Statistical Analysis Plan

Study Title	An Open-label Study to Evaluate the Efficacy and Safety of Avatrombopag for the Treatment of Thrombocytopenia in Japanese Adults with Chronic Immune Thrombocytopenia
Protocol Number:	AVA-ITP-307
NCT Number	05369208
Investigational Product:	Avatrombopag
Sponsor:	Sobi, Inc.
Analysis Plan Date:	14-MAR-2024
Analysis Plan Version:	Version 1.0

Statistical Analysis Plan

Protocol number:	AVA-ITP-307
Title:	An Open-label Study to Evaluate the Efficacy and Safety of Avatrombopag for the Treatment of Thrombocytopenia in Japanese Adults with Chronic Immune Thrombocytopenia
SAP Author:	[redacted]
SAP version:	1.0

[redacted]	14-Mar-2024	[redacted]	14-Mar-2024
Signature	Date	Signature	Date
Approval		Author	
[redacted]		[redacted]	
Director, Biostatistics		[redacted]	
Sobi, Inc.		Statistical Analysis 2nd Dept.	
		Data Science Div.	
		[redacted]	

TABLE OF CONTENTS

1 Abbreviations and Definition of Terms 5
2 Introduction 6
3 Study Objectives and Endpoints 6
3.1 Primary Investigation Phase (Core Phase) 6
3.1.1 Primary Objective 6
3.1.2 Secondary Objectives 6
3.1.3 Exploratory Objectives 6
3.2 Extension Phase 6
3.2.1 Primary Objective 6
3.2.2 Secondary Objective 7
3.3 Study Endpoints 7
3.3.1 Primary Efficacy Endpoint 7
3.3.2 Key Secondary Efficacy Endpoints 7
3.3.3 Other Secondary Efficacy Endpoints 7
4 Study Methods 8
4.1 Overall Study Design and Plan 8
4.2 Selection of Study Population 8
4.3 Randomization and Blinding 8
5 Sequence of Planned Analysis 9
5.1 Changes from Planned Analyses in the Protocol 9
5.2 Interim Analyses 9
5.3 Population PK Analysis 9
5.4 Analyses and Reporting 9
6 Sample Size Determination 9
7 Analysis Populations 10
7.1 Consented Population 10
7.2 Full Analysis Set (FAS) 10
7.3 Per Protocol Set (PPS) 10
7.4 Safety Set (SAF) 10
8 General Issues for Statistical Analysis 10
8.1 Statistical Analysis and Tabulation Software 10
8.2 Dictionaries 11
8.3 Analysis Methods 11
8.3.1 Descriptive Statistics 11
8.3.2 Proportion and Confidence Interval for Proportions 12
8.3.3 Change from Baseline 12

8.3.4 Study Day 12
8.3.5 Statistical Method 12
8.4 Rounding Digits 13
8.4.1 Displaying of Descriptive Statistics 13
8.4.2 Proportions (%), CV (%), Geometric CV (%) and 95% CI for Proportions 13
8.5 Baseline 13
8.6 Visit Windows 13
8.7 Handling of Missing Data 15
8.7.1 Handling of Partial Dates for Adverse Events 15
9 Subject Disposition 15
9.1 Enrolled Subjects and Screen Failures 15
9.2 Subject Disposition 16
9.3 Major Protocol Deviations 18
9.4 Analysis Datasets 19
10 Demographics and Baseline Characteristics 19
10.1 Demographics and Baseline Characteristics 19
10.2 Medical History 21
10.3 Concomitant Medication 21
11 Efficacy Analyses 22
11.1 Primary Efficacy Endpoint 22
11.1.1 Cumulative Number of Weeks of Platelet Response 22
11.1.2 Cumulative Number of Weeks of Platelet Response by Subgroups 23
11.2 Key Secondary Efficacy Endpoint 24
11.2.1 Platelet Response Rate at Visit 4 (Day 8) 24
11.3 Other Efficacy Endpoints 24
11.3.1 Durable Platelet Response 24
11.3.2 Maximum Duration (in weeks) of Platelet Response 25
11.3.3 Platelet Count (10^9/L) and Change from Baseline by Visit 25
11.3.4 Median (Q1, Q3) Platelet Count (10^9/L) of Local Platelet Count Over Treatment Period 26
11.3.5 Platelet Count (10^9/L) of Individual Subjects 26
11.3.6 Platelet Response by Visit 26
11.3.7 Complete Platelet Response Rate by International Working Group (IWG) by Visit 27
11.3.8 Platelet Response Rate by International Working Group (IWG) by Visit 28
11.3.9 Subjects with any Rescue Therapy Use 28
11.3.10 Subjects with a Reduction/Discontinuation in use of Concomitant ITP Medications from Baseline 29
11.3.11 Worst Post-baseline Bleeding Grade (WHO Bleeding Scale) 30

12 Pharmacokinetic Concentrations 30
12.1 Summary of Avatrombopag Concentrations 31
13 Safety Analyses 32
13.1 Drug Exposure 32
13.2 Adverse Events 33
13.2.1 Overview of Treatment-emergent Adverse Events 35
13.2.2 Overview of Treatment-emergent Adverse Events by Subgroups 35
13.2.3 Treatment-emergent Adverse Events by SOC and PT 36
13.2.4 Treatment-emergent Adverse Events of Special Interest by AESI Category and PT 36
13.2.5 Treatment-emergent Adverse Events by SOC and PT by Subgroups 36
13.2.6 Treatment-emergent Adverse Events by PT 37
13.2.7 Treatment-emergent Adverse Events by SOC, PT and Maximum Severity 37
13.2.8 Treatment-emergent Adverse Events by Time to Onset and by PT 37
13.3 Laboratory Data 38
13.3.1 Laboratory Parameters and Change from Baseline by Visit 39
13.3.2 Laboratory Parameters with any Abnormal Measured Values by Visit 39
13.4 Vital Signs 40
13.4.1 Vital Signs Tests and Change from Baseline by Visit 40
14 Listings 41
15 References 42
16 Revision History 42
Appendix 1: Sample Code 42
Appendix 2: Tables of Background Factors for Demographics and Baseline Characteristics 42
Appendix 3: Tables of Test Items of Laboratory Test, Vital Signs, and WHO Bleeding Scale. 43
Table 1: List of Laboratory Test Items collected in Central Laboratory: 43
Table 2: List of Vital Signs Test Items: 44
Table 3: WHO Bleeding Scale: 44

1 Abbreviations and Definition of Terms

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Events of Special Interest
ATC	Anatomical Therapeutic Chemical
BLQ	Below Lower Limit of Quantitation
CI	Confidence Interval
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
EOT	End-of-Treatment
FAS	Full Analysis Set
ITP	Immune Thrombocytopenia
IWG	International Working Group
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic(s)
PPS	Per-Protocol Set
PT	Preferred Term
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SMQ	Standardised MedDRA Query
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
TEAESI	Treatment-emergent Adverse Event of Special Interest
WHO	World Health Organization

2 Introduction

This document is the Statistical Analysis Plan (SAP) containing definitions and descriptions of statistical analysis procedures for "An Open-label Study to Evaluate the Efficacy and Safety of Avatrombopag for the Treatment of Thrombocytopenia in Japanese Adults with Chronic Immune Thrombocytopenia (protocol number: AVA-ITP-307)".

The SAP will be finalized, locked and signed prior to Core Phase database lock.

3 Study Objectives and Endpoints

3.1 Primary Investigation Phase (Core Phase)

3.1.1 Primary Objective

The primary objective of the Core Phase of this study is to evaluate the efficacy of avatrombopag in the treatment of Japanese adult subjects with immune thrombocytopenia (ITP), as measured by cumulative number of weeks of platelet response over 26 weeks.

3.1.2 Secondary Objectives

The secondary objectives are:

- To evaluate the platelet response rate at Day 8
- To evaluate the safety of avatrombopag in Japanese adult subjects with ITP

3.1.3 Exploratory Objectives

The exploratory objectives are:

- To evaluate the durable platelet response
- To evaluate the incidence of bleeding and use of rescue therapy
- To collect population PK data on plasma avatrombopag exposure in Japanese adult subjects with ITP

3.2 Extension Phase

3.2.1 Primary Objective

In the Extension Phase, the primary objective is to evaluate the safety and tolerability of long-term therapy with avatrombopag in Japanese subjects with chronic ITP.

3.2.2 Secondary Objective

The secondary objective in the Extension Phase is to evaluate the effectiveness of long-term therapy with avatrombopag as measured by platelet response, bleeding, and the use of rescue medication.

3.3 Study Endpoints

3.3.1 Primary Efficacy Endpoint

In the Primary Investigation Phase (Core Phase), the primary efficacy endpoint is the cumulative number of weeks in which the platelet count is $\geq 50 \times 10^9$/L during 26 weeks of treatment in the absence of rescue therapy.

Subjects using rescue therapy at any time during the 26-week treatment period will be considered not to have any platelet responses for all subsequent weeks after rescue therapy. A platelet response will be defined as a platelet count of $\geq 50 \times 10^9$/L and nonresponse will be defined as a platelet count $< 50 \times 10^9$/L. All analyses of platelet counts will be based on local laboratory results.

Missing platelet assessments at any given time point will be considered a nonresponse at that time point. Subjects who discontinue the study or who are lost to follow-up before 26 weeks will have all subsequent unobserved scheduled platelet assessments at the scheduled time points as having "missing" platelet values.

3.3.2 Key Secondary Efficacy Endpoints

In the Primary Investigation Phase (Core Phase), the key secondary endpoint is the platelet response rate at Day 8 (as defined by the proportion of subjects with a platelet response $\geq 50 \times 10^9$/L at Day 8). Subjects with missing platelet count at Day 8 or use of rescue therapy before or on Day 8 will be considered platelet non-responders.

3.3.3 Other Secondary Efficacy Endpoints

Other efficacy endpoints in the Primary Investigation Phase (Core Phase) include the following:

- Durable platelet response as defined by proportion of subjects who have at least 6 of 8 (i.e., ≥75%) weekly platelet counts $\geq 50 \times 10^9$/L during the last 8 weeks of treatment over the 26-week treatment period in the absence of rescue therapy
- Incidence and severity of bleeding symptoms associated with ITP, including bleeding, bruising, and petechiae, measured using the World Health Organization (WHO) Bleeding Scale
- Maximum duration (in weeks) of continuous response for each subject
- Proportion of subjects receiving rescue therapy during the 26-week duration of the study

- Proportion of subjects with a reduction/discontinuation in use of concomitant ITP medications from baseline
- Complete responder by International Working Group (IWG) definition: platelet count $\geq 100\times10^9$/L and absence of bleeding
- Responder by IWG definition: platelet count $\geq 30\times10^9$/L and at least a 2-fold increase in baseline count and absence of bleeding

Additionally, in the Extension Phase, effectiveness will be assessed by measuring platelet counts, rescue therapy uses, and bleeding events. Specifically,

- Median platelet count of all subjects at selected time points (monthly)
- Proportion of subjects needing rescue therapy
- Incidence and severity of bleeding (in accordance with the WHO Bleeding Scale)

4 Study Methods

4.1 Overall Study Design and Plan

This confirmatory, open-label study will evaluate the efficacy, safety, and PK of avatrombopag in Japanese adults with ITP. While a placebo control group was included in the pivotal avatrombopag overseas study, the mean number of cumulative weeks with a platelet response in this group was zero (0), a result which is consistent with placebo control groups in other ITP studies. Therefore, inclusion of a placebo control group in this study would not be expected to be informative. To compare this study's data to the data from the pivotal Study 302, the study design (other than not including a placebo control) will replicate that of the overseas study. Avatrombopag will be evaluated over a duration of 26 weeks and the primary efficacy endpoint will be the cumulative number of weeks of platelet response $\geq 50\times10^9$/L. All subjects who complete the Primary Investigation Phase (Core Phase) can continue to receive avatrombopag in the Extension Phase until market authorization in Japan. Safety and efficacy data will be collected monthly in the Extension Phase.

4.2 Selection of Study Population

This study will enroll at least 19 Japanese adults with chronic ITP ($\geq$12 months duration) and an average of 2 platelet counts $<30\times10^9$/L, who meet all eligibility criteria.

4.3 Randomization and Blinding

All subjects enrolled in this study will receive open-label avatrombopag. Therefore, no randomization or blinding is required.

5 Sequence of Planned Analysis

5.1 Changes from Planned Analyses in the Protocol

A secondary efficacy endpoint was included which was not detailed in the protocol: Proportion of subjects with a reduction in use of concomitant ITP medications from baseline.

Bleeding Adverse Events of Special Interest (AESIs) were first identified using a Standardised Medical Dictionary for Regulatory Activities Query (MedDRA SMQ) and then further defined as clinically significant using reported Common Terminology Criteria for Adverse Events (CTCAE) grade for the event rather than the WHO bleeding grade, as WHO bleeding grades collected at study visits are not linked to specific adverse events.

5.2 Interim Analyses

No formal interim analysis is planned for this study.

5.3 Population PK Analysis

Population PK analysis will be described in a separate Pharmacokinetic Analysis Plan.

5.4 Analyses and Reporting

All final, planned analyses identified in the protocol and in this SAP will be performed after the last patient completes the Core Phase and after the last patient completes the Extension Phase.

6 Sample Size Determination

To determine a clinically relevant efficacy hurdle, data from a 26-week open-label extension of eltrombopag study TRA108109 in adult Japanese patients with chronic ITP were used as a benchmark. This study evaluated the endpoint of cumulative number of weeks of platelet response ($\geq 50 \times 10^9$/L) in a comparable population of patients who received eltrombopag for 26 weeks. The results were similar to those in avatrombopag overseas Study 302, with a reported mean of 11.2 weeks with 95% CI of 8.02 and 14.38 weeks.

The lower limit of the 95% CI of the cumulative number of weeks of platelet response, or 8.02, from study TRA108109 is set as the efficacy hurdle for the lower limit of the 95% CI in this study. Assuming a distribution of results (mean of 12.0 cumulative weeks and standard deviation of 8.75) similar to that observed in Study 302, a sample size of 19 subjects would be required to meet this primary efficacy endpoint hurdle.

7 Analysis Populations

7.1 Consented Population

The Consented Population will include all subjects who gave informed consent.

7.2 Full Analysis Set (FAS)

The Core Phase FAS will include all subjects who are enrolled into the study and gave informed consent.

The Extension Phase FAS will include all subjects who enter the Extension Phase.

7.3 Per Protocol Set (PPS)

The Core Phase PPS will include all enrolled subjects who receive protocol-assigned study drug and who do not meet any pre-specified criteria. A comprehensive list of criteria for exclusion from the PPS will be agreed upon by the study team and documented prior to database lock.

Examples of these criteria may include:

- Use of certain prohibited concomitant medications
- Selected Inclusion/Exclusion criteria not met for the Core Phase
- Lack of compliance with study medication during the Core Phase

7.4 Safety Set (SAF)

The Core Phase Safety Set will include all subjects who receive at least 1 dose of study drug and have a post-dose safety assessment. The Extension Phase Safety Set will include all subjects who receive at least 1 dose of study drug in the Extension Phase and have a post-dose safety assessment in the Extension Phase. General Issues for Statistical Analysis.

8 General Issues for Statistical Analysis

8.1 Statistical Analysis and Tabulation Software

Below are the software and its versions used in this study.

	Software/Version
Operating system	Microsoft Windows Server 2016 Standard
Statistical analysis software	SAS 9.4 or later
Tabulation Software	Microsoft Word 2016 or later.

8.2 Dictionaries

Below are the dictionaries used in this study.

Category	Dictionary	Remarks
Adverse Events	MedDRA Version.26.1 or later	System organ class (SOC) and preferred term (PT) will be determined for each adverse event and these will be used in analyses.
Medical Histories	MedDRA Version.26.1 or later	The same as adverse events.
Name of Medication (Prior and Concomitant Medications)	WHO Drug Global September 1, 2023 or later	Anatomical Therapeutic Chemical (ATC) level 2 Preferred Name

8.3 Analysis Methods

8.3.1 Descriptive Statistics

Descriptive statistics:

Continuous data except for PK	PK concentration data
The number of subjects (N)	The number of subjects (N)
Arithmetic Mean	Arithmetic Mean
Standard Deviation (SD)	Standard Deviation (SD)
Median	Median
Minimum and Maximum	Minimum and Maximum
First quartile, Third quartile	-
-	The number and % of BLQ
	Coefficient of variation (CV%) for arithmetic mean
-	Geometric Mean
-	95% confidence interval (CI) of geometric mean
-	Geometric CV%

CV%, Geometric mean, 95% CI of geometric mean, and Geometric CV% are calculated using the following formula:

CV(%) = (standard deviation) / (arithmetic mean)×100

Geometric mean = $\exp\left[\frac{\sum_{i=1}^{n}\log X_i}{n}\right] = \sqrt[n]{\prod_{i=1}^{n} X_i}$

95% CI of geometric mean = exp(μ ± 1.96*s/sqrt(n))

μ: mean on the natural logarithm scale

s: standard error on the natural logarithm scale

Geometric CV(%) = sqrt(exp(s^2) -1)×100

8.3.2 Proportion and Confidence Interval for Proportions

The proportion is calculated by the following formula unless otherwise instructed:

$$\text{Proportion}(\%) = \frac{\text{Applicable subjects}}{\text{Subjects in the analysis population}} \times 100$$

$$\text{AE}(\%) = \frac{\textit{The number of subjects with AEs}}{\textit{Subjects in the analysis population}} \times 100$$

For two-sided 95% CI for proportion, exact test will be used.

Regarding sample code, refer to Appendix 1.

8.3.3 Change from Baseline

Change from baseline at each time point is defined by the following formula:

$$\begin{matrix}\text{Change}\\ \text{from baseline}\end{matrix} = \begin{matrix}\text{Value at each}\\ \text{time point}\end{matrix} - \text{Baseline value}$$

8.3.4 Study Day

Study day is calculated as followings:

Study day = assessment/event date – first dose date (if assessment/event date < first dose date).

Study day = assessment/event date – first dose date + 1 (if the assessment /event date >= first dose date)

8.3.5 Statistical Method

No statistical testing will be conducted unless otherwise noted.

8.4 Rounding Digits

8.4.1 Displaying of Descriptive Statistics

1) Parameters except for avatrombopag concentration

   - Mean, median, first quartile, third quartile and 95% CI for mean will be displayed in one digit lower than the display digit.
   - Standard deviation will be displayed in two digits lower than the display digit.
   - Minimum and maximum will be displayed in display digit.

2) Avatrombopag concentration

Minimum, maximum, mean, standard deviation, median, geometric mean and 95% CI of geometric mean will be rounded and then displayed as 3 significant digits.

The example of rounding and displaying as 3 significant digits:

Value		Displayed as 3 significant digits
1234.5	→	1230
1.2345	→	1.23
243467	→	243000
243667	→	244000
0.057226	→	0.0572
0.057276	→	0.0573

8.4.2 Proportions (%), CV (%), Geometric CV (%) and 95% CI for Proportions

Proportions (%), CV (%), geometric CV (%) and 95% CI for proportions will be rounded and displayed to the first decimal place.

8.5 Baseline

For the platelet count: Baseline will be the average of the assessment of Screening Visit and Day 1 Baseline Visit. The average is recorded in the database and will be used directly.

For other items: Baseline is defined as the last non-missing value taken at or before the study drug administration.

8.6 Visit Windows

No formal visit windowing will be conducted, except assign appropriate visit per study day for the records of the End of Study visit (VISIT 22). Only scheduled visit assessment will be used in

the by visit analyses. If multiple records are found within the visit window, the record closest to target date will be used for analysis purposes.

All assessments will be used when calculating cumulative and maximum duration of platelet response. The visit target date will be used to impute the missing visit date.

All assessments during scheduled and unscheduled visits will be listed in the data listing and presented in individual subject figures.

Analysis Visit	Analysis Window Target	Analysis Window Beginning Timepoint	Analysis Window Ending Timepoint
Baseline	1 day	-	1 day
Visit 3 (Day 5)	5 days	2 days	6 days
Visit 4 (Day 8)	8 days	7 days	11 days
Visit 5 (Week 2)	14 days	12 days	17 days
Visit 6 (Week 3)	21 days	18 days	24 days
Visit 7 (Week 4)	28 days	25 days	35 days
Visit 8 (Week 6)	42 days	36 days	49 days
Visit 9 (Week 8)	56 days	50 days	63 days
Visit 10 (Week 10)	70 days	64 days	77 days
Visit 11 (Week 12)	84 days	78 days	91 days
Visit 12 (Week 14)	98 days	92 days	105 days
Visit 13 (Week 16)	112 days	106 days	119 days
Visit 14 (Week 18)	126 days	120 days	129 days
Visit 15 (Week 19)	133 days	130 days	136 days
Visit 16 (Week 20)	140 days	137 days	143 days
Visit 17 (Week 21)	147 days	144 days	150 days
Visit 18 (Week 22)	154 days	151 days	157 days
Visit 19 (Week 23)	161 days	158 days	164 days
Visit 20 (Week 24)	168 days	165 days	171 days
Visit 21 (Week 25)	175 days	172 days	178 days
Visit 22 (Week 26)	182 days	179 days	299 days

8.7 Handling of Missing Data

8.7.1 Handling of Partial Dates for Adverse Events

When determining treatment-emergent adverse events (TEAEs), partial dates with missing day will be handled as follows:

- If AE onset day is missing, AE onset day will be set to the first day of the month unless it is the same month and year as first dose date. In this case, the start date will be assumed to be the first date of treatment.

*AE onset month and AE onset year won't be missing.

** Causality and Severity won't be missing.

9 Subject Disposition

9.1 Enrolled Subjects and Screen Failures

Population: Consented Subjects

Target Phases: Core Phase

Contents:
- Calculate the number of subjects who consented.
- Calculate the number of subjects and the percentages for the following items:

  Core Phase
  - Subjects who were enrolled
  - Subjects of screen failure
  - Reasons for screen failure
    - Did not satisfy Inclusion/Exclusion criteria
    - Withdrawal by Subject
    - Other
  - Subjects who were treated with study drug/not treated with study drug

Definitions: Enrolled = Consented – Screen failure
For each of the following items, the denominator is defined as noted below
Core Phase

Items	The denominator of percentage
・Consented ・Enrolled ・Screen failures ・Reasons for screen failure ・Not treated ・Treated	The number of Consented Subjects

9.2 Subject Disposition

Population: Safety Set

Target Phases: Core Phase, Extension Phase

Contents:

- Calculate the number of subjects and the percentages for the following items:

  Core Phase

  - Subjects who enrolled into core phase study
  - Subjects who completed study/discontinued study
  - Reasons for discontinuation of study
    - Withdrawal of Consent
    - Subject Non-Compliance
    - Subject failed to meet inclusion/exclusion criterion
    - Significant Medical Condition
    - Adverse Event
    - Pregnancy
    - Investigator discretion
    - Sponsor request
    - Subject requires prohibited concomitant medication
    - Study terminated
    - Lack of efficacy at the maximum dose level (Level 6)
    - Other
  - Subjects who completed treatment/discontinued treatment
  - Reasons for discontinuation of treatment
    - Lack of efficacy at the maximum dose level (Level 6)
    - Subjects who require rescue therapy more than 3 times or continuous rescue therapy for more than 3 weeks
    - Excessive platelet count responses (>400×10^9/L) at the minimum dose level (Level 1)
    - Treatment with certain ITP therapies/procedures, such as vinca alkaloids, cyclophosphamide, rituximab, splenectomy, or other TPO-RAs (eltrombopag, romiplostim)
    - Other

  Extension Phase

  - Subjects who entered Extension Phase
  - Subjects who were treated with study drug
  - Subjects who weren't treated with study drug
  - Subjects who completed study/discontinued study
  - Reasons for discontinuation of study
    - Withdrawal of Consent
    - Subject Non-Compliance
    - Subject failed to meet inclusion/exclusion criterion
    - Significant Medical Condition
    - Adverse Event

- Pregnancy
- Investigator discretion
- Sponsor request
- Subject requires prohibited concomitant medication
- Study terminated
- Lack of efficacy at the maximum dose level (Level 6)
- Other

➢ Subjects who are ongoing in the extension phase*
➢ Subjects who completed treatment/discontinued treatment
➢ Reasons for discontinuation of treatment
- Lack of efficacy at the maximum dose level (Level 6)
- Subjects who require rescue therapy more than 3 times or continuous rescue therapy for more than 3 weeks
- Excessive platelet count responses (>400×10^9/L) at the minimum dose level (Level 1)
- Treatment with certain ITP therapies/procedures, such as vinca alkaloids, cyclophosphamide, rituximab, splenectomy, or other TPO-RAs (eltrombopag, romiplostim)
- Other

*: Item "Subjects who are ongoing in the extension phase" only exists in the first analysis (after the last patient completes the Core Phase).

If a subject has multiple discontinuation reasons, they will be counted for each individual discontinuation reason.

Definitions: For each of the following items, the denominator is defined as noted below.

Core Phase

Items	The denominator of percentage
・ Enrolled into core phase study ・ Completed the core phase study ・ Discontinued the core phase study ・ Reason for discontinuation ・ Completed the core phase treatment ・ Prematurely discontinued the core phase treatment ・ Reason for discontinuation	The number of subjects in Safety Set of Core Phase

Extension Phase

Items	The denominator of percentage
・Entered the Extension Phase ・Treated with study drug ・Not treated with study drug ・Completed study ・Discontinued the study ・Reasons for discontinuation of study	The number of subjects in Safety Set of Extension Phase

・Ongoing in the extension phase ・Completed the treatment ・Discontinued the treatment ・Reasons for discontinuation of treatment	

9.3 Major Protocol Deviations

Population: Full Analysis Set

Target Phases: Core Phase, Extension Phase

Analysis Items:
- Major protocol deviations

Contents:
- Calculate the number of subjects and the percentages of those with and without major deviations from the protocol with their deviation contents.
- Denominator to calculate the percentage are below.

Items	The denominator of percentage
Major Protocol Deviations (Yes/No) Deviation category	The number of subjects in Full Analysis Set

- Deviation category is as below:
  - Safety
  - Informed Consent
  - Eligibility Criteria
  - Protocol Implementation
  - Investigational Products
  - Concomitant and Prohibited Medications or Non-Drug Therapy
  - General GCP Non-Adherence
  - Other
- Subjects with more than one major protocol deviation will be counted once for each category.
- Only major protocol deviations will be presented

9.4 Analysis Datasets

Population: Full Analysis Set

Target Phases: Core Phase, Extension Phase

Analysis Items:
- Analysis datasets

Contents:
- Calculate the number of subjects in the following population.
  - Full Analysis Set (FAS)
  - Per Protocol Set (PPS)/excluded from PPS
  - Reasons for exclusion of PPS
  - Safety Set (SAF)

10 Demographics and Baseline Characteristics

10.1 Demographics and Baseline Characteristics

Population: Safety Set

Target Phases: Core Phase, Extension Phase

Analysis items:
- Refer to the table of Background Factors

Contents:
- Descriptive summaries of demographic and other baseline characteristics will be presented for the subjects in the Safety Set.
- For categorical data and ordinal data, calculate the number of subjects and percentages.
- For continuous data, calculate the descriptive statistics.

Definitions
- Unknown and Missing values: If unknown or missing values are observed, add "Unknown"/"Missing" category.
- For each item, the denominator is as below. Subjects of "Unknown"/"Missing" category are included in the denominator.

Items	The denominator of percentage
Childbearing potential	The number of female subjects
Others	The number of subjects in Safety Set

[Background Factors]

Classification [Unit]	Category
Age (years)	<65, ≥65

Classification [Unit]	Category
Sex	Male, Female
Childbearing potential *only for female	Yes, No
Race	Asian (Japanese)
Height (cm)	-
Weight (kg)	-
BMI (kg/m^2)	-
Medical history	Yes, No
Surgical history	Yes, No
Concomitant ITP medication at baseline[a]	Yes, No
Number of platelet transfusions in the previous 1 year	-
Number of previous hospitalizations for ITP	-
Number of previous significant bleeding events	-
Baseline platelet count[b]	$\leq 15\times10^9$/L, $>15\times10^9$/L
Splenectomy status	Yes, No
Baseline creatinine clearance[c]	30≤ - <60 mL/min, 60≤ - <90 mL/min, ≥90 mL/min, Missing

[a]: Concomitant ITP medication at baseline is defined as medications with ATC level 2 = "CORTICOSTEROIDS FOR SYSTEMIC USE" that (1) start before the first dose of study drug and are continuing at the time of the first dose of study drug of Core Phase, or (2) start on the date of the first dose of study drug of Core Phase.

[b]: Baseline platelet count is the average of the assessment of Screening Visit and Day 1 Baseline Visit. The average is recorded in the database and will be used directly.

[c]: Baseline creatinine clearance is calculated by Cockcroft-Gault formula:

Male: (140 – Age (yrs)) x weight (kg) / (72 x creatinine (mg/dL)).

Female: 0.85 x (140 - Age (yrs)) x weight (kg) / (72 x creatinine (mg/dL)).

Age (yrs), weight (kg), creatinine (mg/dL) are taken at baseline.

10.2 Medical History

Population: Safety Set

Target Phases: Core Phase

Analysis items:
- Medical History

Contents:
- For medical history (Yes/No), calculate the number of subjects and percentages.
- For medical history terms, calculate the number of subjects and percentages by Preferred term (PT) with MedDRA.
- If there are multiple records with the same PT in the same subject, count one record per subject.
- The number of subjects and percentages by PT ordered by decreasing frequency.

Definitions: For each item, the denominator is as below

Items	The denominator of percentage
Medical history (Yes/No) PT (Medical history)	The number of subjects in Safety Set

10.3 Concomitant Medication

Population: Safety Set

Target Phases: Core Phase, Extension Phase

Analysis items:
- Concomitant medication

Contents:
- Concomitant medications are displayed with ATC level 2 and preferred name.
- For Concomitant medication, calculate the number of subjects and percentages by ATC2 and preferred name with WHO Drug.
- If there are multiple records with the same code in the same subject, count one record per subject.

Definitions:

- Prior medications (Core Phase)

Defined as medications that stop prior to the first dose of study drug of Core Phase.

- Concomitant medications (Core Phase)

Defined as medications that (1) start before the first dose of study drug and are continuing at the time of the first dose of study drug of Core Phase, or (2) start on or after the date of the first dose of study drug of Core Phase, up to 30 days after the last dose of study drug during the Core Phase (and before the first dose of Extension Phase if subject continues into the Extension Phase).

- Concomitant medications (Extension Phase)

Defined as medications that start on or after the first day of Extension Phase and up to the last day of treatment period of Extension Phase.

For each item, the denominator is as below

Items	The denominator of percentage
Subjects with at least one concomitant medication ATC level 2 Preferred name	The number of subjects in Safety Set

11 Efficacy Analyses

All analyses of platelet counts will be based on local laboratory results.

11.1 Primary Efficacy Endpoint

11.1.1 Cumulative Number of Weeks of Platelet Response

Population: Full Analysis Set, Per Protocol Set

Target Phases: Core Phase

Analysis items:
- The cumulative number of weeks in which the platelet count is $\geq 50\times10^9$/L during 26 weeks of treatment in the absence of rescue therapy for each subject

Contents:
- Descriptive statistics and 95% CI of mean of the cumulative number of weeks of platelet response during 26 weeks of treatment in the absence of rescue therapy is calculated.

Definitions:
- Platelet response: platelet count of $\geq 50\times10^9$/L

- Cumulative number of weeks of platelet response during 26 weeks of treatment in the absence of rescue therapy is calculated by the formula: (sum of platelet response duration)/7= sum of (last day platelet response - the first day platelet response +1)/7.
- All scheduled and unscheduled visits will be used. If the subject missed a visit, the visit date will be imputed based on analysis target date.
- Platelet response will be defined with consideration referring the handling of data as described in 3 cases below:
  - 1. Subjects who have missing platelet assessments at any scheduled visit of interest will be considered as non-responders at that time point.
  - 2. Subjects who use rescue therapy at any time during the 26-week treatment period will be considered as non-responders for all subsequent days after rescue therapy start date.
  - 3. Subjects who discontinue the study or who are lost to follow-up before 26 weeks will have all subsequent unobserved scheduled platelet assessments at the scheduled time points as having "missing" platelet values.

11.1.2 Cumulative Number of Weeks of Platelet Response by Subgroups

Population:	Full Analysis Set, Per Protocol Set, Safety Set
Target Phases:	Core Phase
Analysis items:	- The cumulative number of weeks in which the platelet count is $\geq 50\times10^9$/L during 26 weeks of treatment in the absence of rescue therapy
Contents:	- Conduct a subgroup analysis for "11.1.1 Cumulative Number of Weeks of Platelet Response". Planned subgroups are defined below: ➢ Sex (Male, Female) ➢ Age (<65 yrs, ≥65 yrs) ➢ Baseline platelet count ($\leq 15\times10^9$/L, $>15\times10^9$/L) ➢ Use of concomitant ITP medications (Yes, No) ➢ Splenectomy status (Yes, No) ➢ Baseline creatinine clearance (30≤ - <60 mL/min, 60≤ - <90 mL/min, ≥90 mL/min, Missing (if any))

11.2 Key Secondary Efficacy Endpoint

11.2.1 Platelet Response Rate at Visit 4 (Day 8)

Population: Full Analysis Set, Per Protocol Set

Target Phases: Core Phase

Analysis items:
- Platelet response rate at Visit 4 (Day 8)

Contents:
- The number of platelet response (Yes/No) at Visit 4 (Day 8) and its proportion with 95% CI is calculated.

Definitions:
- Responders (Yes): Subjects with a platelet count $\geq 50\times10^9$/L at Visit 4 (Day 8) in the absence of rescue therapy before or on Visit 4 (Day 8).
- Non-responders (No): Subjects with a platelet count $<50\times10^9$/L at Visit 4 (Day 8) or with missing platelet counts at Visit 4 (Day 8) or use of a rescue therapy before or on Visit 4 (Day 8).
- Regarding the efficacy data handling, refer to 3 cases below:
  - 1. Subjects who have missing platelet assessments at Visit 4 (Day 8) will be considered as non-responders.
  - 2. Subjects who use rescue therapy before or on Visit 4 (Day 8) will be considered as non-responders at Visit 4 (Day 8).
  - 3. Subjects who discontinue the study or who are lost to follow-up before or on Visit 4 (Day 8) will be considered as non-responders at Visit 4 (Day 8).
- Regarding 95% CI for binomial proportions, refer to 8.3.2 Proportion and Confidence Intervals for proportions

11.3 Other Efficacy Endpoints

11.3.1 Durable Platelet Response

Population: Full Analysis Set, Per Protocol Set

Target Phases: Core Phase

Analysis items:
- Durable platelet response

Contents:
- The number of responders/non-responders and its proportion with 95% CI is calculated.

Definitions:
- Responders (Yes): Subjects who have at least 6 of 8 (i.e., ≥75%) weekly platelet counts $\geq 50\times10^9$/L during the last 8 weeks (from Visit 15 (Week 19) to Visit 22 (Week 26)) of treatment over the 26-week treatment period and not taking any rescue therapy.
- Non-responders (No): Subjects who have less than 6 weekly platelet counts $\geq 50\times10^9$/L during the last 8 weeks over the 26-week treatment

period or taking any rescue therapy.

- Regarding the data handling:
  - 1. Subjects who have missing platelet assessments at scheduled visits of interest will be considered as non-responder at any given time point.
  - 2. Subjects who use rescue therapy at any time during 26-week treatment period will be considered as non-responders for all subsequent days after rescue therapy start date.
  - 3. Subjects who discontinue the study or who are lost to follow-up before 26 weeks will have all subsequent unobserved scheduled platelet assessments at the scheduled time points as having "missing" platelet values.
- Regarding 95% CI for binomial proportions, refer to 8.3.2 Proportion and Confidence Intervals for proportions.
- Regarding Rescue therapy, refer to table 11.3.9 Subjects with any Rescue Therapy Use

11.3.2 Maximum Duration (in weeks) of Platelet Response

Population:	Full Analysis Set, Per Protocol Set
Target Phases:	Core Phase
Analysis items :	- Maximum duration (in weeks) of continuous platelet response
Contents:	- Descriptive statistics of Maximum duration (in weeks) of continuous platelet response for each subject is calculated.
Definitions:	- Maximum duration (in weeks): The maximum value of the platelet response durations (in weeks) is the longest platelet response duration. - For platelet response duration and the handling of data refer to table 11.1.1 Cumulative Number of Weeks of Platelet Response

11.3.3 Platelet Count (10^9/L) and Change from Baseline by Visit

Population:	Full Analysis Set, Per Protocol Set (for Core Phase only)
Target Phases:	Core Phase, Extension Phase
Visits:	- Core Phase: Baseline - Visit 22 (Week 26) - Extension Phase: E 1 (Month 1) - Last Visit
Analysis items:	- Measured value and change from baseline for platelet count
Contents:	- Summary statistics of platelet count from local laboratories for all subjects in each visit are calculated.

11.3.4 Median (Q1, Q3) Platelet Count (10^9/L) of Local Platelet Count Over Treatment Period

Population:	Full Analysis Set, Per Protocol Set (for Core Phase only)
Target Phases:	Core Phase, Extension Phase
Visits:	- Core Phase: Baseline - Visit 22 (Week 26) - Extension Phase: E 1 (Month 1) - Last Visit
Analysis items:	- Median, Q1, and Q3 values of measured values and change from baseline values
Contents:	- Series plot for median (Q1, Q3) platelet count from local laboratories will be presented graphically by visit.

11.3.5 Platelet Count (10^9/L) of Individual Subjects

Population:	Full Analysis Set
Target Phases:	- Core Phase
Analysis items:	- Measured value for platelet count
Contents:	- Spaghetti plot for platelet count from local laboratories will be presented graphically by subject.

11.3.6 Platelet Response by Visit

Population:	Full Analysis Set, Per Protocol Set
Target Phases:	Core Phase
Visit:	Visit 3 (Day 5) - Visit 22 (Week 26)
Analysis items:	- Platelet Response by Visit
Contents:	- The number of subjects with platelet response (Yes/No) at each analysis visit are calculated based on subjects with assessment available at the visit (n).
Definitions:	- Responders (Yes): Subjects who have platelet count $\geq 50\times10^9$/L and in the absence of rescue therapy. - Non-responders (No): Subjects who have platelet count $<50\times10^9$/L or have platelet count $\geq 50\times10^9$/L that occurs within 8 weeks after rescue therapy usage. - Regarding the efficacy data handling, refer to the case below: ➢ 1. Subjects who have missing platelet assessments will be excluded from the summary at that visit.

- 2. If subjects use rescue medication, subjects will be considered as non-responders from the rescue medication start date to rescue medication end date + 8 weeks.

- The denominator to calculate the proportion is the number of subjects in target population by each analysis visit with non-missing data.

11.3.7 Complete Platelet Response Rate by International Working Group (IWG) by Visit

Population: Full Analysis Set, Per Protocol Set

Target Phases: Core Phase

Visits: Visit 3 (Day 5) - Visit 22 (Week 26)

Analysis items:
- Complete platelet response by IWG

Contents:
- The number and proportion of subjects with a complete platelet response (Yes/No) at each analysis visit are calculated based on subjects with assessment available at the visit (n).

Definitions:
- Complete platelet response:
  - Responders (Yes): Subjects with a platelet count $\geq 100\times10^9$/L and in the absence of bleeding or rescue therapy.
  - Non-responders (No): Subjects with a platelet count $<100\times10^9$/L or the presence of bleeding. Platelet assessment with any bleeding event at the same visit or a platelet count that occurs within 8 weeks after rescue therapy is considered as nonresponse.
- Regarding the efficacy data handling, refer to the cases below:
  - 1. Subjects who have missing platelet assessments will be excluded from the summary at that visit.
  - 2. If subjects use rescue medication, subjects will be considered as non-responders from the rescue medication start date to rescue medication end date + 8 weeks.
  - 3. Subject who has WHO bleeding scale grade $\geq$ 1 will be considered as non-responder at that visit.
- The denominator to calculate the proportion is the number of subjects in target population by each analysis visit with non-missing data.

11.3.8 Platelet Response Rate by International Working Group (IWG) by Visit

Population: Full Analysis Set, Per Protocol Set

Target Phases: Core Phase

Visits: Visit 3 (Day 5) - Visit 22 (Week 26)

Analysis items:
- Platelet response by IWG

Contents:
- The number and proportion of subjects with a platelet response (Yes/No) at each analysis visit are calculated based on subjects with assessment available at the visit (n).

Definitions:
- Platelet response:
  - Responders (Yes): Subjects with a platelet count $\geq 30\times10^9$/L and at least a 2-fold increase in baseline count and absence of bleeding or rescue therapy.
  - Non-responders (No): Subjects with a platelet count $<30\times10^9$/L or less than a 2-fold increase in baseline count, or the presence of bleeding or rescue therapy. Platelet assessment with any bleeding event at the same visit or a platelet count that occurs within 8 weeks after rescue therapy is considered as nonresponse.
- Regarding the efficacy data handling, refer to the cases of 11.3.7 Complete Platelet Response Rate by International Working Group (IWG) by Visit

11.3.9 Subjects with any Rescue Therapy Use

Population: Full Analysis Set, Per Protocol Set (for Core Phase only)

Target Phases: Core Phase, Extension Phase

Analysis items:
- Rescue therapy (Yes/No)

Contents:
- The number of subjects with rescue therapy (Yes/ No) and its proportion with 95% CI are calculated.

Definitions:
- Rescue therapy (Yes): The number of subjects who use at least one rescue therapy after the first administration of study drug in each phase (Core Phase (26-week treatment period) or Extension Phase).
- If one subject takes the same therapy in both Core Phase and Extension Phase (e.g. the end date of rescue therapy in Core Phase is ongoing), that subject will be counted in Core Phase and Extension Phase respectively.
- The denominator to calculate the proportion is the target population (the number of subjects in Full Analysis Set/Per Protocol Set)
- Rescue therapy will be defined as the addition of any new ITP medication or medication to treat thrombocytopenia (examples below). TPO receptor agonists are not allowed as rescue therapy.

- Corticosteroids (ATC level 2 = "CORTICOSTEROIDS FOR SYSTEMIC USE")
- Intravenous immunoglobulin (IVIg) therapy (ATC level 2= "IMMUNE SERA AND IMMUNOGLOBULINS")
- Anti-D therapy (PT = "Anti-D (rh) immunoglobulin")
- Mycophenolate mofetil (PT = "Mycophenolate mofetil")
- Azathioprine (PT = "Azathioprine")
- Danazol (PT = "Danazol")
- Cyclosporin A (PT = "Ciclosporin"
- Platelet transfusion (concomitant procedure as "TRANSFUSIONS")
- Any increase in baseline dose of a concomitant ITP medication

- Regarding 95% CI for binomial proportions, refer to 8.3.2 Proportion and Confidence Intervals for proportions.

11.3.10 Subjects with a Reduction/Discontinuation in use of Concomitant ITP Medications from Baseline

Population: Full Analysis Set, Per Protocol Set

Target Phases: Core Phase

Analysis items:
- Reduction in use of concomitant ITP medications
- Discontinuation in use of concomitant ITP medications

Contents:
- Calculate the number of subjects who have a reduction/discontinuation of Concomitant ITP medications after baseline.

For each item, the denominator is as below

Items	The denominator of percentage
・Reduction of Concomitant ITP medications after baseline ・Discontinuation of Concomitant ITP medications after baseline	The number of subjects who used concomitant ITP medications at baseline

Definitions: ITP medications are defined as the medications with ATC level 2 = "CORTICOSTEROIDS FOR SYSTEMIC USE"

Baseline ITP medications are defined as the ITP medications that are taken on the day of first administration; and concomitant ITP medications use at Core Phase are defined as ITP medications that start after the day of first administration and up to the last day of 26-week treatment period (excluding dose-tapering period) of Core Phase.

Only subjects with use of concomitant ITP medications at baseline will be included in the analysis. If a subject has use of concomitant ITP medication at baseline and has all post-baseline total daily doses for same medications (by PT) reduced without later increasing to the baseline or higher dose, or has no use of concomitant ITP medication post-baseline during 26-week

treatment, this subject is considered as having a reduction in use of concomitant ITP medication from baseline.

Subjects who discontinue all concomitant ITP medications before the last dose date of 26-week treatment will be considered as having a discontinuation of concomitant ITP medications.

11.3.11 Worst Post-baseline Bleeding Grade (WHO Bleeding Scale)

Population: Full Analysis Set, Per Protocol Set (for Core Phase only)

Target Phases: Core Phase, Extension Phase

Analysis items:
- The worst post-baseline bleeding grade based on WHO Bleeding Scale

Contents:
- The number and proportion of subjects with the worst post-baseline bleeding grade (WHO Bleeding Scale) reported in Core Phase (up to End of Study visit (excluding dose tapering and follow-up period)) and in Extension Phase (from E1 (Month 1) to Last Visit).

Definitions:
- WHO Bleeding Scale:

  Grade 0: No bleeding

  Grade 1: Petechial bleeding

  Grade 2: Mild blood loss (clinically significant)

  Grade 3: Gross blood loss

  Grade 4: Debilitating blood loss.
- Worst post-baseline bleeding grade (WHO Bleeding Scale) is the highest grade reported after baseline.
- The denominator is the number of subjects in the analysis population.

12 Pharmacokinetic Concentrations

Blood samples for serial PK assessments will be collected during Visit 5 (Week 2) and Visit 10 (Week 10) of the Core Phase. Regardless of the subject's current treatment regimen (e.g., once daily, three times a week), the serial PK sampling at Visit 5 (Week 2) and Visit 10 (Week 10) must occur on a day the subject is scheduled to take their dose of study drug. Therefore, if study drug has been held or the dosing regimen has changed within the past week, the serial PK samples should be collected at a visit later than Visit 5 (Week 2) or Visit 10 (Week 10). This is to ensure that serial PK samples will be obtained when the subject has been on a stable dose for at least 1 week.

During the serial PK sampling visits, subjects will have three blood samples (2 mL each) drawn: pre-dose; between 2 and 4 hours post-dose; and between 6 and 8 hours post-dose.

Blood samples for sparse PK assessments (2 mL each) will be collected while the subject is at the clinic during Visit 4 (Day 8), Visit 7 (Week 4), Visit 8 (Week 6), Visit 13 (Week 16) and Visit 22 (Week 26)/End of Treatment (EOT) (2 mL each).

The pharmacokinetic sampling schedule is presented in following table:

Study Day	**Sparse/Serial**	**Sampling Times**
Visit 4 (Day 8)	Sparse	During clinic visit
Visit 5 (Week 2)	**Serial**	• **Pre-dose** • **Between 2 and 4 hours post-dose** • **Between 6 and 8 hours post-dose**
Visit 7 (Week 4)	Sparse	During clinic visit
Visit 8 (Week 6)	Sparse	During clinic visit
Visit 10 (Week 10)	**Serial**	• **Pre-dose** • **Between 2 and 4 hours post-dose** • **Between 6 and 8 hours post-dose**
Visit 13 (Week 16)	Sparse	During clinic visit
Visit 22 (Week 26)	Sparse	During clinic visit

The data handling methods for Pharmacokinetic Concentrations are presented below:

1) Data Handling for Below the Lower Limit of Quantification (BLQ)

If the recorded plasma avatrombopag concentration is below the limit of quantification (BLQ), the measured value of the concentration will be treated as the following:

- For tables, BLQ will be substituted by 0.
- For listings, display BLQ as “BLQ”.

2) Data Handling for Missing Value

If missing data is recorded for plasma avatrombopag concentration, imputation of the records will not be performed. Thus, any missing records for plasma avatrombopag concentration will be excluded from analysis.

If blood concentration is not measured (not done) then it is considered as missing.

12.1 Summary of Avatrombopag Concentrations

Population:	Full Analysis Set
Target Phases:	Core Phase
Analysis items:	- Avatrombopag concentrations in plasma
Visits:	- Visit 5 (Week 2), Visit 10 (Week 10): Pre-dose, Between 2 and 4 hours postdose, Between 6 and 8 hours postdose. - Visit 4 (Day 8), Visit 7 (Week 4), Visit 8 (Week 6), Visit 13 (Week 16), Visit 22 (Week 26).
Contents:	- Calculate the descriptive statistics of avatrombopag concentrations in plasma by analysis visits/time points.

Definitions:
- Regarding summary statistics of avatrombopag concentrations, refer to 8.3.1 Descriptive Statistics.

13 Safety Analyses

13.1 Drug Exposure

Population: Safety Set

Target Phases: Core Phase, Core Phase and Extension Phase

Analysis Items:
- Duration of treatment (week), Total actual dose (mg), Total planned dose (mg), Average weekly dose (mg/week), Compliance rate (%)

Contents:
- The descriptive statistics for Core Phase and Extension Phase are calculated separately as below:
  - Core Phase: Duration of treatment (week), Total planned dose (mg).
  - Extension Phase: Duration of treatment (week), Total actual dose (mg), Total planned dose (mg), Average weekly dose (mg/week), Compliance rate (%).
- The number and proportion of subjects in subcategories of Duration of treatment (week), Average weekly dose (mg/week), and Compliance rate (%) as below are calculated:
- Any exposure, n
  - Core Phase:
    - ≥ 6 weeks
    - ≥ 18 weeks
    - ≥ 26 weeks
  - Core Phase and Extension Phase:
    - ≥ 6 weeks
    - ≥ 18 weeks
    - ≥ 26 weeks
    - ≥ 32 weeks
    - ≥ 52 weeks
    - ≥ 122 weeks
    - ≥ 126 weeks
- Average weekly dose (mg/week):
  - <60 mg
  - 60≤ - <120 mg
  - 120≤ - <160 mg
  - ≥160 mg
- Compliance rate (%):
  - <90
  - 90≤ - <110
  - ≥110

Definitions:

- Duration of treatment (week) = (the last treatment day – the first treatment day + 1) / 7
- Total actual dose (mg) = Sum of (Tablets dispensed amount – Tablets returned amount – Tablets lost amount) * 20
- Total planned dose (mg) = Sum of ((Regimen end date in each regimen duration – Regimen start date in each regimen duration + 1) * Daily dose[a])

  [a]: Daily dose is calculated by using dose description, dose unit and dosing frequency. For Core Phase, calculate total planned dose until the last dose date of Core Phase.
- Average weekly dose (mg/week) = Total actual dose (mg) / Duration of treatment (week)
- Compliance rate (%) = (Total actual dose / Total planned dose) * 100

13.2 Adverse Events

Term	Definition
Adverse Event (AE)	An adverse event is defined as any untoward medical occurrence in a subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.
Treatment-emergent Adverse Event (TEAE)	A treatment-emergent adverse event is an event that emerges during treatment having been absent pre-treatment, or worsens relative to the pre-treatment state.
Causality Assessment	The relationship of an AE to the administration of the study drug is to be assessed according to the following definitions: - No (unrelated, not related, no relation) – The time course between the administration of study drug and the occurrence or worsening of the AE rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected. - Yes (related) – The time course between the administration of study drug and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.
Related TEAE	A related treatment-emergent adverse event is a treatment-emergent adverse event whose Investigator causality assessment is related.

Serious TEAE/ Serious Related TEAE	A serious TEAE is a treatment-emergent adverse event which is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes: - Death - A life-threatening adverse event - Requires hospitalization or prolongation of existing hospitalization - A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions - A congenital anomaly/birth defect - An important medical event A serious related TEAE is a serious TEAE whose Investigator causality assessment is related.
TEAE of Special Interest (TEAESI)/Related TEAESI	TEAE of Special Interest (TEAESI) is a treatment-emergent adverse event which meets the following descriptions: - Thromboembolic events include the adverse events with MedDRA PT belonging to Standard MedDRA Queries (SMQ Narrow PTs) 'Embolic and thrombotic events'. - Bleeding events include the adverse events with MedDRA PT belonging to 2nd level SMQ (Narrow PTs) 'Haemorrhage terms (excl laboratory terms)' with CTCAE Grades 3 and 4. A related TEAESI is a TEAESI whose Investigator causality assessment is related.
Adverse Event Severity	The severity of all AEs should be graded according to the Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE). For those AEs not listed in the CTCAE, the following grading system should be used: - Mild (CTCAE Grade 1): Transient symptoms, awareness of sign/symptom, but easily tolerated and no interference with subject's daily activities. - Moderate (CTCAE Grade 2): Marked signs/symptoms that interfere with subject's usual activities, but still acceptable. - Severe (CTCAE Grade 3): Incapacitating signs/symptoms which cause considerable interference with the subject's daily activities, unacceptable. - Life-threatening (CTCAE Grade 4): Life-threatening or disabling AE. - Death (CTCAE Grade 5): Death-related AE.

The data handling methods for Adverse Events are presented below:

Only TEAEs will be tabulated in the tables. Non-TEAEs are only included in the listings.

- Number of Subjects with Multiple Events:
- For overview summary:
    - If multiple AEs occurred in the same subject, the subject will only be counted once.

- If AEs with multiple grades occurred in the same subject, the subject will be counted once in the highest reported grade.

- For summary by SOC and PT:
  - If multiple AEs of same SOC or PT occurred in the same subject, the subject will only be counted once in the SOC or PT.
  - If multiple AEs of same SOC or PT with different grades occurred in the same subject, the subject will be counted once in the highest reported grade.

- For summary by PT:
  - If multiple AEs of same PT occurred in the same subject, the subject will only be counted once in the PT.

- For summary by AESI category and PT:
  - If multiple AEs of same AESI category or PT occurred in the same subject, the subject will only be counted once in the AESI category or PT.

13.2.1 Overview of Treatment-emergent Adverse Events

Population:	Safety Set
Target Phases:	Core Phase, Core Phase and Extension Phase
Analysis items:	- TEAEs, Related TEAEs, Serious TEAEs, Serious Related TEAEs, TEAEs by maximum severity (Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, Grade ≥3), TEAEs of Special Interest (Thromboembolic events, Bleeding events (CTCAE Grades 3 and 4)), Related TEAEs of Special Interest, TEAEs leading to death
Contents:	- The number of events and the number and proportion of subjects who experienced at least 1 event in the Analysis items are calculated.
Definitions:	- The denominator to calculate the proportion is the target population.

13.2.2 Overview of Treatment-emergent Adverse Events by Subgroups

Population:	Safety Set
Target Phases:	Core Phase, Core Phase and Extension Phase
Analysis items:	- TEAEs, Related TEAEs, Serious TEAEs, Serious Related TEAEs, TEAEs by maximum severity (Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, Grade ≥3), TEAEs of Special Interest (Thromboembolic events, Bleeding events (CTCAE Grades 3 and 4)), Related TEAEs of Special Interest, TEAEs leading to death
Contents:	- Conduct a subgroup analysis for "13.2.1 Overview of Treatment-emergent Adverse Events". Subgroups are below: ➢ Sex (Male, Female) ➢ Age (<65 yrs, ≥65 yrs)

- Baseline platelet count (≤15×10^9/L, >15×10^9/L)
- Use of concomitant ITP medications (Yes, No)
- Splenectomy status (Yes, No)
- Baseline creatinine clearance (30≤ - <60 mL/min, 60≤ - <90 mL/min, ≥90 mL/min, Missing (if any))

Definitions:
- The denominator to calculate the proportion is the number of subjects in each subgroup.

13.2.3 Treatment-emergent Adverse Events by SOC and PT

Population: Safety Set

Target Phases: Core Phase, Core Phase and Extension Phase

Analysis items:
- TEAEs, Related TEAEs, Serious TEAEs, TEAEs leading to death

Contents:
- The number and proportion of subjects with the Analysis items are calculated.
- The number and proportion of subjects in case of the other Analysis items are calculated by SOC and PT.

Definitions:
- The denominator to calculate the proportion is the target population.

13.2.4 Treatment-emergent Adverse Events of Special Interest by AESI Category and PT

Population: Safety Set

Target Phases: Core Phase, Core Phase and Extension Phase

Analysis items:
- TEAEs of Special Interest (Thromboembolic events, Bleeding events (CTCAE Grades 3 and 4))

Contents:
- The number and proportion of subjects with the Analysis items are calculated.
- The number and proportion of subjects in case of the other Analysis items are calculated by AESI Category and PT.

Definitions:
- The denominator to calculate the proportion is the target population.

13.2.5 Treatment-emergent Adverse Events by SOC and PT by Subgroups

Population: Safety Set

Target Phases: Core Phase, Core Phase and Extension Phase

Analysis items:
- TEAEs

Contents:	- Conduct a subgroup analysis for "13.2.3 Treatment-emergent Adverse Events by SOC and PT". Subgroups are below: ➢ Sex (Male, Female) ➢ Age (<65 yrs, ≥65 yrs) ➢ Baseline platelet count (≤15×10^9/L, >15×10^9/L) ➢ Use of concomitant ITP medications (Yes, No) ➢ Splenectomy status (Yes, No) ➢ Baseline creatinine clearance (30≤ - <60 mL/min, 60≤ - <90 mL/min, ≥90 mL/min, Missing (if any))
Definitions:	- The denominator to calculate the proportion is the number of subjects in Subgroup.

13.2.6 Treatment-emergent Adverse Events by PT

Population:	Safety Set
Target Phases:	Core Phase, Core Phase and Extension Phase
Analysis items:	- TEAEs
Contents:	- The number and proportion of subjects with TEAEs are calculated by PT and ordered by decreasing frequency.
Definitions:	- The denominator to calculate the proportion is the target population.

13.2.7 Treatment-emergent Adverse Events by SOC, PT and Maximum Severity

Population:	Safety Set
Target Phases:	Core Phase, Core Phase and Extension Phase
Analysis items:	- TEAEs
Contents:	- The number and proportion of subjects with the Analysis items are calculated by severity. - The number and proportion of subjects with the Analysis items are calculated by SOC and PT and by severity.
Definitions:	- Severity: Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, ≥ Grade 3 - The denominator to calculate the proportion is the target population.

13.2.8 Treatment-emergent Adverse Events by Time to Onset and by PT

Population:	Safety Set
Target Phases:	Core Phase, Core Phase and Extension Phase

Analysis items: - TEAEs

Contents: - The number and proportion of subjects with the Analysis items are calculated by Time to Onset and by PT.

Definitions:
- Time to Onset (months) = (Date of onset of TEAE - Date of start of treatment in Core Phase + 1) / 30.4375
- Time to Onset (Category):
  - Core Phase: [<3 months, 3≤ - <6 months, ≥ 6 months]
  - Extension Phase: [<3 months, 3≤ - <6 months, 6≤ - <9 months, 9≤ - <12 months, 12≤ - <15 months, 15≤ - <18 months, ≥18 months]
- The denominator to calculate the proportion is the target population.

13.3 Laboratory Data

The list of laboratory parameters evaluated in this study is presented as below:

Table 1: List of Laboratory Test Items collected in Central Laboratory:

Category	Items	Standard Units	Digit	Remarks
Hematology	Hematocrit	fraction of 1	0.001	Set based on current data
	Hemoglobin	g/L	1	
	Platelets	10^9/L	1	
	Erythrocytes	10^12/L	0.01	
	Basophils/Leukocytes	fraction of 1	0.001	
	Eosinophils/Leukocytes	fraction of 1	0.001	
	Lymphocytes/Leukocytes	fraction of 1	0.001	
	Neutrophils/Leukocytes	fraction of 1	0.001	
	Monocytes/Leukocytes	fraction of 1	0.001	
	Leukocytes	fraction of 1	0.001	
Chemistry	Alanine aminotransferase	ukat/L	0.0001	
	Aspartate aminotransferase	ukat/L	0.0001	
	Alkaline phosphatase (ALP)	ukat/L	0.0001	
	Direct bilirubin	umol/L	0.0001	
	Total bilirubin	umol/L	0.0001	
	Urea Nitrogen	mmol/L	0.0001	
	Sodium	mmol/L	1	
	Chloride	mmol/L	1	
	Bicarbonate	mmol/L	0.1	
	Creatinine	umol/L	0.001	
	Potassium	mmol/L	0.1	
	Glucose	mmol/L	0.0001	
	Calcium	mmol/L	0.001	
	Phosphate	mmol/L	0.0001	
Coagulation	Activated Partial Thromboplastin Time	s	0.1	

Category	Items	Standard Units	Digit	Remarks
	Prothrombin Intl. Normalized Ratio		0.01	
	Prothrombin Times	s	0.1	

Values under the lower limit of quantification (LLOQ) will be reported with inequality sign "<" and values over upper limit of quantification (ULOQ) will be reported with inequality sign ">". Thus, the inequality signs should be removed and remaining values will be used in analyses.

13.3.1 Laboratory Parameters and Change from Baseline by Visit

Population: Safety Set

Target Phases: Core Phase, Extension Phase

Visits:
- Core Phase: Baseline, Visit 4 (Day 8), Visit 10 (Week 10), Visit 13 (Week 16), Visit 22 (Week 26), Follow-up (Week 1), Follow-up (Week 2), Follow-up (Week 3), Follow-up (Week 4)
- Extension Phase: E 1 (Month 1), E 2 (Month 2), E 4 (Month 4), E 5 (Month 5), E 7 (Month 7), E 8 (Month 8), E 10 (Month 10), E 11 (Month 11), E 13 (Month 13), E 14 (Month 14), E 16 (Month 16), E 17 (Month 17), E 19 (Month 19), E 20 (Month 20), E 22 (Month 22), E 23 (Month 23), E 24 (Month 24)

Analysis items:
- For the parameters to be analyzed refer to Table 1 in 13.3 Laboratory data

Contents:
- Summary statistics of actual value and change from baseline of laboratory tests for each visit are calculated.

13.3.2 Laboratory Parameters with any Abnormal Measured Values by Visit

Population: Safety Set

Target Phases:
- Core Phase, Extension Phase

Visits:
- Core Phase: Baseline, Visit 4 (Day 8), Visit 10 (Week 10), Visit 13 (Week 16), Visit 22 (Week 26), Follow-up (Week 1), Follow-up (Week 2), Follow-up (Week 3), Follow-up (Week 4)
- Phase: E 1 (Month 1), E 2 (Month 2), E 4 (Month 4), E 5 (Month 5), E 7 (Month 7), E 8 (Month 8), E 10 (Month 10), E 11 (Month 11), E 13 (Month 13), E 14 (Month 14), E 16 (Month 16), E 17 (Month 17), E 19 (Month 19), E 20 (Month 20), E 22 (Month 22), E 23 (Month 23), E 24 (Month 24)

Analysis items:
- For the parameters to be analyzed refer to Table 1 in 13.3 Laboratory data

Contents:
- The number and proportion of subjects with any abnormal measured values (High/Low) at each visit are calculated.

Definitions:

- The number of target population by each analysis visit is calculated.
- Abnormal measured values are defined as below:
  - High: actual value > upper limit of normal
  - Low: actual value < lower limit of normal
- The denominator to calculate proportion of subject with any abnormal measured values (High/Low) is the number of target population by each analysis visit (excluding discontinued subject before or at that visit).

13.4 Vital Signs

The list of vital signs evaluated in this study is presented as below:

Table 2: List of Vital Signs Test Items:

Item	Unit	Display Digit	Remarks
Systolic blood pressure	mmHg	1	Set based on current data
Diastolic blood pressure	mmHg	1	
Pulse rate	Beats/min	1	
Height	cm	1	
Weight	kg	0.1	

13.4.1 Vital Signs Tests and Change from Baseline by Visit

Population: Safety Set

Target Phases: Core Phase, Extension Phase

Visits:

- Core Phase: Baseline, Visit 3 (Day 5), Visit 4 (Day 8), Visit 5 (Week 2), Visit 6 (Week 3), Visit 7 (Week 4), Visit 8 (Week 6), Visit 9 (Week 8), Visit 10 (Week 10), Visit 11 (Week 12), Visit 12 (Week 14), Visit 13 (Week 16), Visit 14 (Week 18), Visit 15 (Week 19), Visit 16 (Week 20), Visit 17 (Week 21), Visit 18 (Week 22), Visit 19 (Week 23), Visit 20 (Week 24), Visit 21 (Week 25), Visit 22 (Week 26), Dose Tapering (Week 1), Dose Tapering (Week 2), Dose Tapering(Week 3), Dose Tapering (Week 4), Follow-up (Week 1), Follow-up (Week 2), Follow-up (Week 3), Follow-up (Week 4)
- Extension Phase (Visit): E 1 (Month 1), E 2 (Month 2), E 3 (Month3), E 4 (Month 4), E 5 (Month 5), E 6 (Month 6), E 7 (Month 7), E 8 (Month 8), E 9 (Month 9), E 10 (Month 10), E 11 (Month 11), E 12 (Month 12), E 13 (Month 13), E 14 (Month 14), E 15 (Month 15), E 16(Month 16), E 17 (Month 17), E 18 (Month 18), E 19 (Month 19), E 20 (Month 20), E 21 (Month 21), E 22 (Month 22), E 23 (Month 23), E 24 (Month 24)

Analysis items:

- For the parameters to be analyzed, refer to Table 2 in 13.4 Vital signs

Contents: - Summary statistics of actual value and change from baseline of vital signs tests at each visit are calculated.

14 Listings

16.2.1.1 Subject Disposition (Core Phase and Extension Phase, FAS of Core Phase)

16.2.1.2 Screen Failure Subjects (Screen Failures)

16.2.2 Subjects with Protocol Deviation (Core Phase and Extension Phase, FAS of Core Phase)

16.2.3 Analysis Populations (Core Phase and Extension Phase, FAS of Core Phase)

16.2.4.1 Demographics and Baseline Characteristics (SAF of Core Phase)

16.2.4.2 Medical History (SAF of Core Phase)

16.2.4.3 Surgical History (SAF of Core Phase)

16.2.4.4. ITP History (FAS of Core Phase)

16.2.4.5 Prior and Concomitant Medication (Core Phase and Extension Phase, SAF of Core Phase)

16.2.4.6 Concomitant Procedures (Core Phase and Extension Phase, SAF of Core Phase)

16.2.4.7 Concomitant ITP Medication (Core Phase and Extension Phase, SAF of Core Phase)

16.2.4.8 Rescue Therapy (Core Phase and Extension Phase, SAF of Core Phase)

16.2.5.1 Study Drug Administration (Core Phase, SAF of Core Phase)

16.2.5.2 Dosing Regimen Log (Core Phase and Extension Phase, SAF of Core Phase)

16.2.5.3 Study Drug Accountability (Core Phase and Extension Phase, SAF of Core Phase)

16.2.5.4 Extent of Exposure and Treatment Compliance (Core Phase and Extension Phase, SAF of Core Phase)

16.2.5.5 Individual Avatrombopag Concentrations (Core Phase, SAF of Core Phase)

16.2.6.1 Primary, Secondary, and Other Efficacy Endpoints (Core Phase, FAS of Core Phase)

16.2.6.2 Local Platelet Count (Core Phase and Extension Phase, FAS of Core Phase)

16.2.6.3 WHO Bleeding Scores (Core Phase and Extension Phase, FAS of Core Phase)

16.2.7 Adverse Events (Core Phase and Extension Phase, SAF of Core Phase)

14.3.2.1 Treatment-emergent Adverse Events Leading to Death (Core Phase and Extension Phase, SAF of Core Phase)

14.3.2.2 Serious Treatment-emergent Adverse Events (Core Phase and Extension Phase, SAF of Core Phase)

14.3.2.3 Treatment-emergent Adverse Events of Special Interest (Core Phase and Extension Phase, SAF of Core Phase)

16.2.8.1 Laboratory Parameters (Core Phase and Extension Phase, SAF of Core Phase)

16.2.8.2 Vital Signs (Core Phase and Extension Phase, SAF of Core Phase)

16.2.8.3 Physical Examination (Core Phase and Extension Phase, SAF of Core Phase)

16.2.8.4 Pregnancy Test (Core Phase and Extension Phase, SAF of Core Phase)

16.2.9 COVID-19 Impact (Core Phase and Extension Phase, SAF of Core Phase)

15 References

None

16 Revision History

Appendix 1: Sample Code

- Confidence Intervals for proportions

```
proc freq data=data;
    tables targvar /out=cnt binomial alpha=0.05;
    exact binomial;
    ods output binomial= binomial;
run;
```

Exact CI should be used.

- Confidence Intervals for mean

```
proc ttest data=data  alpha=0.05;
   class param;
   var Height;
run;
```

Appendix 2: Tables of Background Factors for Demographics and Baseline Characteristics

Classification [Unit]	Category
Age (years)	<65, ≥65
Sex	Male, Female
Childbearing potential *only for female	Yes, No

Classification [Unit]	Category
Race	Asian (Japanese)
Height (cm)	-
Weight (kg)	-
BMI (kg/m^2)	-
Medical history	Yes, No
Surgical history	Yes, No
Concomitant ITP medication at baseline[a]	Yes, No
Number of platelet transfusions in the previous 1 year	-
Number of previous hospitalizations for ITP	-
Number of previous significant bleeding events	-
Baseline platelet count[b]	≤15×10^9/L, >15×10^9/L
Splenectomy status	Yes, No
Baseline creatinine clearance[c]	30≤ - <60 mL/min, 60≤ - <90 mL/min, ≥90 mL/min, Missing

Appendix 3: Tables of Test Items of Laboratory Test, Vital Signs, and WHO Bleeding Scale.

Table 1: List of Laboratory Test Items collected in Central Laboratory:

Category	Items	Standard Units	Digit	Remarks
Hematology	Hematocrit	fraction of 1	0.001	Set based on current data
	Hemoglobin	g/L	1	
	Platelets	10^9/L	1	
	Erythrocytes	10^12/L	0.01	
	Basophils/Leukocytes	fraction of 1	0.001	
	Eosinophils/Leukocytes	fraction of 1	0.001	
	Lymphocytes/Leukocytes	fraction of 1	0.001	
	Neutrophils/Leukocytes	fraction of 1	0.001	
	Monocytes/Leukocytes	fraction of 1	0.001	
	Leukocytes	fraction of 1	0.001	

Category	Items	Standard Units	Digit	Remarks
Chemistry	Alanine aminotransferase	ukat/L	0.0001	
	Aspartate aminotransferase	ukat/L	0.0001	
	Alkaline phosphatase (ALP)	ukat/L	0.0001	
	Direct bilirubin	umol/L	0.0001	
	Total bilirubin	umol/L	0.0001	
	Urea Nitrogen	mmol/L	0.0001	
	Sodium	mmol/L	1	
	Chloride	mmol/L	1	
	Bicarbonate	mmol/L	0.1	
	Creatinine	umol/L	0.001	
	Potassium	mmol/L	0.1	
	Glucose	mmol/L	0.0001	
	Calcium	mmol/L	0.001	
	Phosphate	mmol/L	0.0001	
Coagulation	Activated Partial Thromboplastin Time	s	0.1	
	Prothrombin Intl. Normalized Ratio		0.01	
	Prothrombin Times	s	0.1	

Table 2: List of Vital Signs Test Items:

Item	Unit	Display Digit	Remarks
Systolic blood pressure	mmHg	1	Set based on current data
Diastolic blood pressure	mmHg	1	
Pulse rate	Beats/min	1	
Height	cm	1	
Weight	kg	0.1	

Table 3: WHO Bleeding Scale:

Grade 0	No bleeding
Grade 1	Petechial bleeding
Grade 2	Mild blood loss (clinically significant)
Grade 3	Gross blood loss
Grade 4	Debilitating blood loss