Shionogi study title	A Phase 3 Randomised, Double-blind, Placebo-controlled Study to Assess the Safety and Efficacy of S-888711 (Lusutrombopag) for the Treatment of Thrombocytopenia in Patients with Chronic Liver Disease Undergoing Elective Invasive Procedures (L-PLUS 2)
Shionogi study no.	1423M0634
ClinicalTrials.gov registration no.	NCT02389621
Study document	Statistical analysis plan

STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3 Randomised, Double-blind, Placebo-controlled Study to Assess the Safety and Efficacy of S-888711 (Lusutrombopag) for the Treatment of Thrombocytopenia in Patients with Chronic Liver Disease Undergoing Elective Invasive Procedures (L-PLUS 2)
Study Number:	1423M0634
Study Phase:	3
Product Name:	S-888711 (Lusutrombopag)
Sponsor:	Shionogi & Co., Ltd., Shionogi Inc., Shionogi Ltd.
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SIGNATURE PAGE

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Approved by:

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6 JUN 2017
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Prepared by:

[redacted]

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AMENDMENT HISTORY

Version	Date	Author	Remarks
1.0	17 Apr 2015	[redacted]	First version
2.0	5 Jun 2017		Major revisions are as follows. • Added an ITT analysis for the duration of the increase in platelet count (see Sections 6.2 and 9.2.3). • Added a sensitivity analysis for the primary endpoint based on platelet count at platelet transfusion assessment. • Removed summary of significant TEAEs from Section 10.1. • Revised the descriptions to clarify the definition or data handling. • Added Appendix 3.

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LIST OF TABLES

ABBREVIATIONS

AE(s)	adverse event(s)
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
CI	confidence interval
CLD	chronic liver disease
CMH	Cochran-Mantel-Haenszel
CRO	Contact Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
EIS	endoscopic injection sclerotherapy
EVL	endoscopic variceal ligation
ICSA	Individual Clinically Significant Abnormalities
ITT	intention-to-treat
IVRS/IWRS	Interactive Voice or Web Response System
MCT	microwave coagulation therapy
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamics
PK	pharmacokinetics
PP	per protocol
PT-INR	prothrombin time-international normalized ratio
RFA	radiofrequency ablation
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SMQ	standard MedDRA queries
SUSAR	suspected unexpected serious adverse reaction
TACE	transcatheter arterial chemoembolization
TAE	transcatheter arterial embolization
TEAE(s)	treatment-emergent adverse event(s)
WHO	World Health Organization

1. INTRODUCTION

This "Statistical Analysis Plan (SAP)" presents details, including technical matters, of the efficacy and safety analyses described in Section "8. STATISTICAL ANALYSIS" of the protocol 1423M0634 for the clinical trial entitled "A Phase 3 Randomised, Double-blind, Placebo-controlled Study to Assess the Safety and Efficacy of S-888711 (Lusutrombopag) for the Treatment of Thrombocytopenia in Patients with Chronic Liver Disease (CLD) Undergoing Elective Invasive Procedures (L-PLUS2)". Details of output (or mock-ups of tables, listings and figures) from analyses in this SAP, will be included in the document prepared separately. Details of the analyses of pharmacokinetics (PK) and pharmacokinetics/pharmacodynamics will also be described in a separate document.

All the analyses described in this SAP will be performed in the Biostatistics Dept., Shionogi & Co., Ltd.

2. STUDY OVERVIEW

This is a phase 3, multinational, randomized, double-blind, placebo-controlled study to assess the safety and efficacy of S-888711 for the treatment of thrombocytopenia in patients with CLD undergoing elective invasive procedures. The study consists of 3 periods:

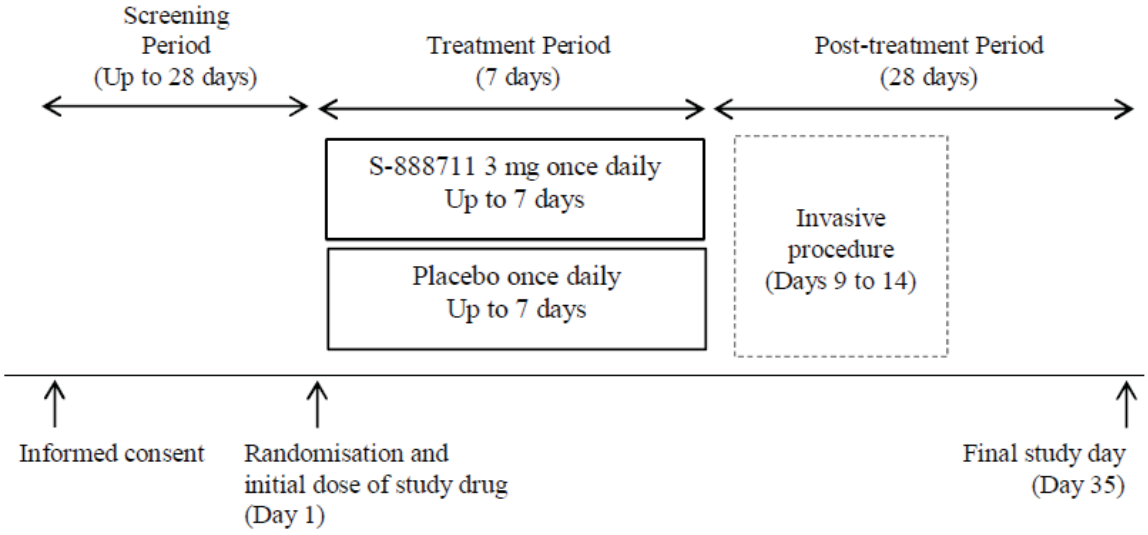
- Screening period: up to 28 days prior to randomization
- Treatment period: up to 7 days (Days 1 to 7)
- Post-treatment period: through 28 days post-treatment

The maximum study duration for each patient will be 63 days. Potential patients who provide written informed consent will be screened for eligibility, and eligible patients will be randomized in a 1:1 ratio to either S-888711 3 mg once daily for up to 7 days or matched placebo control. The randomization will be stratified by primary invasive procedure (liver ablation/coagulation or other invasive procedures) and baseline platelet count ($< 35 \times 10^9$/L or $\geq 35 \times 10^9$/L).

Patients will begin once daily treatment with assigned study medication on Day 1 after randomization and will receive study medication for up to 7 days. A platelet count will be performed on Days 5, 6, and 7 prior to administration of study medication. After the final dose of study medication, patients will continue the protocol-specified assessments and procedures in the Post-treatment period.

The planned invasive procedure will be performed in the Post-treatment period between Days 9 and 14. A platelet count will be performed on or after Day 8, but no more than 2 days prior to the elective invasive procedure in order to assess the need for a platelet transfusion before the planned elective procedure. A preoperative platelet transfusion must be performed if the platelet count is $< 50 \times 10^9$/L.

Study Schematic



3. STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this study is to compare the efficacy of S-888711 with placebo for the treatment of thrombocytopenia in patients with CLD who are undergoing elective invasive procedures.

3.2 Secondary Objective(s)

The secondary objectives of the study are:

- To assess the safety and tolerability of S-888711 treatment compared with placebo.
- To assess the platelet response following treatment with S-888711 compared with placebo.
- To assess the pharmacodynamics (PD) and PK of S-888711.

4. STUDY DESIGN

4.1 Schedule of Assessments

Schedule of assessments is shown in Appendix 1.

4.2 Study Blinding and Randomization

The study will be conducted in a double-blind manner using a placebo matching the active drug in appearance, labelling and packaging. An IVRS/IWRS will be used for central patient randomization and study drug assignment. IVRS/IWRS will assign drug identifiers according to a randomization schedule. Only an unblinded Contract Research Organization (CRO) or designee will have the authority to assign the drug identifiers. All patients, the investigator, all study personnel, and data analysts will be blinded to the

treatment assigned at randomization until database lock. The randomization schedule will be kept confidential and will not be accessible to anyone until unblinding, except for Drug Supply Management staff, IVRS/IWRS Clinical Coordinator(s), IVRS/IWRS vendor staff, unblinded statistician on the Independent Safety Committee, and for reporting suspected unexpected serious adverse reaction (SUSAR) as required by local regulation.

Eligible patients will be randomized to one of the two treatment groups (S-888711 3 mg/day for up to 7 days, or placebo for up to 7 days) in a ratio of 1:1. Randomization will be stratified by the primary invasive procedure and the platelet count at baseline as follows:

- Primary invasive procedure: liver ablation/coagulation or other invasive procedures
- Platelet count at baseline: $< 35 \times 10^9$/L or $\geq 35 \times 10^9$/L

4.3 Determination of Sample Size

Two hundred patients with CLD and thrombocytopenia who are scheduled to undergo elective invasive procedures will be randomized into either of two treatment groups (100 patients per group).

In the phase 3 study (Study 1304M0631) conducted in Japan, the proportion of patients who required no platelet transfusion prior to the primary invasive procedure was 79.2% in the S-888711 3 mg group and 12.5% in the placebo group. The difference in the proportion of patients was 66.7% and its 95% confidence interval (CI) was [51.9%, 81.5%]. Based on the results, it was assumed that the difference in the primary endpoint to be obtained in this study is 50% between S-888711 and placebo groups. Assuming that the proportion of patients who meet the primary endpoint is 20% in the placebo group and 70% in the S-888711 treatment group, 100 patients per arm will provide 99% power to detect a difference of 50% between S-888711 and placebo groups at a two-sided significance level of 0.05.

With 100 patients per arm, from the safety point of view, the sample size will assure at least 95% probability to detect an adverse event (AE) with an incidence of 3% or more.

5. ANALYSIS POPULATIONS

5.1 Intention-to-Treat (ITT) Population

Intention-to-Treat (ITT) Population will include all randomized patients. Patients will be analyzed according to the treatment to which they were randomized. This population is the primary population for the analysis of efficacy.

5.2 Per Protocol (PP) Population

Per Protocol (PP) Population will include all randomized patients who have no major protocol deviations pertaining to the efficacy evaluation. These deviations will be

determined prior to unblinding of the study data. This population will be used in a sensitivity analysis of the primary endpoint.

5.3 Safety Analysis Population

Safety Analysis Population will include all randomized patients who actually receive at least 1 dose of the study drug. Patients will be analyzed by the treatment they actually received, rather than by the designated treatment to which they were randomized. If patients received both S-888711 and placebo, they will be considered as the S-888711 group. This population is the primary population for the analysis of safety.

6. OVERALL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

6.1 Statistical Reporting

In principle, summary statistics, including the number of patients, arithmetic mean, standard deviation (SD), median, and minimum and maximum values, will be calculated for continuous variables. The number and proportion of patients in each category will be calculated for categorical variables.

In general, all tabulations will be presented by treatment group. Individual patient data and any derived data will be summarized by treatment group and listed by patient. All the analyses and listings will be performed using SAS Version 9.2 or higher.

6.2 Statistical Testing

Unless otherwise noted, all statistical tests will be performed at a two-sided significance level of 0.05.

A gatekeeping procedure will be employed for sequentially testing the important secondary endpoints (see Appendix 2). If the primary endpoint is statistically significant, the secondary endpoints will be tested at the 0.05 level (two-sided) in sequence. Sequential testing for the secondary endpoints will be conducted in the following order:

- The comparison between S-888711 and placebo in the proportion of patients who require no platelet transfusion during the study
- The comparison between S-888711 and placebo in the proportion of responders: patients who achieve a platelet count of $\geq 50 \times 10^9$/L, with an increase of $\geq 20 \times 10^9$/L from baseline at any time during the study
- The comparison between S-888711 and placebo in the duration of platelet count $\geq 50 \times 10^9$/L
- The comparison between S-888711 without platelet transfusion and placebo with platelet transfusion in the duration of platelet count $\geq 50 \times 10^9$/L

6.3 Analysis Visit

Analysis visit windows are defined as shown in Table 1 to determine the analysis value for each study visit. Measurements collected outside of the visit window will be considered missing for that study visit. For all patients with multiple values within a visit window, the value obtained closest to the target study day will be used. In the case of multiple observations equidistant to the study visit date, the later one will be used, unless otherwise noted. Only for screening visit, the earliest one will be used for analysis if multiple values were obtained within 28 days prior to randomization.

In regard to "after the invasive procedure", which is the analysis visit for WHO Bleeding Scale, Portal Vein Thrombosis, and Portal Blood Flow, the allowance is within 3 days to 10 days after the first invasive procedure. In the case of multiple observations equidistant to the study visit date, the earlier one will be used, unless otherwise noted.

Table 1 Analysis Visit Windows

Study Day for Analysis	Allowance
Screening	Within 28 days prior to randomization
Day 1 (Baseline)	Within 7 days before initiation of study medication
Days 5-7	±0 day
Day 8	±0 day
Day 10	±1 day
Days 12 and 14	+1 day
Days 17 and 21	−1 day to +2 days
Day 28	±2 days
Day 35	−2 day to +7 days

6.4 Handling of Missing Data

Unless otherwise noted, missing values will not be imputed. All analyses will be performed using actual observations.

If a patient received platelet transfusion on the same day as an invasive procedure but the time of either platelet transfusion or invasive procedure was missing, the patient will be considered as he/she underwent the invasive procedure after receiving platelet transfusion.

If a patient had a platelet transfusion and platelet count on the same day but the time of either platelet transfusion or collection of blood sample for platelet count was missing, the patient will be considered as he/she received the platelet transfusion after collection of the blood sample for platelet count.

6.5 Definition

6.5.1 Study Day

Study Day 1 corresponds to the date of initial dose of the study drug. Other study days are defined relative to Study Day 1. Screening will be expressed as Day -28 for descriptive purpose.

6.5.2 Baseline

The baseline value is defined as a value obtained on Day 1 before administration of the initial dose of study drug. If this value is missing, the most recent value obtained prior to Day 1 within the 7 preceding days will be used as the baseline value. Regarding body weight, height, and body mass index (BMI), the measurement at screening visit will be used as the baseline value.

6.5.3 Last Observation

Last observation will refer to the last nonmissing observation after baseline which is within the analysis visit window and used in the analysis (see Section 6.3) or is within 7 days after the day of early termination of study assessment.

7. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

7.1 Patient Disposition and Withdrawals

The number and proportion of patients who completed the study (which is defined as completing both the treatment period and the posttreatment period) and the number and proportion of patients who prematurely discontinued from the study will be calculated by treatment group for all randomized patients. Withdrawals in the treatment and the posttreatment periods and the reasons leading to discontinuation will also be summarized.

The number of patients who were administered at least one dose of study drug and the number and proportion of patients who completed 7 days of dosing period will be calculated by treatment group for all randomized patients. The reason for the discontinued administration of study drug (i.e., administration for less than 7 days) will be summarized by treatment group for all randomized patients who completed and did not complete the study, respectively.

The number and proportion of patients in each analysis population will be summarized by treatment group, as well as the reasons for exclusion from ITT, PP and Safety Populations.

7.2 Demographic and Baseline Characteristics

Demographics and baseline characteristics shown in Table 2 will be tabulated by treatment group for the ITT population. Summary statistics will be calculated for continuous variables, and the frequency and proportion of patients in each category will be obtained for categorical variables.

Table 2 Demographic and Baseline Characteristics

Continuous Variable	age, height, weight, BMI, platelet count at baseline
Categorical Variable	sex, race, ethnicity, presence or absence of any transfusion history, presence or absence of history of CLD due to: - hepatitis B, - hepatitis C, - alcoholic hepatitis, - non-alcoholic hepatitis, - autoimmune hepatitis, Child-Pugh class, WHO Bleeding Scale, planned invasive procedure (liver ablation/coagulation, other), platelet count at baseline ($< 35 \times 10^9$/L, $\geq 35 \times 10^9$/L), platelet count at randomization ($< 35 \times 10^9$/L, $\geq 35 \times 10^9$/L) ECOG performance status, presence or absence of gastro oesophageal varices, presence or absence of splenomegaly, presence or absence of ascites

Details of medical history will be summarized by treatment group. The reported medical history terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 18.0 or higher.

8. STUDY CONDUCT

8.1 Protocol Deviation

Protocol deviations/violations will be provided in a patient data listing. Major protocol deviations will be specified in the "Blinded Data Review Plan" and its final list will be determined based on blinded data review prior to database lock. The number and proportion of patients with major protocol deviations will be summarized by treatment group. The summary will be based on all randomized patients.

Emergency unblinding information will be listed, if needed.

8.2 Treatment Exposure

The number of days of study drug dosing will be tabulated using summary statistics by treatment group for the safety analysis population.

8.3 Concomitant Medication

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (version Mar2015 B2 or higher), and summarized based on the safety analysis population.

The number and proportion of patients who received at least one dose of concomitant medication during the study will be calculated by treatment group, with details of concomitant medications with WHO Drug Dictionary preferred term. Patients for whom a particular preferred term was reported more than once will be counted only once for that preferred term.

The number and proportion of patients who received at least one session of concomitant therapy during the study will be calculated by treatment group, with details of concomitant therapy names. Patients for whom a particular concomitant therapy was reported more than once will be counted only once for that therapy.

9. EFFICACY

Unless otherwise specified, efficacy analyses will be performed for the ITT population.

9.1 Primary Endpoint

The primary endpoint is the proportion of patients who require no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from the date of randomization until 7 days after the primary elective procedure. The patients will be determined as a success for the primary endpoint if all of the following conditions are satisfied:

- Patients received no platelet transfusion from the date of randomization through at least 7 days after the primary invasive procedure (i.e., the first invasive procedure in the study)
- Patients received no rescue therapy for bleeding (including any of the following) from the date of randomization through 7 days after the primary invasive procedure
  - Platelet preparations
  - Other blood preparations, including red blood cells and plasma
  - Volume expanders
- Patients underwent an invasive procedure

In contrast, the following patients will be considered as failures for the primary endpoint if any of the following conditions is satisfied:

- Patients received at least one platelet transfusion prior to the primary invasive procedure
- Patients received at least one rescue therapy for bleeding from the date of randomization through 7 days after the primary invasive procedure
- Patients withdrew from the study before undergoing the primary invasive procedure
- Patients did not undergo an invasive procedure

9.1.1 Primary Analysis

The number and proportion of patients who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from the date of randomization through 7 days after the primary elective procedure will be calculated by treatment group. The primary endpoint will be presented along with 95% confidence intervals (CIs), which will be calculated with the Clopper-Pearson method.

The proportion of patients who required no platelet transfusion in the S-888711 group will be compared with that in the placebo group using the Cochran-Mantel-Haenszel (CMH) test adjusted by the stratification factors, i.e., the four strata:

- Platelet count at randomization $< 35 \times 10^9$/L and liver ablation/coagulation
- Platelet count at randomization $< 35 \times 10^9$/L and other invasive procedure
- Platelet count at randomization $\geq 35 \times 10^9$/L and liver ablation/coagulation
- Platelet count at randomization $\geq 35 \times 10^9$/L and other invasive procedure.

In addition, the differences in the primary endpoint and its 95% CI using Wald method (see Appendix 3) will be calculated.

9.1.1.1 Subgroup Analysis

The primary endpoint will be analyzed separately for the following subgroups:

- Platelet count at baseline: $< 35 \times 10^9$/L, $\geq 35 \times 10^9$/L
- Received primary invasive procedure: Percutaneous RFA/MCT, Laparoscopic RFA/MCT, EVL, EIS, TACE, TAE, other, and not performed
- Sex: male, female
- Age: < 65 years, ≥ 65 years
- Baseline body weight: < 75 kg, ≥ 75 kg
- Race: White, NonWhite
- Child-Pugh class: A, B, C

The number and proportion of patients will be calculated by treatment group. The proportion of patients will be reported and will be compared between the S-888711 and placebo groups by Fisher's exact test. In addition, the interaction between subgroup (except received invasive procedure and Child-Pugh class C) and treatment group will be tested with Breslow-Day test.

9.1.2 Sensitivity Analysis

The following sensitivity analyses for the primary endpoint will be performed for the ITT population, unless otherwise noted.

1) PP Population

   The primary efficacy analysis will be repeated for PP population.

2) Handling of Withdrawal

   For classification of patients into success and failure, the primary endpoint will be modified as follows to explore the impact of missing data, withdrawals, or patients who did not undergo an invasive procedure.

   – Patients who withdrew from the study before undergoing the primary invasive procedure but whose last observation of platelet count was $\geq 50 \times 10^9$/L with an increase of $\geq 20 \times 10^9$/L from baseline will be classified as success, if he/she did not receive platelet transfusion and rescue therapy for bleeding.

   – Patients who did not undergo an invasive procedure but whose platelet count was $\geq 50 \times 10^9$/L with an increase of $\geq 20 \times 10^9$/L from baseline at least once within 14 days after randomization will be classified as success, if he/she did not receive platelet transfusion and rescue therapy for bleeding.

3) Patients Data Based Analysis

   For classification of patients into success and failure, the primary endpoint will be modified as follows based on platelet count at platelet transfusion assessment.

   – Patents whose platelet count was $\geq 50 \times 10^9$/L at platelet transfusion assessment will be considered as success regardless of preoperative platelet transfusion, if he/she (1) underwent invasive procedure, (2) did not receive platelet transfusion within 7 days after the primary invasive procedure, and (3) did not receive rescue therapy for bleeding from the date of randomization through 7 days after the primary invasive procedure. If platelet count at platelet transfusion assessment was missing, the patients will be considered as failure.

9.2 Secondary Endpoints

The following analyses for secondary endpoints will be conducted in the ITT population.

9.2.1 Proportion of Patients Requiring no Platelet Transfusion During the Study

A secondary endpoint is the proportion of patients who required no platelet transfusion during the study. A patient will be considered as success for this endpoint if he/she required no platelet transfusion and received the invasive procedure during the study. All other patients will be considered as failures.

9.2.1.1 Analysis

The number and proportion of patients who required no platelet transfusion during the study will be calculated by treatment group. The proportions will be presented along with 95% CIs. The proportion of patients who required no platelet transfusion during the study in the S-888711 group will be compared with that in the placebo group using the CMH test adjusted by the stratification factors. In addition, the differences in the secondary endpoint and its 95% CI will be calculated.

9.2.2 Proportion of Responders

A responder will be defined as the patient who achieved the following criterion, that is a platelet count of $\geq 50 \times 10^9$/L with an increase of $\geq 20 \times 10^9$/L from baseline without platelet transfusion at least once during the study. All patients in the ITT population will be classified into either responder or nonresponder for evaluating the proportion of responders during the study. A patient who had platelet transfusion will be considered as a responder if he/she achieved the responder criterion before receiving the first platelet transfusion. However, a patient will be considered as nonresponder if their platelet count met the responder criterion only after platelet transfusion.

In evaluating the proportion of responders at each scheduled time point (Day 5, 6, 7, 8, 10, 12, 14, 17, 21, 28, and 35), a patient will be counted as a responder if all of the following conditions are satisfied:

- Patients achieved a platelet count of $\geq 50 \times 10^9$/L with an increase of $\geq 20 \times 10^9$/L from baseline at the evaluation point.
- Patients received no platelet transfusion through the evaluation point.

Missing platelet count at each scheduled time point will not be imputed.

9.2.2.1 Analysis

The number and proportion of responders during the study will be calculated by treatment group. The responder rates will be presented along with 95% CIs, which will be calculated with the Clopper-Pearson method. The proportion of responders during the study in the S-888711 group will be compared with that in the placebo group using the CMH test adjusted by the stratification factors. In addition, the differences in the responder rate and its 95% CI will be calculated.

The number and proportion of responders will be calculated by treatment group at each time point. This analysis will be performed for the ITT population with observed values.

9.2.3 Duration of the Increase in Platelet Count

The duration of the increase in platelet count will be defined as the number of days during which the platelet count was maintained as $\geq 50 \times 10^9$/L, and it will be calculated based on the platelet count at scheduled time points (Days 1, 5, 6, 7, 8, 10, 12, 14, 17, 21, 28, and 35). The detail of the calculation is as follows.

Let (x_i, y_i) be the observed value at scheduled time point i, where $i = 1, 2, ..., c$ and c (≤ 12) can be different for each patient. For $i > 1$, x_i is the day from initial administration of the study drug to Visit i defined as (the measurement date at Visit i) – (date of initial dose of the study drug) + 1, and y_i is the observed platelet count [$\times 10^9$/L], respectively. The baseline value represents (x_1, y_1), where $x_1 = 1$. Let L_i be the line connecting (x_i, y_i) and (x_{i+1}, y_{i+1}), and $(z_i, 50)$ be the intersection point between L_i and $y = 50$. Then, the duration of the platelet count will be calculated as $D = \sum_i d_i$, where

$$d_i = \begin{cases} x_{i+1} - x_i, & \text{if } y_i \geq 50 \text{ and } y_{i+1} \geq 50 \\ x_{i+1} - z_i, & \text{if } y_i < 50 \text{ and } y_{i+1} \geq 50 \\ z_i - x_i, & \text{if } y_i \geq 50 \text{ and } y_{i+1} < 50 \\ 0, & \text{if } y_i < 50 \text{ and } y_{i+1} < 50 \end{cases}.$$

If there is a missing assessment at Visit (i+1), L_i should be the line connecting (x_i, y_i) and (x_{i+2}, y_{i+2}), where (x_{i+2}, y_{i+2}) represents the next visit with data available.

9.2.3.1 Analysis

Median and quartiles for the duration of the increase in platelet count will be calculated by treatment group with or without platelet transfusions. The duration in the S-888711 group will be compared with that in the placebo group using van Elteren test stratified with platelet transfusion during the study. In addition, to explore an efficacy of S-888711 compared to platelet transfusion, the duration in the S-888711 group without platelet transfusion will be compared with that in the placebo group with platelet transfusion using Wilcoxon rank sum test.

9.2.4 Proportion of Patients who Required Rescue Therapy

The number and proportion of patients who received rescue therapy for bleeding events during the study will be calculated for each treatment group. Platelet preparations, other blood preparations including red blood cells and plasma, and volume expanders will be considered as rescue therapy for bleeding events.

The number and proportion of patients who received antithrombotic drugs for thrombotic events during the study will be summarized similarly.

9.2.5 Frequency of Platelet Transfusion and Dose (Unit) Transfused During the Study

The number and proportion of patients who received platelet transfusion during the study will be calculated for each treatment group, and the reasons for platelet transfusion will be summarized. For the patients who received at least one platelet transfusion, the number of platelet transfusions during the study will be summarized by treatment group.

Average dose (unit/bags) of platelet transfusion will be calculated for each patient and then summarized by treatment group if appropriate. If the total amount of transfused platelets is able to be estimated for patients, it will be performed with reference to a minimum contents based on a guidance on platelet preparations in each country taking into account the method for collection (apheresis/pooled).

9.2.6 Time Course of Platelet Count

Unless otherwise specified, the following analyses will be performed for patients who received and who didn't receive platelet transfusions.

Summary statistics for platelet count will be calculated at each scheduled time point (Days 1, 5, 6, 7, 8, 10, 12, 14, 17, 21, 28, and 35) by treatment group. Summary statistics for the change in platelet count from baseline will also be calculated.

The time course of the median, 25% and 75% quartile of platelet count will be graphically displayed by treatment group. Reference line which shows $y = 50 \times 10^9$/L will be drawn in the figure. In addition, the time course of the mean and standard deviation of platelet count change from baseline will be graphically displayed by treatment group. Reference line which shows $y = 20 \times 10^9$/L will be drawn in the figure.

Summary statistics for the maximum platelet count and the maximum change in platelet count of each patient will be calculated by treatment group. Baseline value will not be included in this analysis.

For the patients who received no platelet transfusion, the time point at which each patient showed the maximum platelet count will be summarized by treatment group. If maximum platelet count for the patient is observed at more than one time point, the earliest time point will be used in this analysis.

10. SAFETY

Safety analyses will be performed for the safety analysis population.

10.1 Adverse Events

Adverse events will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) Version 18.0 or higher. Unless otherwise specified, treatment-emergent adverse events (TEAEs), that is any AEs reported after initiation of treatment with S-888711 or placebo, will be used for the analyses of safety.

The number of patients who experienced at least 1 TEAE and corresponding incidence will be calculated by treatment group. The incidence of TEAEs will be reported along with 95% CIs, which will be calculated with Clopper-Pearson method. The number of TEAEs, counted by cases reported, will also be presented. Death, treatment-emergent serious adverse events (SAEs), TEAEs leading to withdrawal of the study drug, and treatment-related AEs will be summarized in the same manner as the overall summary of TEAEs. The definitions of death, treatment-emergent SAEs, TEAEs leading to withdrawal of the study drug, and treatment-related AEs are shown below.

Term	Definition
Death	TEAEs with “Fatal” in terms of outcome.
Treatment-emergent SAEs	TEAEs with “Serious” in terms of seriousness
TEAEs leading to withdrawal of the study drug	TEAEs with “Drug withdrawn” in terms of the action taken for study drug.
Treatment-related AEs	TEAEs with “Related” in terms of the causal relationship with study drug.

The number of patients who experienced TEAEs and corresponding incidence will be calculated by system organ class (SOC) and preferred term (PT) for each treatment group. In the calculation, a patient who experienced a particular TEAE more than once will be counted only once within a SOC and PT. Treatment-emergent SAEs, TEAEs leading to withdrawal of the study drug, and treatment-related AEs will be summarized in a similar manner.

The number of patients who experienced TEAEs in each category of severity and outcome will be counted by SOC and PT for each treatment group, and the corresponding incidence in each category will be calculated. For patients who experienced a particular TEAE more than once in different categories, the patient will be counted only once using the highest priority category shown in Table 3. Treatment-related AEs will be summarized in a similar manner.

Table 3 Priority of Categories

Priority	Category	
	Severity	Outcome
1	Severe	Fatal
2	Moderate	Recovered/resolved with sequelae
3	Mild	Not recovered/not resolved
4		Recovering/resolving
5		Recovered/resolved
6		Unknown

For the patients who underwent invasive procedure in safety analysis population, the summary of TEAEs before and after the primary invasive procedure will be presented by SOC and PT for each treatment group. In the calculation of the number of patients and corresponding incidence, a patient who experienced a particular TEAE more than once will be counted only once. Treatment-related AEs will be summarized in a similar manner.

The number of patients who experienced bleeding-related TEAEs and corresponding incidence will be calculated by SOC and PT for each treatment group. A patient who experienced a particular TEAE more than once will be counted only once within a SOC and PT. Bleeding-related TEAEs will be defined as TEAEs which were classified as “haemorrhage terms (except laboratory terms)” using Standard MedDRA Queries (SMQ).

10.2 Adverse Events of Special Interest

Thrombotic/thromboembolic events will be considered as adverse events of special interest in this study. The definition of thrombotic/thromboembolic TEAEs is described as TEAEs which are classified as follows using the SMQ:

- "embolic and thrombotic events, arterial"
- "embolic and thrombotic events, venous"
- "embolic and thrombotic events, vessel type unspecified and mixed arterial and venous".

The number of patients who experienced thrombotic/thromboembolic TEAEs and corresponding incidence will be calculated by SOC and PT for each treatment group. A patient who experienced a particular TEAE more than once will be counted only once within a SOC and PT.

10.3 WHO Bleeding Scale

For each WHO Bleeding Scale, the number and proportion of patients will be calculated by treatment group at each scheduled time point (Days 1, 8, 35, after the primary invasive procedure and last observation).

10.4 Vital Signs

For systolic blood pressure, diastolic blood pressure, and pulse rate, summary statistics of observations and their changes from baseline will be calculated at each scheduled time point (Days 1, 5, 8, 10, 12, 14, 21, 28, 35 and last observation) by treatment group.

10.5 Electrocardiography

The number and proportion of patients with an abnormal ECG finding will be calculated by treatment group at Day 35 and last observation.

10.6 Laboratory Tests

For laboratory tests listed in Table 4, summary statistics of observations and their changes from baseline will be calculated at each scheduled time point (Days 1, 8, 14, 35 and last observation) by treatment group.

Table 4 List of Laboratory Tests

Test	Items Evaluated
Haematology (except for platelet count)	Red blood cell count, white blood cell count, haemoglobin, and haematocrit
Blood Chemistry	Aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase, gamma glutamyl transferase, alkaline phosphatase, total bilirubin, bilirubin direct, indirect bilirubin, total protein, albumin, blood urea nitrogen, serum creatinine, sodium, potassium, chloride, and calcium
Blood Coagulation/Fibrinolysis Assay	Prothrombin time-international normalized ratio (PT-INR), activated partial thromboplastin time

Individual clinically significant abnormalities (ICSA) will be summarized based on criteria which are determined by reference to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (see Appendix 4). For each CTCAE term shown in Appendix 4, the number and proportion of patients with a laboratory test result classified as grade 2 or more will be calculated at each scheduled time point (Days 1, 8, 14, 35) by treatment group. In addition, the number and proportion of patients with a laboratory test result classified as grade 2 or more at least once after the initiation of study drug will be calculated. For the term "hyponatremia", the number and proportion of patients with a laboratory test result classified as grade 3 or more will be summarized because the term doesn't have criteria for grade 2. The upper limit of normal range for PT-INR is regarded as 1 if it will not be specified by the central laboratory.

The number and proportion of patients who met the following criteria for liver function abnormalities will be calculated at each scheduled time point (Days 1, 8, 14, 35) by treatment group. The number and proportion of patients with liver function abnormalities after the initiation of study drug will also be calculated.

- AST or ALT $\geq 3 \times$ upper limit of normal (ULN) and total bilirubin $\geq 2 \times$ ULN
- AST or ALT $\geq 3 \times$ ULN and PT-INR ≥ 1.5
- AST/ALT ≥ 3

10.7 Portal Vein Thrombosis and Portal Blood Flow

For the patients who underwent diagnostic imaging in safety analysis population, the number and proportion of patients who experienced portal vein thrombosis at screening and after the primary invasive procedure will be calculated by treatment group. The patients who underwent an invasive procedure more than once will be regarded as having portal vein thrombosis if they experienced it at least once after the primary invasive procedure. If a patient received an invasive procedure and underwent assessment of portal vein thrombosis on the same day, the assessment will be considered as being after invasive procedure (see Section 6.3).

For the patients who underwent Doppler ultrasonography in safety analysis population, summary statistics by category for the direction of portal blood flow (i.e., hepatofugal, hepatopetal, stasis) at screening and after the primary invasive procedure will be calculated by treatment group. If a patient received an invasive procedure and underwent Doppler ultrasonography on the same day, the assessment will be considered as being after invasive procedure (see Section 6.3).

11. INTERIM ANALYSES

No interim analyses are planned for this study.

12. PROGRAMMING CONVENTIONS

In principle, displayed digits of calculated summary statistics and percentages will be defined in Table 5.

Table 5 Displayed Digits of Statistics

Statistics	Displayed Digits
Number	Integer
Mean, Standard Deviation, 25% quartile, 75% quartile and Median	Rounded to decimal places that are greater than those of the raw data by 1. For data were rounded off to eight decimal places, the required statistics are to be calculated and then rounded off to two decimal places.
Maximum and Minimum	Displayed by respective displayed digits of the raw data. For data rounded off to eight decimal places, required statistics are to be calculated and then rounded off to one decimal place.
Percentage (%)	Rounded to one decimal place.
P-value	Rounded off to four decimal places. Values less than 0.0001 will be reported as <.0001.

13. CHANGES FROM PROTOCOL

- An analysis using the van Elteren is added in order to compare the duration of the increase in platelet count between S-888711 and placebo group for the ITT population (see Section 9.2.3)
- Summary of significant TEAEs is removed because this event was not defined in the protocol.

Appendix 1 Time and Events Schedule

	Screening		Treatment Period						Post-treatment Period (Invasive Procedure, Days 9 to 14)											With-drawal[a]	Unscheduled[b]
Study Day	From Day −28	Day 1 Pre-dosing	Day 1 Post-dosing	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 17	Day 21	Day 28	Day 35		
Informed consent	X																					
Inclusion/exclusion criteria	X																					
Demography (including body weight and height)	X																					
Medical history	X																					
Enrolment (IVRS/IWRS)	X																					
Randomisation (IVRS/IWRS)		X																				
Drug assignment (IVRS/IWRS)							X[c]	(X)[c]	(X)[c]													
Concomitant medication	←																					→
ECOG performance status	X																					
Type of CLD and severity of liver disorder (Child-Pugh)	X																					
Gastro-oesophageal varices[d]	X																					
Splenomegaly and severity of ascites[e]	X																					
Pregnancy test (urine)	X																			X	X	
Physical examination	X	X					X	X	X	X		X		X		X		X	X	X	X	X[b]
Portal vein thrombosis assessment[f]	X													←		X[g]	→				X	X[b]
Portal blood flow (direction)[h]	X													←		X[g]	→				X	X[b]
WHO Bleeding Scale	X	X								X				←		X[g]	→			X	X	
Blood pressure, pulse rate	X	X					X			X		X		X		X		X	X	X	X	X[b]
Electrocardiography	X																			X	X	X[b]
Platelet count (local laboratory)	X	X					X[i]	X[i]	X[i]	X		X		X		X	X	X	X	X	X	X[b]
Haematology except for platelet count (central laboratory)	X	X								X						X				X	X	X[b]

	Screening		Treatment Period							Post-treatment Period (Invasive Procedure, Days 9 to 14)											Withdrawal[a]	Unscheduled[b]
Study Day	From Day −28	Day 1 Pre-dosing	Day 1 Post-dosing	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 17	Day 21	Day 28	Day 35		
Blood chemistry	X	X								X						X				X	X	X[b]
Blood coagulation/fibrinolysis assay[j]	X	X								X						X				X	X	X[b]
Immunological tests/other tests	X																					
Adverse events	◄	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	►
Administration of study medication			X	X	X	X	X[c,k]	X[c,k]	X[c,k]													
Invasive procedure											◄	—	X[l]	—	—	►						
Sampling for plasma drug concentration (Sparse PK)[m]							X	X	X													
Sampling for plasma drug concentration (Intensive PK)[n]							X	X	X													

a Except for a patient with drug withdrawn because of the administration stopping criterion (ie, platelet count $\geq 50 \times 10^9$/L with an increase of $\geq 20 \times 10^9$/L from baseline).

b Only necessary assessments will be performed.

c If platelet count on Day 5, 6 or Day 7 is $\geq 50 \times 10^9$/L with an increase of $\geq 20 \times 10^9$/L from baseline, a patient must stop taking study medication.

d Confirmed by upper gastrointestinal endoscopy. If data on upper gastrointestinal endoscopy are obtained within 180 days before randomisation, the data can be used.

e Confirmed by ultrasonography, CT, or MRI. If ultrasonography, CT, or MRI is performed within 28 days before randomisation, the image can be used for assessing the presence or absence of splenomegaly.

f Confirmed by ultrasonography, CT, or MRI in the Screening period and after the invasive procedure. The Screening investigation should be arranged as close to randomisation as possible. However, if gastro-oesophageal varices are treated, portal vein thrombosis will be confirmed with the image obtained after the treatment.

g Performed within 3 to 10 days after the invasive procedure. When any additional invasive procedure is performed, the assessment of bleeding events as graded on the WHO Bleeding Scale, portal vein thrombosis, and portal blood flow will be performed before and after the invasive procedure.

h Confirmed by Doppler ultrasonography (at Screening, the investigation should be as close to randomisation as possible).

i Blood samples will be collected before study medication.

j Antithrombin III activity, fibrinogen, fibrin degradation products, D-dimer, Protein C activity, free protein S antigen, von Willebrand factor activity will be performed only at Screening. Prothrombin time (international normalised ratio value) and activated partial thromboplastin time will be performed at Screening, Day 1, Day 8, Day 14, and Day 35.

k Administered after platelet count is confirmed and drug assignment.

l Performed between Days 9 and 14.

m All patients except for Intensive PK; pre-dose, 2 to 4 hours post-dose on Day 5, and pre-dose on Days 6 and 7.

n At least 20 patients; pre-dose, 2, 4, 6, 8 hours post-dose on Day 5, pre-dose on Days 6 and 7.

Appendix 2 Testing Procedure for Primary and Important Secondary Endpoints

S-888711 for up to 7 days vs. Placebo

Testing the Primary Efficacy Endpoint:
The null hypothesis is that there is no difference between S-888711 for up to 7 days and placebo groups regarding the proportion of patients, who require no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomization until 7 days after the primary elective procedure.

↓ if rejected[a]

Testing the Secondary Efficacy Endpoint 1:
The null hypothesis is that there is no difference between S-888711 for up to 7 days and placebo groups regarding the proportion of patients who require no platelet transfusion during the study.

↓ if rejected[a]

Testing the Secondary Efficacy Endpoint 2:
The null hypothesis is that there is no difference between S-888711 for up to 7 days and placebo groups regarding the proportion of patients who achieve a platelet count of $\geq 50 \times 10^9$/L with an increase of $\geq 20 \times 10^9$/L from baseline at any time during the study.

↓ if rejected[a]

Testing the Secondary Efficacy Endpoint 3:
The null hypothesis is that there is no difference between S-888711 and placebo groups regarding the duration of the platelet count $\geq 50 \times 10^9$/L.

↓ if rejected[a]

Testing the Secondary Efficacy Endpoint 4:
The null hypothesis is that there is no difference between S-888711 for up to 7 days without platelet transfusion and placebo with platelet transfusion groups regarding the duration of the platelet count $\geq 50 \times 10^9$/L.

[a] If superiority of S-888711 to placebo is demonstrated at the two-sided significance level of 0.05, then the next hypothesis will be tested.

Appendix 3 Calculation p-value and Confidence Interval for Cochran-Mantel-Haenzel Test

Let x_{ij} and n_{ij} denote the number of responders and the total number of patients in treatment i and stratum j, respectively, where i=1,2 represents the treatment group (S-888711 or Placebo) and $j = 1,2,3,4$ represents the stratum, the following 2 × 2 contingency table shows the total number of subjects and the number of responders in each treatment arm at stratum j.

Category	S-888711	Placebo
Response	x_{1j}	x_{2j}
No Response	$n_{1j} - x_{1j}$	$n_{2j} - x_{2j}$
Total	n_{1j}	n_{2j}

The proportion of patients with response (π_{ij}) in treatment i and stratum j can be estimated by:

$$\hat{\pi}_{ij} = x_{ij}/n_{ij}$$

and the stratum-specific proportion difference (d_j) is estimated by:

$$\hat{d}_j = \hat{\pi}_{1j} - \hat{\pi}_{2j}.$$

The adjusted estimate of the difference in the rate of responders between the two treatment groups (d_{adj}) is given as:

$$\hat{d}_{adj} = \sum_{j=1}^{4} w_j d_j$$

using the CMH weights defined as $w_j = \left(\frac{n_{1j}n_{2j}}{n_{1j}+n_{2j}}\right) \Big/ \left\{\sum_{j=1}^{4} \frac{n_{1j}n_{2j}}{n_{1j}+n_{2j}}\right\}$.

Hence, the 2-sided stratified 95% Wald-type confidence intervals of d_{adj} based on the CMH weights is constructed as:

$$\hat{d}_{adj} \pm z_{\alpha/2}\mathrm{Var}(\hat{d}_{adj}),$$

where the variance of d_{adj} is given as:

$$\mathrm{Var}(\hat{d}_{adj}) = \sqrt{\sum_{j=1}^{4} \hat{w}_j^2 \left(\frac{\hat{\pi}_{1j}(1-\hat{\pi}_{1j})}{n_{1j}} + \frac{\hat{\pi}_{2j}(1-\hat{\pi}_{2j})}{n_{2j}}\right)},$$

and $z_{\alpha/2}$ is the 97.5th percentile of the standard normal distribution.

Two-sided p-value will be obtained by:

$$2 \times \left\{1 - \Phi\left(\left|\frac{\hat{d}_{adj}}{Var(\hat{d}_{adj})}\right|\right)\right\},$$

where Φ is the cumulative distribution of standard normal distribution.

Appendix 4 CTCAE Term and Criteria for Classification*

CTCAE Term	Grade				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Blood and lymphatic system disorders					
Anemia	10.0 g/dL ≤ HGB < LLN	8.0 g/dL ≤ HGB < 10.0 g/dL	HGB < 8.0 g/dL	---	---
Investigations					
Activated partial thromboplastin time prolonged	ULN < APTT ≤ 1.5×ULN	1.5×ULN < APTT ≤ 2.5×ULN	APTT > 2.5×ULN	---	---
Alanine aminotransferase increased	ULN < ALT ≤ 3.0×ULN	3.0×ULN < ALT ≤ 5.0×ULN	5.0×ULN < ALT ≤ 20.0×ULN	ALT > 20.0×ULN	---
Alkaline phosphatase increased	ULN < ALP ≤ 2.5×ULN	2.5×ULN < ALP ≤ 5.0×ULN	5.0×ULN < ALP ≤ 20.0×ULN	ALP > 20.0×ULN	---
Aspartate aminotransferase increased	ULN < AST ≤ 3.0×ULN	3.0×ULN < AST ≤ 5.0×ULN	5.0×ULN AST ≤ 20.0×ULN	AST > 20.0×ULN	---
Blood bilirubin increased	ULN < T. Bil ≤ 1.5×ULN	1.5×ULN < T. Bil ≤ 3.0×ULN	3.0×ULN < T.Bil ≤ 10.0×ULN	T.Bil> 10.0×ULN	---
Creatinine increased	BL < CREAT ≤ 1.5×BL, or ULN < CREAT ≤ 1.5×ULN	1.5×BL < CREAT ≤ 3.0×BL, or 1.5×ULN < CREAT ≤ 3.0×ULN	CREAT > 3.0×BL, or 3.0×ULN < CREAT ≤ 6.0×ULN	CREAT > 6.0×ULN	---
GGT increased	ULN < γ-GTP ≤ 2.5×ULN	2.5×ULN < γ-GTP ≤ 5.0×ULN	5.0×ULN < γ-GTP ≤ 20.0×ULN	γ-GTP > 20.0×ULN	---
Hemoglobin increased	In the case BL ≤ ULN, ULN < HGB ≤ ULN + 2 g/dL, In the case BL > ULN, BL < HGB ≤ BL + 2 g/dL	In the case BL ≤ ULN, ULN + 2 g/dL< HGB ≤ ULN + 4 g/dL, In the case BL > ULN, BL + 2 g/dL < HGB ≤ BL + 4 g/dL	In the case BL ≤ ULN, HGB > ULN + 4 g/dL, In the case BL > ULN, HGB > BL + 4 g/dL	---	---
INR increased	ULN *< PT-INR ≤ 1.5×ULN*	1.5×ULN* < PT-INR ≤ 2.5×ULN*	PT-INR* > 2.5×ULN*	---	---
White blood cell decreased	3×10^3/μL ≤ WBC < LLN	2×10^3 /μL ≤ WBC < 3×10^3/μL	1×10^3/μL ≤ WBC < 2×10^3/μL	WBC < 1×10^3/μL	---

* Classification criteria are determined by reference to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 [Published: May 28, 2009].

CTCAE Term	Grade				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Metabolism and nutrition disorders					
Hypercalcemia	ULN < Ca ≤ 11.5 mg/dL	11.5 mg/dL < Ca ≤ 12.5 mg/dL	12.5 mg/dL < Ca ≤ 13.5 mg/dL	Ca > 13.5 mg/dL	---
Hyperkalemia	ULN < K ≤ 5.5 mEq/L	5.5 mEq/L < K ≤ 6.0 mEq/L	6.0 mEq/L < K ≤ 7.0 mEq/L	K > 7.0 mEq/L	---
Hypernatremia	ULN < Na ≤ 150 mEq/L	150 mEq/L < Na ≤ 155 mEq/L	155 mEq/L < Na ≤ 160 mEq/L	Na > 160 mEq/L	---
Hypoalbuminemia	3 g/dL ≤ ALB < LLN	2 g/dL ≤ ALB < 3 g/dL	ALB < 2 g/dL	---	---
Hypocalcemia	8.0 mg/dL ≤ Ca < LLN	7.0 mg/dL ≤ Ca < 8.0 mg/dL	6.0 mg/dL ≤ Ca < 7.0 mg/dL	Ca < 6.0 mg/dL	---
Hypokalemia	3.0 mEq/L ≤ K <LLN	3.0 mEq/L ≤ K <LLN	2.5 Eq/L ≤ K < 3.0 mEq/L	K < 2.5 mEq/L	---
Hyponatremia	130 mEq/L ≤ Na <LLN	---	120 mEq/L ≤ Na < 130 mEq/L	＜120 mEq/L	---

ALB = Albumin; APTT = Activated partial thromboplastin time; BL = Baseline value; CREAT = Creatinine; FIBRINO = Fibrinogen; HGB = Hemoglobin; LLN = Lower limit of normal range; PT-INR = International normalized ratio of prothrombin time; T.Bil = Total bilirubin; ULN = Upper limit of normal range

*: ULN for International normalized ratio of prothrombin time (PT-INR) is regarded as 1 if it will not be specified by the central laboratory.