Statistical Analysis Plan

Study Title	A Phase 3b, Multi-center, Randomized, Double-blind, Placebo-controlled, Parallel-group Trial with an Open-label Extension Phase to Evaluate the Efficacy and Safety of Avatrombopag for the Treatment of Thrombocytopenia in Pediatric Subjects With Immune Thrombocytopenia for ≥6 Months
Protocol Number:	AVA-PED-301
NCT Number	04516967
Investigational Product:	Avatrombopag
Sponsor:	Sobi, Inc.
Analysis Plan Date:	15-MAR-2023
Analysis Plan Version:	Version 1.1

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Protocol Version and Date:	Version 3.0, 02Nov2021 Version 2.0, 17Dec2020 Version 1.0, 24June2020
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SPONSOR SIGNATURE PAGE

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Protocol Number: AVA-PED-301

Sponsor: Sobi, Inc.
240 Leigh Farm Road, Suite 245
Durham, NC 27707

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol and all applicable regulatory guidance and guidelines.

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Change History

Version/Date	Author	Summary of Changes
1.0	[redacted]	Original Version
1.1	[redacted]	Updates per Sponsor comments

ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse event
AESI	Adverse events of special interest
ATC	Anatomical therapeutic chemical
BMI	Body mass index
CI	Confidence interval
CMH	Cochran-Mantel-Haenzel
EMA	European Medicines Agency
FAS	Full Analysis Set
IDMC	Independent Data Monitoring Committee
IRT	Interactive response technology
ITP	Immune thrombocytopenia
IVIg	Intravenous immune globulin
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamic
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
PPS	Per-protocol analysis set
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
SAE	Serious adverse event
SD	Standard deviation
SOC	System organ class
TEAE	Treatment emergent adverse event
TPO	Thrombopoietin
TPO-RA	Thrombopoietin receptor agonist
US	United States
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan is designed to outline the statistical methods for study AVA-PED-301 to evaluate the efficacy, safety, tolerability, and PK/PD profile of avatrombopag, as well as provide data on palatability/acceptability, dosing parameters, and response to treatment.

This document has been prepared based on protocol version 3.0 dated 02Nov2021 and Case Report Form (CRF) dated 10Jan2023.

Analysis for PK/PD will be addressed in a separate statistical analysis plan.

2. STUDY DESIGN

2.1 Summary of Study Design

AVA-PED-301 is a multi-center, randomized, double-blind, placebo-controlled, parallel-group study in pediatric subjects with a 12 week Core Phase followed by a 2-year open-label Extension Phase to evaluate the efficacy, safety, tolerability, and PK/PD profile of avatrombopag, as well as to provide data on palatability/acceptability, dosing parameters, and response to treatment.

The study will enroll at least 72 pediatric subjects, aged ≥1 to <18 years (Figure 1). Subjects will be assigned to 3 age cohorts in a 2:2:1 ratio and subjects will be randomized within each cohort in a 3:1 ratio to receive either avatrombopag or placebo. Subject age at the time of randomization will be used. Cohort 1 and Cohort 2 will each enroll more subjects than will be enrolled in Cohort 3 in order to minimize the exposure of the youngest age group to placebo. Randomization will be stratified by age cohort. Subjects will also be stratified by an average baseline platelet count of $\leq 15\times10^9$/L or $>15\times10^9$/L to $<30\times10^9$/L in order to ensure treatment groups are approximately balanced.

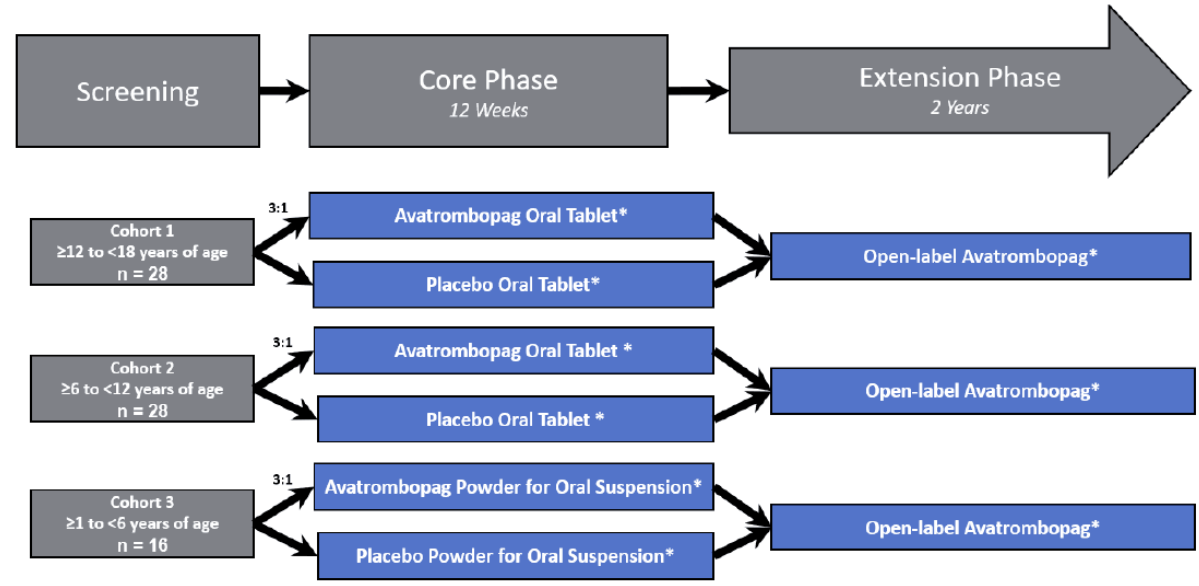
Enrollment into the Core Phase will be staggered by descending age cohort.

- Cohort 1: ≥12 to <18 years (n = 21 avatrombopag; 7 placebo)
- Cohort 2: ≥6 to <12 years (n = 21 avatrombopag; 7 placebo)
- Cohort 3: ≥1 to <6 years (n = 12 avatrombopag; 4 placebo)

All available PK and safety data through Week 10 of the Core Phase will be reviewed by the Sponsor and/or the Sponsor's designee (e.g., for unblinded PK data) for the first 10 subjects enrolled into Cohort 1 prior to opening enrollment into the Core Phase for subjects in Cohort 2. Likewise, all available PK and safety data through Week 10 will be reviewed by the Sponsor and/or the Sponsor's designee (e.g., for unblinded PK data) for the first 10 subjects enrolled into Cohort 2, prior to opening enrollment into the Core Phase for Cohort 3. As the study progresses and more data become available, the PK/PD model will be updated with emerging data in order to confirm the appropriate dose of avatrombopag in each cohort. Enrollment will not stop in the current cohort for the data review after Week 10, or for the data review after each cohort is fully enrolled. The dose of avatrombopag may be modified during the study based on results of the PK and safety data

review. In addition, safety data will be reviewed on an ongoing basis and new enrollment may be paused for any serious unexpected and related AEs that occur.

Figure 1: AVA-PED-301 Study Design



*Dose titration based on platelet count.

In order to minimize the number of blood draws subjects are subjected to, blood samples for *serial* PK assessments will only be collected during Visit 4 (Week 2) and Visit 12 (Week 10) of the 12 week Core Phase. For all age groups, blood samples for *sparse* PK assessments (2 mL each) will be collected while the subject is at the clinic during Visit 3 (Week 1) and at each weekly visit during the period from Visit 5 (Week 3) to Visit 11 (Week 9) (there will be 8 total PK samples drawn across these visits, 2 mL each). This frequency of sparse and serial PK blood sampling will allow for a comparison of PK values between pediatric and adult ITP patients and to confirm the appropriate dose of avatrombopag prior to opening the next cohort for enrollment.

Subjects who are not showing a platelet response (i.e., a lack of treatment effect) at the highest dose of study drug based on the subject's age cohort may be terminated from the Core Phase and directly enrolled into the open-label Extension Phase.

Lack of treatment effect will be defined as:

- Platelet count remains $<30\times10^9$/L after more than 3 weeks at the maximum dose of study drug per cohort. Subjects may also be terminated from the Core Phase and directly enrolled into the Extension Phase after 7 days of therapy at the maximum dose if they have dangerously low platelet counts (in the opinion of the Investigator), or
- Subjects who require rescue therapy more than 3 times or continuous rescue therapy for more than 3 weeks.

The Core Phase of the study will last 12 weeks (approximately 84 days), which does not include the 4 week Follow-up Period, with study visits occurring once weekly through the end of Week 12.

Subjects who complete the 12 week Core Phase of the study, or who meet the stopping criteria and are discontinued from the Core Phase, will be eligible to enter the open-label Extension Phase, if they continue to meet the inclusion criteria and do not meet any exclusion criteria for this phase of the study. The Extension Phase of the study will last 2 years during which time the subject will have monthly clinic visits. Subjects may be early terminated from the Extension Phase if they have a platelet count >250×10^9/L after 2 weeks of once weekly dosing for any age cohort or if they have a platelet count <30×10^9/L after 3 weeks of once daily dosing at the cohort defined maximum dose.

2.2 Sample Size Determination

The proposed sample size is based on the anticipated response rates for avatrombopag and placebo for the primary endpoint (durable response) and the key secondary endpoint (platelet response for 2 consecutive weeks).

Based on the eltrombopag PETIT2 study conducted in pediatric patients with chronic ITP, the durable response rates were 41.3% and 3.4% for eltrombopag and placebo, respectively (Grainger, 2015). It is reasonable to assume that the treatment effect of avatrombopag will be very similar to that of eltrombopag, due to both drugs being in the same class, having similar mechanisms of action, and treating similar patient populations (e.g., patients aged ≥1 to <18 years with relapsed or refractory disease after 1 or more previous treatments for ITP and a Baseline platelet count <30×10^9/L). With the 3:1 ratio of avatrombopag to placebo, a total of 72 subjects (54 avatrombopag and 18 placebo) will provide at least 90% power to detect a treatment difference of 37.9% in durable response at α=0.05, based on the Fisher's exact test.

In addition, a 12 week study of romiplostim in treating pediatric ITP patients showed that 88% of romiplostim treated subjects achieved a platelet count ≥50×10^9/L for 2 consecutive weeks (key secondary endpoint), whereas none of the placebo treated subjects achieved the same endpoint (Bussel, 2011).With the 3:1 ratio of avatrombopag to placebo, a total of 72 subjects (54 avatrombopag and 18 placebo) will provide ≥99% power to detect a treatment difference of 80% in proportion of subjects achieving a platelet count ≥50×10^9/L for 2 consecutive weeks at α=0.05, based on the Fisher's exact test.

2.3 Randomization and Blinding

During Day 1/Visit 2 of the Core Phase, after study eligibility has been confirmed, randomization assignment will be performed using interactive response technology (IRT). Randomization will be stratified by age cohort. Subjects will also be stratified by a baseline platelet count of ≤15×10^9/L or >15×10^9/L to <30×10^9/L in order to ensure treatment groups are approximately balanced. Following randomization, study drug will be dispensed in a double-blind manner. The Sponsor, the subject, and the clinical site personnel will be blinded to the treatment assignment.

No randomization or blinding is necessary for the Extension Phase as all subjects will receive open-label avatrombopag.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

- **Primary Objective**
  - to demonstrate that the efficacy of avatrombopag is superior to placebo for the treatment of pediatric subjects with ITP of ≥ 6 months duration who have had an insufficient response to a previous treatment
- **Secondary Objectives**
  - to evaluate the safety and tolerability of avatrombopag
  - to evaluate the PK and PD of avatrombopag
- **Exploratory Objective**
  - to provide data on the palatability and parent/caregiver reported acceptability of the avatrombopag powder for oral suspension

3.2 Study Endpoints

3.2.1 Efficacy Endpoints

- **Primary Efficacy Endpoint**
  - Durable platelet response defined as the proportion of subjects achieving at least 6 out of 8 weekly platelet counts $\geq 50\times10^9$/L during the last 8 weeks of the 12 week Treatment Period in the Core Phase in the absence of rescue medication
- **Alternative Primary Efficacy Endpoint (per EMA PIP)**
  - Platelet response as defined by the proportion of subjects for whom at least 2 consecutive platelet assessments are $\geq 50\times10^9$/L over the 12 week Treatment Period in the Core Phase in the absence of rescue medication
- **Additional Secondary Efficacy Endpoints**
  - The percentage of weeks subjects have a platelet count $\geq 50\times10^9$/L during 12 weeks of treatment in the Core Phase, in the absence of rescue therapy.
  - Platelet response at Day 8 (defined by the proportion of subjects with a platelet count $\geq 50\times10^9$/L at Day 8, in the absence of rescue therapy).
  - The percentage of weeks subjects have a platelet count between $\geq 50\times10^9$/L and $\leq 150\times10^9$/L, during 12 weeks of treatment in the Core Phase, in the absence of rescue therapy.
  - The proportion of subjects who require rescue medications during 12 weeks of treatment in the Core Phase of the study.
  - Incidence and severity of bleeding symptoms associated with ITP measured using the WHO Bleeding Scale

3.2.2 Safety Endpoints

- Incidence of AEs, SAEs, and AEs of special interest (AESI) during the study
- Measurement of clinical laboratory tests during the study
- Measurement of vital signs during the study

3.2.3 Exploratory Endpoints

- Platelet count assessments and platelet response during the Extension Phase
- Subject reported palatability and parent/caregiver reported acceptability assessed by a palatability/acceptability questionnaire administered after the first dose of the powder for oral suspension
- Month 3 durable platelet response defined as the proportion of subjects achieving at least 3 out of 4 weekly platelet counts $\geq 50 \times 10^9$/L during the last 4 weeks of the 12 week Treatment Period in the Core Phase in the absence of rescue medication

4. DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

4.1 Study Periods

Study periods are defined as follows:

Screening Period: Starting the day of signature of informed consent up to and including the day before randomization. For subjects who are not randomized, the screening period will end on the day the subject is determined to be a screen failure.

Randomized Control Period / Core Phase: Starting the day of randomization up to Visit 14 or the day of study drug discontinuation.

Follow-up Period in Core Phase: Starting the day after last dose of study drug in the Core Phase up to 30 days (±7 days) following the last dose of study drug in the Core Phase (only for subjects not entering the open label extension period).

Open Label Extension Period: Starting the day of Visit E-1/Day 1 to early termination or end of study. Visit 14 and Visit E-1 occur on the same day, and as a result are part of both the Randomized Control Period and the Open Label Extension Period.

4.2 Visit Windows

No formal visit windowing will be conducted. Only the scheduled visit assessments 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. If two records with equal distance to the target date, the average value of the two records will be used for analysis. The exceptions are for analyses of the worst post-baseline or all post-baselines; both scheduled and unscheduled visit assessments will

be used for these analyses. Additionally, records of the End of Study visit will be assigned to the appropriate visit per the study day.

4.3 Definition of Baseline

4.3.1 Baseline Platelet Count

In the efficacy analysis, baseline platelet count is the average of the platelet count obtained at the Screening Visit/Visit 1 and 1 other platelet count taken within 28 days on either side of the Screening Visit (may use a historical value collected per standard of care if within 28 days of the Screening Visit). The 2 samples must be obtained ≥24 hours and ≤28 days apart and the results must be available prior to randomization. This baseline platelet count will also be used as the stratification factor.

In the safety analysis, baseline platelet count is defined as the most recent non-missing measurement prior to first dose date/time of study drug in randomized control period.

4.3.2 Baseline for Other Evaluations

For all other evaluations (except WHO bleeding scale), baseline is defined as the most recent non-missing measurement prior to first dose date/time of study drug in the randomized control period.

For WHO bleeding scale, baseline is defined as the most severe (worst) bleeding event recorded prior to the first dose date/time of study drug in the randomized control period.

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

4.4 Definition of Study Days

Unless otherwise noted, study days of an evaluation are defined as number of days relative to the first dose date in each study phase.

- If evaluation date is on or after first dose date, then study days are calculated as

  Evaluation date - first dose date + 1

- If evaluation date is before first dose date, then relative study days are calculated as

  Evaluation date - first dose date

4.5 Handling Rules for Platelet Counts

Platelet counts are collected at local laboratories for eligibility and efficacy assessments. Platelet count is also included in the hematology panel sent to the central laboratory as a safety evaluation. For the efficacy analyses, only platelet counts assessed by the local laboratories will be included in

the calculations and summaries. For the safety analyses, only platelet counts assessed by the central laboratory will be included in the summaries.

4.6 Clinical Laboratory Tests

- Clinical laboratory results beyond the detectable limits will be reported as detectable limits for calculating descriptive statistics.
- All the laboratory test results will be included in the data listings as reported.

4.7 Handling of Partial Dates for Medications

When determining prior or concomitant medications, partial start dates of prior and concomitant medications will be assumed to be the earliest possible date consistent with the partial date.

For the purposes of analysis, incomplete medication starts and stop dates will be imputed.

- If a medication start date is incomplete, January will be imputed for missing month and/or the first day of the month will be imputed for missing day.
- If a medication stop date is incomplete, December will be imputed for missing month and the last day of the month will be imputed for missing day.
- If the imputed medication stop date is after the date of study completion, the date of study completion will be used instead.

4.8 Handling Partial Date for Adverse Events

When determining treatment emergent AEs, partial dates will be handled as follows.

- If the day of the month is missing, the 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 onset date will be assumed to be the first date of treatment.
- If the onset day and month are both missing, the day and month will be assumed to be January 1, unless the event occurred in the same year as the study treatment start. In this case, the event onset will be coded to the day of treatment start to conservatively report the event as treatment-emergent.
- A missing onset date will be coded as the day of treatment start. If the resulting onset date is after a reported date of resolution, the onset date will be set equal to the date of resolution.
- Imputation of partial dates is used only to determine whether an event is treatment-emergent; data listings will present the partial date as recorded in the eCRF.

4.9 Handling Partial Date for Date of Diagnosis & Platelet Transfusion Date

- If a date of diagnosis is incomplete, July will be imputed for missing month and the 15th day of the month will be imputed for missing day.

5. PLANNED ANALYSIS

5.1 Changes from Planned Analyses in the Protocol

An exploratory efficacy endpoint was included which was not detailed in the protocol: Month 3 durable platelet response defined as the proportion of subjects achieving at least 3 out of 4 weekly platelet counts $\geq 50 \times 10^9$/L during the last 4 weeks of the 12 week Treatment Period in the Core Phase in the absence of rescue medication.

Bleeding Adverse Events of Special Interest identified using a MedDRA SMQ were further defined as clinically significant blood loss using reported CTCAE grades instead of WHO bleeding grades, as WHO bleeding grades collected at study visits are not linked to individual adverse events.

5.2 Interim Analysis

No formal interim analysis is planned for this study. An IDMC will be convened for this study, primarily to monitor safety at regular intervals. An IDMC charter, detailing all aspects of the IDMC's scope of review and procedures, will be described in a separate document. In addition, ongoing safety data will be reviewed by the Sponsor in a blinded fashion for each age cohort. Interim PK/PD data will be analyzed by an unblinded designee.

5.3 Final Analyses and Reporting

This study consists of a double-blind, placebo-controlled period (Core Phase) and an open-label extension period (Extension Phase). The database will be locked, and the treatment assignment will be unblinded, when the last subject completes the Core Phase of the study. All data from the Core Phase and Open Label Extension Phase available in the locked database will be included in the statistical analyses. When the last subject completes the Extension Phase, additional extension data will be summarized and included in an updated Clinical Study Report.

6. ANALYSIS POPULATION

6.1 Screened Set

Screened Set includes all subjects with a signed informed consent form.

6.2 Core Phase Full Analysis Set (FAS)

The Core Phase Full Analysis Set (FAS) will include all randomized subjects.

Core Phase FAS is used for efficacy analysis in Core Phase. The analysis will be performed based on the randomized study drug.

6.3 Extension Phase Full Analysis Set (FAS)

The Extension Phase Full Analysis Set (FAS) will include all randomized subjects who entered Open Label Extension.

Extension Phase FAS is used for efficacy analysis in Extension Phase. The analysis will be performed based on the open label study drug.

6.4 Core Phase Safety Analysis Set

The Core Phase Safety Analysis Set includes all subjects who receive at least one dose of study drug.

The analysis will be performed based on the actual study drug received.

6.5 Extension Phase Safety Analysis Set

The Extension Phase Safety Analysis Set includes all subjects who receive at least one dose of study drug during Open Label Extension Phase.

The analysis will be performed based on the actual study drug received.

6.6 Per-Protocol Analysis Set (PPS)

The per-Protocol Analysis Set (PPS) will include a subset of subjects from the FAS who do not meet any criteria that would potentially impact the evaluation of the efficacy endpoints. A full list of the specific criteria will be finalized in a separate document prior to database lock and unblinding. 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
- Study Discontinuation resulting in an inability to assess the primary efficacy endpoint
- Assigned to incorrect treatment (mis-randomization) or receiving incorrect study medication

The analysis will be based on the actual study drug received.

6.7 Application of Analysis Set

The analysis sets that will be used for creating the summary tables of each type are provided in Table 1 (Core Phase) and Table 12 (Extension Phase).

Table 1. Application of Populations to Tables in Core Phase

Type	Safety	FAS	PPS
Disposition		X	
Demographics and baseline characteristics		X	
Protocol deviations		X	
Medical history and disease history		X	
Prior/concomitant medications/procedure		X	
Safety evaluations	X		

Type	Safety	FAS	PPS
Primary efficacy evaluations		X	X
Secondary efficacy evaluations		X	X

Table 2. Application of Populations to Tables in Extension Phase

Type	Safety	FAS
Disposition	X	
Demographics and baseline characteristics	X	
Protocol deviations	X	
Medical history and disease history	X	
Prior/concomitant medications/procedure	X	
Safety evaluations	X	
Primary efficacy evaluations		X
Secondary efficacy evaluations		X

7. STATISTICAL CONSIDERATIONS

All analyses described in this plan are considered a priori analyses in that they have been defined prior to locking the database. All other analyses, if any, designed subsequently to locking the database will be considered post hoc analyses and will be described as exploratory analyses in the Clinical Study Report.

All summaries and statistical analysis will be performed using SAS v9.4 or later.

7.1 General Statistical Procedures

Categorical variables will be summarized with number and percentage of subjects with a response in the category. Percentages will be based on number of subjects in the given population as noted. Number of subjects with missing information will also be included. Percentages will be reported to one decimal place.

A 2-sided 95% exact binomial (Clopper-Pearson) confidence interval (CI) for categorical variables without multiplicity adjustment will be provided where appropriate for efficacy analysis.

Continuous variables will be summarized with number of subjects (n), mean, standard deviation (SD), median, minimum (min) and maximum (max). Mean and median will be reported to 1 more decimal place than the raw data, while the SD will be reported to 2 more decimal places than the raw data. Minimum and maximum will be reported with the same number of decimals as the original data.

Unless otherwise stated, statistical summaries will be performed for each study phase (Core Phase and Extension Phase). Core Phase analysis will be performed by treatment for each cohort and overall. Open Label Extension Phase analysis will be performed by cohort and overall.

Data that is not summarized will be listed only. Unless otherwise specified in the text, all listings will be provided for the Full Analysis Set and will be ordered by subject number, study phase (Core Phase and Extension Phase) and visit and repeated by cohort for available data.

7.2 Subject Enrollment and Disposition

7.2.1 Subject Enrollment

The number of subjects screened, number of screen failure subjects and number of subjects in each analysis set will be provided.

Listing will be provided for Screened Set.

7.2.2 Subject Disposition

Subject disposition will be summarized (based on Section 7.1) for each phase including:

- Number and percentage of subjects who completed the study phase (Core/Extension)
- Number and percentage of subjects still on treatment (Core/Extension)
- Number and percentage of subjects who discontinued from the study phase (Core/Extension) and reasons for study discontinuation
- Number and percentage of subjects who discontinued the study drug and reasons for study drug discontinuation

Subject disposition will be listed for the Full Analysis Set. A separate listing will be provided for screen failure subjects with reasons for screen failure.

7.2.3 Protocol Deviations

Protocol deviations will be reviewed, assessed and documented by sponsor personnel before database lock.

The number and percentage of subjects with a major protocol deviation will be tabulated by category for the Full Analysis Set for each phase. Details of the major protocol deviations will be provided in a listing.

The number and percentage of subjects who are excluded from the PPS will be summarized by treatment group, along with reasons for exclusion. Subjects excluded from PPS will also be presented in a data listing.

7.3 Demographic and Baseline Disease Characteristics

7.3.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized (based on Section 7.1) including:

- Age (years) at randomization
- Sex
- Ethnicity
- Race
- Region (US, Europe)
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)

Demographics and baseline characteristics will be listed for the Full Analysis Set.

7.3.2 ITP History

ITP history will be summarized (based on Section 7.1) including the following information:

- Time from primary ITP diagnosis to first dose date (weeks), calculated as (first dose date – date of diagnosis of primary ITP+1)/7
- Number and percentage of subjects with splenectomy
- Number and percentage of subjects who received a previous platelet transfusion
- Time from last platelet transfusion to first dose date (weeks) defined as (first dose date – last platelet transfusion date + 1)/7
- Number and percentage of subjects who received different types of ITP medications since diagnosis
- Number and percentage of subjects treated with a TPO agonist
- Number and percentage of subjects by type of treatment received (Eltrombopag, Romiplostim, rhTPO and Other)
- Number and percentage of subjects who responded to any prior TPO agonist treatment

ITP history will be listed for the Full Analysis Set.

7.3.3 Disease Characteristics

Disease characteristics will be summarized (based on Section 7.1) including:

- Baseline platelet count (see Section 4.3.1 for definition)
- Baseline platelet count category ($\leq 15\times10^9$/L, $>15\times10^9$/L to $<30\times10^9$/L)
- Number and percentage of subjects with any bruising or bleeding
- WHO bleeding scale at baseline (a response of "No" is equivalent to Grade 0). If multiple bleeding events are reported at baseline, the worst (most severe) will be chosen as baseline.

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

- Number and percentage of subjects with any surgery

Disease characteristics will be listed for the Full Analysis Set.

7.3.4 Medical History

Medical history will be coded using MedDRA version 23.0 or higher.

The frequency and percentage of subjects experiencing any medical conditions will be tabulated by System Organ Class (SOC) and Preferred Term (PT). If a PT or SOC was reported more than once for a subject, the subject will be counted once in the incidence for that PT or SOC.

Medical history will be listed for the Full Analysis Set.

7.3.5 Prior and Concomitant Medications

All medications will be coded using Anatomical Therapeutic Chemical (ATC) classification based on World Health Organization (WHO) Drug Dictionary (March 2020, B3 or higher). The coding version may be updated prior to database lock if a newer version is available.

Prior medications are medications taken and stopped prior to first dose of study drug.

Concomitant medications during the Core Phase are medications being taken on or after the first dose of study drug in the randomized control period and prior to the first dose of the study drug in the Open Label Extension period.

Medications that start before the first dose of study drug in the randomized control period and continue into the randomized control period will be considered as concomitant medications for the Core Phase.

Concomitant medications for the Open Label Extension period are those which begin prior to the open label extension period and continue into the Open Label Extension period or those which start on or after the first day of study treatment in the Open Label Extension period.

Medications that begin in the Core Phase and have missing end dates are assumed to be

concomitant medications in both Core Phase and Open Label Extension Phase.

The number and percentage of subjects who have taken prior or concomitant medications will be summarized by ATC Level 2 Category and Preferred Name. A subject will be counted only once for medications taken more than once.

Rescue therapy may include:

- The addition of any new ITP medication or medication to treat thrombocytopenia, such as:
  - Corticosteroids - ATC level 2: CORTICOSTEROIDS FOR SYSTEMIC USE
  - IVIg - ATC level 2: IMMUNE SERA AND IMMUNOGLOBULINS
  - Anti-D - Preferred Term: Anti-D (rh) immunoglobulin
  - Platelet transfusion - Concomitant Procedure
- Any increase in the Day 1/Visit 2 dose of a concomitant ITP medication

TPO-RAs are not allowed as rescue therapy.

The following summary will be provided:

- Concomitant medications by study phase (Core Phase and Open Label Extension Phase)
- Concomitant Medications taken as rescue for a bleeding event by study phase (Core Phase and Open Label Extension Phase)
- Rescue Therapy used by study phase (Core Phase and Open Label Extension Phase)

Prior and concomitant medications will be listed for the Full Analysis Set.

7.3.6 Prior and Concomitant Procedures

Prior procedures are procedures performed prior to first dose of study drug.

Concomitant procedures during the Core Phase are procedures being performed on or after the first dose of study drug in the randomized control period and prior to the first dose of the study drug in the Open Label Extension period.

Concomitant procedures for the Open Label Extension period are those which start on or after the first day of study treatment in the Open Label Extension period.

Prior and concomitant procedures will be listed for the Full Analysis Set.

7.4 Efficacy Analysis

Unless otherwise stated, all primary and secondary efficacy endpoints defined in Section 3.2.1 will be analyzed for the FAS and PPS.

For the efficacy evaluation of the platelet count responses, platelet counts assessed by local labs will be used. Platelet counts collected via the central lab will be used in the safety assessments of

clinical laboratory tests.

The methods used for efficacy analysis for the Core Phase are summarized in **Error! Reference source not found.**3. All Cochran-Mantel-Haenzel (CMH) tests at alpha=0.05 within each age cohort will be performed adjusting for baseline platelet count category ($\leq 15\times10^9$/L vs $>15\times10^9$/L). For the CMH test in the overall group, the test will be performed adjusting for age cohort and baseline platelet count category. Fisher's exact test will be used if the number of durable platelet responders is spare in the strata (less than 3 in a specific subgroup). Durable platelet response with 2-sided 95% exact binomial (Clopper-Pearson) confidence interval (CI) will be provided. The difference in response rate (avatrombopag – placebo) with 2-sided 95% CI (Wald) will also be provided.

Subjects without sufficient data for the determination of response status (i.e., responder versus non-responder) will be treated as non-responders in the analysis.

For the primary efficacy endpoint determination, a subject must have remained in the Core phase through at least Week 10 (to have at least 6 weeks of platelet count data starting from week 5 to either week 12 if the subject completes the core phase or the last week if the subject prematurely terminates the core phase). If a subject terminates the Core phase prior to Week 10, they would be considered a non-responder for the primary efficacy endpoint.

Table 3. Efficacy Analysis Methods for Core Phase

Endpoint	Analysis Method
Primary Efficacy Endpoint	
Durable platelet response defined as proportion of subjects achieving at least 6 out of 8 weekly platelet counts $\geq 50\times10^9$/L during the last 8 weeks of the 12 week treatment period in the Core Phase in the absence of rescue medication. In the case of rescue medication being used, platelet count assessments from the start date of rescue medication up until 4 weeks after the end date of rescue medication will be excluded from analysis.	CMH test
Alternative Primary Efficacy Endpoint	
• Platelet response defined as proportion of subjects for whom at least 2 consecutive platelet assessments are $\geq 50\times10^9$/L during last 8 weeks of the 12 week treatment in the Core Phase in the absence of rescue medication	CMH test
Secondary Efficacy Endpoints	
• Percentage of weeks subjects have a platelet count $\geq 50\times10^9$/L during 12 weeks of treatment in the Core Phase, in the absence of rescue therapy. Denominator for this calculation is based on the number of weeks the subject was on treatment (up to 12 weeks)	Nonparametric Wilcoxon Rank Sum tests
• Platelet response at Day 8 (defined by the proportion of subjects with a platelet count $\geq 50\times10^9$/L at Day 8, in the absence of rescue therapy)	CMH test

Endpoint	Analysis Method
• Percentage of weeks subjects have a platelet count between $\geq 50\times10^9$/L and $\leq 150\times10^9$/L, during 12 weeks of treatment in the Core Phase, in the absence of rescue therapy. Denominator for this calculation is based on the number of weeks the subject was on treatment (up to 12 weeks)	Nonparametric Wilcoxon Rank Sum tests
• Proportion of subjects who require rescue medications during 12 weeks of treatment in the Core Phase of the study	CMH test
• Overall incidence and incidence of severe bleeding symptoms (scale 3 and 4) associated with ITP measured using the WHO Bleeding Scale	CMH test
Exploratory Efficacy Endpoint	
• Month 3 durable platelet response defined as the proportion of subjects achieving at least 3 out of 4 weekly platelet counts $\geq 50\times10^9$/L during the last 4 weeks of the 12 week Treatment Period in the Core Phase in the absence of rescue medication	CMH test

Note: Fisher's exact test will be used if CMH test fails.

If the test of the treatment effect on the primary efficacy endpoint is statistically significant, the statistical tests on the secondary efficacy endpoints will be considered inferential; otherwise, the tests will be considered descriptive and no statistical inference can be drawn with regards to the secondary efficacy endpoints.

To control the family-wise Type I error rate at a significance level of $\alpha = 0.05$ (2-sided), a step-down closed testing procedure will be used when testing the secondary efficacy endpoints. Starting with the key secondary efficacy endpoint, if the test is significant at $\alpha = 0.05$, then the test on the next endpoint will be considered inferential; otherwise, the tests on the subsequent endpoints will be considered descriptive only. This process will be repeated from the top of the hierarchy for the remaining endpoints.

The efficacy variables collected during the Open Label Extension Phase will be summarized descriptively.

For the Core Phase, observed values and change from baseline over time for platelet counts will be summarized. For the Core Phase, WHO bleeding scale will be summarized by visit.

For the Extension phase, observed values for platelet counts and WHO bleeding scale will be summarized by visit.

Blood product transfusions will be summarized for both the Core Phase and the Open Label Extension Phase including the following variables:

- Number and percentage of subjects with at least one blood product transfusion
- Total number of blood product transfusions
- Type of blood product
- Reasons for transfusion
- Number of packs/units per transfusion

Platelet count and blood transfusions will be listed for the Full Analysis Set.

7.5 Safety Analysis

7.5.1 Extent of Study Drug Exposure

Study drug exposure will be summarized by study phase (based on Section 7.1) and for the entire study for the Safety Analysis Set including:

- Duration of treatment (weeks), calculated as (last dose date – first dose date + 1)/7
- Total number of tablets/capsules taken, calculated as total number of tablets/capsules dispensed – total number of tablets/capsules returned
- Total dosage taken, calculated as total number of tablets taken * 20mg/tablets (or total number of capsules taken *10 mg/capsules)
- Weekly average dose (mg/week) received defined as total dosage taken (mg)/duration of treatment (weeks)
- Compliance (%), calculated as total dosage taken/sum of (planned dosing regimen * regimen period (days)) * 100.

Study drug administration, study drug regimen, overall study drug exposure and study drug compliance will be listed for the Safety Analysis Set.

7.5.2 Adverse Events

Adverse events (AEs) will be coded using MedDRA version 23.0 or higher and will be classified by SOC and PT of MedDRA. The coding may be updated according to newly released versions of the dictionary. Severity of AEs will be graded according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

A treatment emergent adverse event (TEAE) is defined as any AE that occurs after administration of the first dose of study drug.

AEs are classified as related or not related to the study drug based on investigator assessment. AEs with missing or unknown relationship to the study drug will be considered as related AEs.

TEAEs with starting date prior to the first dose date in the Open Label Extension Phase will be classified as TEAEs in the Core Phase. TEAEs with starting date on or after the first dose date in the Open Label Extension Phase will be classified as TEAEs in the Open Label Extension Phase. An overall summary of TEAEs will be provided for each phase and the entire study including:

- Any TEAE

- Any related TEAE
- Any Grade 3-5 TEAE
- Any TEAE leading to study discontinuation
- Any TEAE leading to drug withdrawn
- Any TEAE leading to dose reduction/interruption
- Any serious TEAE
- Any serious TEAE by relationship to study drug (related, unrelated)
- Any death
- Any AESI (AE of special interest) (Thromboembolic events, CTCAE Grade ≥3 Bleeding events)

The following events will be tabulated and summarized. The output will be sorted by decreasing frequency of PT within SOC which is sorted alphabetically in overall events.

- TEAEs by SOC and PT
- TEAEs by PT
- Drug-related TEAEs by SOC and PT
- Drug-related TEAEs by PT
- TEAEs by maximum toxicity grade, SOC and PT
- TEAEs leading to study discontinuation by SOC and PT
- Serious TEAEs by SOC and PT
- Drug-related serious TEAEs by SOC and PT
- AESIs by AESI category and PT

Two categories for Adverse Events of Special Interest (AESI) will be summarized and are defined based on terms in Standardized MedDRA Queries (SMQs) from MedDRA v26.1 or later:

- Thromboembolic events - Any thrombotic or embolic event, whether arterial or venous – SMQ = Embolic and thrombotic events
- Bleeding Events - Any clinically significant blood loss [e.g., bleeding events with CTCAE grade 3+ (based on AE severity [AESEV]>=3] – SMQ = Haemorrhage terms (excl laboratory terms)

If a SOC or PT is reported more than once for a subject, the subject will be counted only once in the incidence for that SOC or PT.

The following listing will be provided for the Safety Analysis Set:

- AEs
- Serious TEAEs

- Death
- Grade 3-5 TEAEs
- TEAE leading to study discontinuation
- AESIs

7.5.3 Clinical Laboratory Tests

Observed and changes from baseline for clinical laboratory (serum chemistry and hematology) parameters will be summarized (based on Section 7.1) by visit for Safety Analysis Set in the Core Phase. Observed values for clinical laboratory (serum chemistry and hematology) parameters will be summarized by visit for Safety Analysis Set in the Extension Phase.

Number and percentage of subjects with abnormal values will be tabulated by visit for applicable parameters.

Platelet count results from the central lab will be used in the safety assessments of clinical laboratory tests.

Laboratory results will be listed for the Safety Analysis Set.

7.5.4 Weight and BMI

Observed and changes from baseline for weight and BMI will be presented in a listing for the Safety Analysis Set.

7.5.5 Vital Signs

Observed and changes from baseline for vital signs (temperature, blood pressure, and heart rate) will be summarized (based on Section 7.1) by visit for Safety Analysis Set in the Core Phase. Observed values for vital signs (temperature, blood pressure, and heart rate) will be summarized (based on Section 7.1) by visit for Safety Analysis Set in the Extension Phase.

Vital signs will be listed for the Safety Analysis Set.

7.5.6 Acceptability Questionnaire and Palatability Questionnaire

Acceptability questionnaire and palatability questionnaire responses will be summarized (based on Section 7.1) for subjects in Cohort 3 who receive the suspension product for the Safety Analysis Set.

Acceptability and palatability questionnaire responses will be listed for the Safety Analysis Set.

8. REFERENCES

Bussel JB, Garcia de Miguel P, Despotovic JM, Grainger JD, Sevilla J, Blanchette VS, et al. Eltrombopag for the Treatment of Children with Persistent and Chronic Immune Thrombocytopenia (PETIT): a Randomized, Multicentre, Placebo-controlled Study. *Lancet Hematol*. 2015; 2: e315-325.

Grainger JD, Locatelli F, Chotampancharoen T, Donyush E, Pongtanakul B, Komvilaisak P, et al. Eltrombopag for Children with Chronic Immune Thrombocytopenia (PETIT2): a Randomized, Multicentre, Placebo-Controlled Trial. *Lancet*. 2015; 386: 1649-1658.