; Splenic infarction; Splenic thrombosis; Stroke in evolution; Subclavian artery embolism; Subclavian artery occlusion; Subclavian artery thrombosis; Thalamic infarction; Thrombotic cerebral infarction; Thrombotic microangiopathy; Thrombotic stroke; Thyroid infarction; Transient ischaemic attack; Truncus coeliacus thrombosis; Vertebral artery occlusion; Vertebral artery thrombosis

- Venous and Mixed/Unspecified Thrombotic Events

  Arteriovenous fistula occlusion; Arteriovenous fistula thrombosis; Atrial thrombosis; Axillary vein thrombosis; Budd-Chiari syndrome; Cardiac ventricular thrombosis; Cavernous sinus thrombosis; Cerebral venous thrombosis; Cerebrospinal thrombotic tamponade; Deep vein thrombosis; Deep vein thrombosis postoperative; Embolism venous; Graft thrombosis; Haemorrhoids thrombosed; Hepatic vascular thrombosis; Hepatic vein occlusion; Hepatic vein thrombosis; Homans' sign positive; Iliac vein occlusion; Implant site thrombosis; Inferior vena cava syndrome; Inferior vena caval occlusion; Infusion site thrombosis; Injection site thrombosis; Instillation site thrombosis; Intracardiac thrombus; Intracranial venous sinus thrombosis; Jugular vein thrombosis; Mesenteric vascular occlusion; Mesenteric vein thrombosis; Mesenteric venous occlusion; Microembolism; Obstetrical pulmonary embolism; Ophthalmic vein thrombosis; Ovarian vein thrombosis; Paget-Schroetter syndrome; Paradoxical embolism; Pelvic venous thrombosis; Penile vein thrombosis; Portal vein occlusion; Portal vein thrombosis; Post procedural pulmonary embolism; Post thrombotic syndrome; Postoperative thrombosis; Postpartum venous thrombosis; Pulmonary artery thrombosis; Pulmonary embolism; Pulmonary infarction; Pulmonary microemboli; Pulmonary thrombosis; Pulmonary vein occlusion; Pulmonary veno-occlusive disease; Pulmonary venous thrombosis; Renal vascular thrombosis; Renal

vein embolism; Renal vein occlusion; Renal vein thrombosis; Retinal vein occlusion; Retinal vein thrombosis; Shunt occlusion; Shunt thrombosis; Splenic vein occlusion; Splenic vein thrombosis; Stoma site thrombosis; Subclavian vein thrombosis; Superior sagittal sinus thrombosis; Superior vena cava occlusion; Superior vena cava syndrome; Thrombophlebitis; Thrombophlebitis migrans; Thrombophlebitis neonatal; Thrombophlebitis superficial; Thrombosed varicose vein; Thrombosis; Thrombosis corpora cavernosa; Thrombosis in device; Thrombosis mesenteric vessel; Transverse sinus thrombosis; Tumour thrombosis; Umbilical cord thrombosis; Vascular graft thrombosis; Vena cava embolism; Vena cava thrombosis; Venoocclusive disease; Venoocclusive liver disease; Venous occlusion; Venous thrombosis; Venous thrombosis in pregnancy; Venous thrombosis limb; Venous thrombosis neonatal; Vessel puncture site thrombosis

- Wound Complication

  Abdominal wound dehiscence; Ciliary zonular dehiscence; Culture wound positive; Fungating wound; Impaired healing; Incision site cellulitis; Incision site complication; Incision site ulcer; Incisional drainage; Incisional hernia; Incisional hernia gangrenous; Incisional hernia repair; Incisional hernia, obstructive; Inflammation of wound; Postoperative wound complication; Postoperative wound infection; Uterine dehiscence; Wound complication; Wound contamination; Wound decomposition; Wound dehiscence; Wound drainage; Wound evisceration; Wound infection; Wound infection bacterial; Wound infection fungal; Wound infection helminthic; Wound infection pseudomonas; Wound infection staphylococcal; Wound infection viral; Wound necrosis; Wound secretion; Wound sepsis

- Hypertension

  Accelerated hypertension; Blood pressure ambulatory increased; Blood pressure diastolic increased; Blood pressure inadequately controlled; Blood pressure increased; Blood pressure management; Blood pressure orthostatic increased; Blood pressure systolic increased; Diastolic hypertension; Eclampsia; Endocrine hypertension; Essential hypertension; Gestational hypertension; HELLP syndrome; Hyperaldosteronism; Hypertension; Hypertension neonatal; Hypertensive angiopathy; Hypertensive cardiomegaly; Hypertensive cardiomyopathy; Hypertensive crisis; Hypertensive emergency; Hypertensive encephalopathy; Hypertensive heart disease; Hypertensive nephropathy; Labile hypertension; Malignant hypertension; Malignant hypertensive heart disease; Malignant renal hypertension; Maternal hypertension affecting foetus; Mean arterial pressure increased; Metabolic syndrome; Neurogenic hypertension; Orthostatic hypertension; Pre-eclampsia; Prehypertension; Procedural hypertension; Renal hypertension; Renal sympathetic nerve ablation; Renovascular hypertension; Retinopathy hypertensive; Secondary aldosteronism; Secondary hypertension; Systolic hypertension; Withdrawal hypertension

- Osteonecrosis

  Alveolar osteitis; Bone debridement; Bone infarction; Dental necrosis; Exposed bone in jaw; Osteonecrosis; Osteonecrosis of jaw; Osteoradionecrosis; Periodontal destruction; Primary sequestrum; Secondary sequestrum; Tertiary sequestrum

- PPES

  Palmar-plantar erythrodysaesthesia syndrome

- Proteinuria

  Albumin urine; Albuminuria; Nephrotic syndrome; Protein urine; Proteinuria

- RPLS

  Posterior reversible encephalopathy syndrome

- Diarrhea

  Antidiarrhoeal supportive care; Bacterial diarrhoea; Diarrhoea; Diarrhoea haemorrhagic; Diarrhoea infectious; Diarrhoea infectious neonatal; Diarrhoea neonatal; Post procedural diarrhoea; Prophylaxis against diarrhoea; Viral diarrhoea

- QT Prolongation

  Electrocardiogram QT interval abnormal; Electrocardiogram QT prolonged; Long QT syndrome; Torsade de pointes

- Renal Failure

  Anuria; Diabetic end stage renal disease; Oliguria; Renal failure; Renal failure neonatal; Renal impairment neonatal; Neonatal anuria; Crush syndrome; Pancreatorenal syndrome; Postrenal failure; Renal injury; Renal impairment; Scleroderma renal crisis; Chronic kidney disease; Acute kidney injury; Prerenal failure; End stage renal disease; Foetal renal impairment

- Hypothyroidism

  Hypothyroidism

- Hepatotoxicity

  Acquired hepatocerebral degeneration; Acute hepatic failure; Acute on chronic liver failure; Acute yellow liver atrophy; Ascites; Asterixis; Bacterascites; Biliary cirrhosis; Biliary fibrosis; Cholestatic liver injury; Chronic hepatic failure; Coma hepatic; Cryptogenic cirrhosis; Diabetic hepatopathy; Drug-induced liver injury; Duodenal varices; Gallbladder varices; Gastric variceal injection; Gastric variceal ligation; Gastric varices; Gastric varices haemorrhage; Hepatectomy; Hepatic atrophy; Hepatic calcification; Hepatic cirrhosis; Hepatic encephalopathy; Hepatic encephalopathy prophylaxis; Hepatic failure; Hepatic fibrosis; Hepatic hydrothorax; Hepatic infiltration eosinophilic; Hepatic lesion; Hepatic necrosis; Hepatic steato-fibrosis; Hepatic steatosis; Hepatitis fulminant; Hepatobiliary

disease; Hepatocellular foamy cell syndrome; Hepatocellular injury; Hepatopulmonary syndrome; Hepatorenal failure; Hepatorenal syndrome; Hepatotoxicity; Intestinal varices; Intestinal varices haemorrhage; Liver and small intestine transplant; Liver dialysis; Liver disorder; Liver injury; Liver operation; Liver transplant; Lupoid hepatic cirrhosis; Minimal hepatic encephalopathy; Mixed liver injury; Nodular regenerative hyperplasia; Non-alcoholic fatty liver; Non-alcoholic steatohepatitis; Non-cirrhotic portal hypertension; Oedema due to hepatic disease; Oesophageal varices haemorrhage; Peripancreatic varices; Portal fibrosis; Portal hypertension; Portal hypertensive colopathy; Portal hypertensive enteropathy; Portal hypertensive gastropathy; Portal vein cavernous transformation; Portal vein dilatation; Portopulmonary hypertension; Primary biliary cholangitis; Regenerative siderotic hepatic nodule; Renal and liver transplant; Retrograde portal vein flow; Reye's syndrome; Reynold's syndrome; Splenic varices; Splenic varices haemorrhage; Steatohepatitis; Subacute hepatic failure; Varices oesophageal; Varicose veins of abdominal wall; White nipple sign; Anorectal varices; Anorectal varices haemorrhage; Intrahepatic portal hepatic venous fistula; Peritoneovenous shunt; Portal shunt; Portal shunt procedure; Small-for-size liver syndrome; Spider naevus; Splenorenal shunt; Splenorenal shunt procedure; Spontaneous intrahepatic portosystemic venous shunt; Stomal varices; Acute graft versus host disease in liver; Allergic hepatitis; Alloimmune hepatitis; Autoimmune hepatitis; Chronic graft versus host disease in liver; Chronic hepatitis; Graft versus host disease in liver; Hepatitis; Hepatitis acute; Hepatitis cholestatic; Hepatitis chronic active; Hepatitis chronic persistent; Hepatitis fulminant; Hepatitis toxic; Immune-mediated hepatitis; Ischaemic hepatitis; Lupus hepatitis; Non-alcoholic steatohepatitis; Radiation hepatitis; Steatohepatitis; Granulomatous liver disease; Liver sarcoidosis; Portal tract inflammation; Benign hepatic neoplasm; Benign hepatobiliary neoplasm; Focal nodular hyperplasia; Haemangioma of liver; Haemorrhagic hepatic cyst; Hepatic adenoma; Hepatic cyst; Hepatic cyst ruptured; Hepatic haemangioma rupture; Hepatic hamartoma; Hepatobiliary cyst; Cholangiosarcoma; Hepatic angiosarcoma; Hepatic cancer; Hepatic cancer metastatic; Hepatic cancer recurrent; Hepatic cancer stage I; Hepatic cancer stage II; Hepatic cancer stage III; Hepatic cancer stage IV; Hepatobiliary cancer; Hepatobiliary cancer in situ; Hepatoblastoma; Hepatoblastoma recurrent; Hepatocellular carcinoma; Liver carcinoma ruptured; Mixed hepatocellular cholangiocarcinoma; Liver ablation; Hepatic neoplasm; Hepatobiliary neoplasm

## ELECTRONIC SIGNATURES

| Signed by | Meaning of Signature | Server Date (dd-MMM-yyyy HH:mm 'UTC') |
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