Statistical Analysis Plan

Study Title	Prospective, Multi-center, Open-label Study Measuring Safety and Treatment Satisfaction in Adult Subjects with Chronic Immune Thrombocytopenia (ITP) after Switching to Avatrombopag from Eltrombopag or Romiplostim
Protocol Number:	AVA-ITP-401
NCT Number	04638829
Investigational Product:	Avatrombopag
Sponsor:	Sobi, Inc.
Analysis Plan Date:	31-JAN-2024
Analysis Plan Version:	Version 2.0

Signature Page for AVA_ITP_401_SAP
Study AVA-ITP-401 v2.0

eSignature for Approval	[redacted] Sponsor 30-Jan-2024 22:09:34 GMT+0000
eSignature for Approval	[redacted] [redacted] Statistician n-2024 22:10:14 GMT+0000
eSignature for Approval	[redacted] Sponsor 31-Jan-2024 15:41:39 GMT+0000
eSignature for Approval	[redacted] [redacted] Statistician n-2024 15:55:34 GMT+0000

Signature Page for AVA_ITP_401_SAP
Study AVA-ITP-401 v2.0

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Statistical Analysis Plan

SPONSOR:	Sobi
PROTOCOL TITLE:	Prospective, Multi-center, Open-label Study Measuring Safety and Treatment Satisfaction in Adult Subjects with Chronic Immune Thrombocytopenia (ITP) after Switching to Avatrombopag from Eltrombopag or Romiplostim
STUDY CODE:	AVA-ITP-401

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[redacted]

[redacted]

Change History

Version Date	Author	Summary of Changes
29APR2021	[redacted]	N/A – First Version
04JUN2021	[redacted]	• General wording/language clarifications and alignment with protocol. • Figure clarity. • Updated TSQM scoring algorithm based on IQVIA TSQM manual. • Added language to clarify that a separate table for bleeding, listing for platelet count, and two listings for exposure/treatment compliance will be included. • Moved WHO Bleeding assessments to safety evaluation section.
09JUL2021	[redacted]	• Added link to study design figure • General language for addition of table to compare prior TPO-RA with stable dose of Ava. To be finalized after discussion • Added listing of procedures to prior/concomitant treatment section • Added clarification describing WHO bleeding leading question at Baseline vs other visits in section 9.3.2
30JUL2021	[redacted]	• Added text describing summary of prior TPO-RA table vs stable dose in section 6.4
23JUN2023	[redacted]	• Added section 8.1 "Study Endpoints" • In section 8.2, added secondary analysis of using paired t-test to the other three domains of TSQM (global satisfaction, effectiveness, and side effects) • Added clarity to the definition of AESI in section 9.2 • Added procedure to identify AESI • Added definition to "Post screening exclusion" under disposition • Updated footer of the SAP per [redacted]-FRM-TPL-0105 • Add subgroup analysis by prior history of TPO-RA (eltrombopag vs romiplostim) and Overall. • Updated format/layouts and numberings • Updated MedDRA version to 26.1 or later
10NOV2023	[redacted]	• Last category of treatment compliance was updated to >100-110%

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		• Bleeding evaluation for overall study period was added and defined. • Specified subgroup analysis by prior history of TPO-RA (eltrombopag vs romiplostim) and Overall, in some additional sections. • Definition of concomitant medication updated. • Added a sentence to reflect number of adverse events to be summarised by SOC and PT. • Removed "surgical" from "Medical and Surgical History" as surgical history is not collected. • TSQM and Analysis of platelets counts were grouped into a separate "Efficacy/Effectiveness Evaluation" section.

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1. List of Abbreviations and Definition of Terms

Abbreviation	Term
AE	*Adverse Event*
AESI	*Adverse Event of Special Interest*
ATC	*Anatomical Therapeutic Classification*
eCRF	*Electronic Case Report Form*
ICH	*International Conference on Harmonization*
MedDRA	*Medical Dictionary for Regulatory Activities*
PT	*MedDRA Preferred Term*
SAE	*Serious adverse event*
SAP	*Statistical Analysis Plan*
SMQ	*Standardized MedDRA Query*
SOC	*MedDRA System Organ Class*
TEAE	*Treatment-Emergent Adverse Event*
TPO-RA	*Thrombopoietin receptor agonist*
TSQM	*Treatment Satisfaction Questionnaire for Medication*
USPI	*United States Prescribing Information*
WHO	*World Health Organization*

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2. Introduction

This Statistical Analysis Plan (SAP) describes the statistical methodology and data handling for the clinical trial for Sobi, Inc. (formerly Dova Pharmaceuticals) with Protocol Number: AVA-ITP-401 (Prospective, Multi-center, Open-label Study Measuring Safety and Treatment Satisfaction in Adult Subjects with Chronic Immune Thrombocytopenia (ITP) after Switching to Avatrombopag from Eltrombopag or Romiplostim).

The ICH guideline E3 "Structure and Content of Clinical Study Reports" was used as a guide to the writing of the plan.

This SAP is based on the following study document(s):

- Clinical Study Protocol V2.0, dated 28 Jan 2022
- Electronic Case Report Form V3.0, dated 15 March 2021

3. Study Design and Objectives

3.1 Study Objectives

3.1.1 Primary Objective

The primary objective of this study is to characterize the safety and tolerability of avatrombopag given for 90 days after stopping treatment with eltrombopag or romiplostim.

3.1.2 Secondary Objectives

The secondary objectives of this study are the following:

- Evaluate the change in subject reported outcomes (TSQM) from Baseline after switching to avatrombopag from eltrombopag or romiplostim.
- Evaluate the platelet counts after switching to avatrombopag from eltrombopag or romiplostim.

3.2 Study Endpoints

3.2.1 Primary Endpoint

Occurrence of adverse events (AEs) and serious adverse events (SAEs).

3.2.2 Secondary Endpoints

Change from Baseline in each of the 4 domains of the TSQM Version 1.4 (e.g., convenience, global satisfaction, effectiveness, and side effects) to Day 90 or End of Study.

Proportion of subjects who have a platelet count between $\geq 50 \times 10^9$/L to $\leq 200 \times 10^9$/L at Day 15, Day 30, Day 60, and Day 90.

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3.3 Study Design

This is a Phase 4, prospective, multi-center, open-label study to evaluate safety, platelet count, and subject reported medication satisfaction in adult subjects with chronic ITP after switching to avatrombopag from eltrombopag or romiplostim.

At least 100 subjects are planned to be enrolled, 50 (±10) who have received eltrombopag and 50 (±10) who have received romiplostim for at least 90 days prior to study entry. An overview of the study design is provided in Figure 1.

The initial dose and dose adjustments of avatrombopag will be determined by the Investigator in conjunction with the DOPTELET® USPI (United States Prescribing Information). There is no protocol-required washout period between treatment with TPO-RAs (Thrombopoietin receptor agonists), however avatrombopag should not be administered on the same day as another TPO-RA. The start and stop dates of all prior and concomitant medications should be recorded in the electronic case report form (eCRF).

Safety will be evaluated throughout the study. Bleeding severity will be captured using the World Health Organization (WHO) Bleeding Scale at each visit. Platelet counts will be collected per protocol at Baseline, Day 15, Day 30, Day 60, and Day 90, however, all other platelet counts collected per the subject's standard of care while they are enrolled in the study should be recorded in the eCRF. The TSQM (Treatment Satisfaction Questionnaire for Medication) will be administered prior to the first dose of avatrombopag (at Baseline), at Day 30, and at Day 90 or at the time of early termination from the study. Compliance with the Investigator prescribed avatrombopag dosing regimen will be captured via a subject reported Dosing Diary which should be evaluated by the study team during each visit to the clinic, per the subject's standard of care.

Subjects may be screened within 28 days of the Baseline Visit/Visit 2; however, the Screening Visit/Visit 1 may be combined with the Baseline Visit/Visit 2. The duration of subject participation and collection of clinical data will be a minimum of 90 days from the Screening Visit/Visit 1 to Day 90. The only protocol-required clinic visits during the study are the Baseline Visit/Visit 2, Day 15, Day 30, Day 60, and the Day 90 or Early Termination Visit.

If a subject is early terminated, the early termination assessments should be completed prior to discharge from the study.

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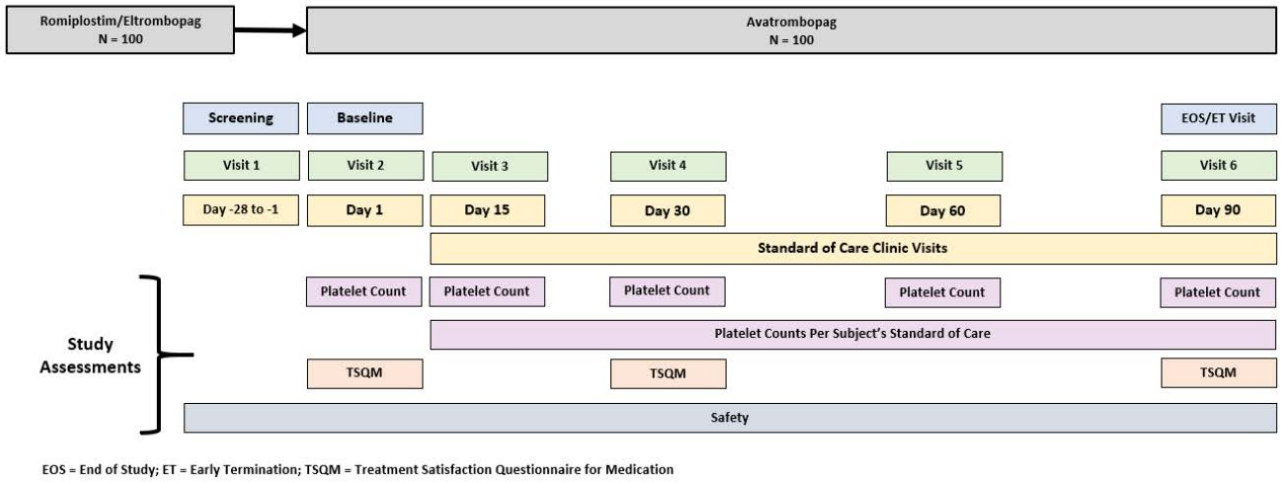
Figure 1: AVA-ITP-401 Study Schematic



EOS = End of Study; ET = Early Termination; TSQM = Treatment Satisfaction Questionnaire for Medication

3.4 Sample Size Justification

The primary interest in assessing the TSQM in this study is the convenience domain score. An observational, retrospective study conducted in 2011 and supported by GlaxoSmithKline showed that the mean convenience score for eltrombopag-treated and romiplostim-treated subjects were 76.11 and 62.12, respectively. Study E5501-G000-302, a 6-month, randomized, placebo-controlled study in chronic ITP patients, showed that the mean TSQM convenience score assessed at Week 12 and at the End of Study for avatrombopag-treated patients was approximately 85 with a standard deviation (SD) which ranged from 12.2 – 14.8. Likewise, E5501-G000-305, a 6-month, randomized, active-control study in chronic ITP patients, showed that the mean TSQM convenience score assessed at the End of Study was 78.9 (SD = 15.4) for avatrombopag-treated patients and 68.2 (SD = 21.0) for eltrombopag-treated patients.

Assuming a mean TSQM convenience score at Baseline and at the End of Study of 74 and 82, respectively, with a SD of 19, 50 subjects will provide 83% power to detect a change from Baseline of 8 at a 2-sided significance level of 0.05 based on a paired t-test. The total sample size will be 100 subjects; approximately 50 subjects who received prior treatment with eltrombopag and approximately 50 subjects who received prior treatment with romiplostim.

4. General Analysis Definitions

4.1 Study Period and Visit Window Definitions

4.1.1 Study Periods

Screening Period: Starting the day of the Screening Visit/Visit 1 in which informed consent is signed up to the day before the Baseline Visit/Visit 2 during which avatrombopag is first administered. The Screening Visit must be completed

[redacted]

[redacted]

within 28 days prior to the Baseline Visit, however, the Screening and Baseline visits may be combined.

Treatment Period: Starting from the Baseline Visit/Visit 2 (or combined Visit 1/Visit 2, if applicable) through the End of Study Visit on Day 90 (±2 days) or the Early Termination Visit, whichever occurs first.

4.1.2 Visit Windows

The recommended and allowed intervals between study visits are presented in the protocol Section 7, Study Procedures (Appendix A). No recalculation of time windows or formal visit windowing will be conducted. By-visit tabular summaries will assume that observations are from the scheduled visit recorded in the eCRF irrespective of the date specified.

4.2 Definition of Populations

4.2.1 All Screened Population

The All Screened Population is defined as all patients who have completed a Screening Visit. The summary of disposition and the listing of inclusion/exclusion criteria not met will be based on the All Screened Population.

4.2.2 All Enrolled Population

The All Enrolled Population is defined as all subjects who receive at least 1 dose of study drug. Analyses and summaries of demographic and Baseline characteristics, safety assessments, and subject reported outcomes will be based on the All Enrolled Population.

4.3 Data Handling Conventions

4.3.1 General Conventions

Data will be analyzed using SAS (Version 9.4 or later). Descriptive analyses will be performed on demographic and baseline characteristics, safety assessments, platelet counts, and subject reported outcomes.

Descriptive statistics will be tabulated as follows:

- Categorical data will be summarized in contingency tables presenting frequencies and percentages, and
- Continuous data will be summarized using number of non-missing values (n), mean, standard deviation, median, minimum, and maximum values.

4.3.2 Definition of Study Day

The first day of study treatment with avatrombopag will be during the Baseline Visit/Visit 2 and will be referenced as Study Day 1. There is no Study Day 0. The day before the first day of study treatment will be Study Day -1. If an event occurs on or after the first day of study treatment, Study Day will be calculated as (Date of Event - Date of first study treatment + 1). If the event occurs prior to the first day of study treatment, Study Day will be calculated as (Date of Event - Date of first study treatment).

[redacted]

[redacted]

4.3.3 Definition of Baseline

Baseline is defined as the last non-missing assessment done on or before the start of study treatment on Study Day 1. Assessments done on the date of study treatment administration are assumed to take place before the administration, unless specified otherwise.

4.3.4 Handling Missing Data

All available data will be included in data listings and tabulations.

No imputation of missing data is planned for study endpoints.

4.3.5 Partial Dates

For the purpose of inclusion of appropriate data records in the analysis, some partially missing dates will have date imputation performed. However, these imputations will be limited to table summaries; listings will retain the date as entered in the database. The following imputations will be performed:

Medications:

- If a start date is missing the day
  - Set to the 1st of the month
- If a start date is missing the day and month
  - Set to January 1st if study treatment began the year prior to the year of medication start
  - Set to January 1st if the medication is known to start in a year prior to study treatment
  - If the medication and the study treatment start the same year, the medication start date will be set to the study treatment start date.
- No medication end dates will be imputed
- No completely missing dates will be imputed. If, after imputation, it cannot be determined whether a medication was taken prior or concomitantly, it will be considered a concomitant medication.

Adverse Events:

- If a start date is missing the day
  - Set to the 1st of the month, or the same day as treatment start if it is the same month and year as treatment start
- If a start date is missing the day and month
  - Set to treatment start date if it is the same year as treatment start; otherwise set to January 1st if it is the year after treatment start.
- No adverse event end dates will be imputed
- No completely missing start dates will be imputed. If, after imputation, it cannot be determined if an adverse event is treatment-emergent, it will be considered treatment-emergent for analysis purposes.

4.4 Treatment Groups

All subjects enrolled in the study will receive open-label avatrombopag. Data displays will have three columns for All Enrolled Population, presented by prior

[redacted]

[redacted]

TPO-RA (romiplostim and eltrombopag) and overall, unless otherwise specified in the mock TLFs.

4.5 Data Listings

Data listings will generally include Subject ID, Age, Sex, Race, and as applicable, prior TPO-RA by default.

5. Study Patients

5.1 Disposition of Patients

A summary table by prior TPO-RA (romiplostim and eltrombopag) and overall group will include the total number of subjects screened and the numbers and percentages of screened subjects who enrolled in the study, subjects who failed screening, and the reason for screen failure. In addition, if any subjects are excluded after screening it will be reported as "Post screening exclusion" defined as subjects who screened but not enrolled to study and take medication yet.

The summary table will also contain the numbers and percentages of patients who completed the study, discontinued the study early, and the primary reason for early discontinuation.

A disposition listing will include the verbatim "Other" specified text from the eCRF if the reason for screen failure or the reason for early discontinuation from the study is entered as "Other." If the reason for discontinuation is adverse event, then the listing will display the associated adverse event (AE) preferred term.

5.2 Inclusion and Exclusion Criteria Details

Details of inclusion/exclusion criteria for subjects in the All Screened Population will be provided in a listing. This listing will indicate the protocol version, informed consent date, whether the subject rescreened, and if the subject enrolled. Details of inclusion and exclusion criteria not satisfied for subjects who did not enroll will be provided. The listing will also indicate if the subject's Screening and Baseline visits were combined.

6. Demographic and other Baseline Characteristics

Demographics and Baseline Characteristics will be summarized for subjects by prior TPO-RA (romiplostim and eltrombopag) and overall for all enrolled subjects.

6.1 Demographics and Baseline Characteristics

Descriptive statistics with respect to subject characteristics at baseline will be displayed by prior TPO-RA (romiplostim and eltrombopag) and overall for all enrolled subjects. The variables to be summarized are:

Demographics

- Age at enrollment (years)
- Sex
- Race
- Ethnicity

[redacted]

[redacted]

Baseline subject characteristics

- TSQM domain scores of effectiveness, side effects, convenience, and global satisfaction
- Summary of WHO Bleeding Scale assessment (within the previous 7 days)
- Platelet count as assessed by local lab (10^9/L)

A listing of demographic and baseline characteristics will also be provided.

6.2 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Authorities (MedDRA) version 26.1 or later. The coding version may be updated prior to database lock if a newer version is available.

Medical history will be tabulated by Preferred Term (PT) by prior TPO-RA (romiplostim and eltrombopag) and overall for all enrolled subjects. Subjects with more than one medical history event in a PT will only be counted once per PT. Only those PTs with >5% of enrolled subjects will be displayed in the summary table. However, all medical history details will be provided in a data listing.

6.3 Immune Thrombocytopenia (ITP) History

Descriptive statistics with respect to ITP history will be displayed by prior TPO-RA (romiplostim and eltrombopag) and overall for all enrolled subjects. The variables to be summarized are:

- Time since ITP diagnosis (years), defined as (Date of enrollment – Date of Diagnosis+1)/365.25
- Number of platelet transfusions in the previous 1 year
- Number of previous hospitalizations for ITP
- Number of previous significant bleeding events
- History of splenectomy (yes/no)
- History of thromboembolic events (yes/no)

A listing of ITP history will also be provided. It will include the variables above along with the date of last platelet transfusion and the reason for switching to avatrombopag from eltrombopag or romiplostim.

6.4 Administration of Prior TPO-RA

Descriptive statistics of variables related to the administration of prior TPO-RA will be displayed for all enrolled subjects. The table will be divided in 2 sections (one for romiplostim and one for eltrombopag) and include a summary of:

- Duration of prior treatment with romiplostim and eltrombopag (weeks) as a continuous variable
- Most recent dose level of eltrombopag and romiplostim (mg or mcg/kg) as a categorical variable

[redacted]

[redacted]

- Subject-reported responses to the 3 brief questions in the romiplostim and eltrombopag eCRF pages

An additional table will be created comparing the most recent dose level of prior TPO-RA (romiplostim and eltrombopag) recorded at the Baseline Visit to the stable dose of avatrombopag at the end of study. The stable dose of avatrombopag at the end of the study will be defined as the final avatrombopag dose recorded in the eCRF at the End of Study Visit on Day 90. The prior TPO-RA dose will be categorized into 3 dose groups (low, medium, and high), and the table will summarize the stable dose of avatrombopag by prior TPO-RA within each group.

Listings (one for romiplostim and one for eltrombopag) will present each individual subject's duration of prior treatment, most recent dose level (units), date of last dose, and answers to the 3 questions in the romiplostim and eltrombopag eCRF pages.

7. Prior and Concomitant Treatment

Prior and Concomitant medications will be classified according to the World Health Organization (WHO) Drug Dictionary Global (Enhanced w/WHO Herbal Dictionary). The coding version may be updated prior to database lock if a newer version is available. Medications will be coded per the Anatomical Therapeutic Classification (ATC). All medications will be documented from the time of informed consent up to the End of Study/Early Termination Visit.

Prior medications are those which start and stop before the first day of study treatment. Concomitant medications are those which are being taken on or after the first day of study treatment.

Tabular summaries will display the number and percentage of subjects with at least one medication in ATC Level 2 and preferred name categories by prior TPO-RA (romiplostim and eltrombopag) and overall groups. Subjects who have taken a medication more than once will only be summarized once per ATC Level 2 or preferred name.

The tabular summaries to be provided are as follows:

- Prior Medications
- Concomitant Medications
- Concomitant Medications taken as rescue for a bleeding event

An overall listing of medications will be provided. The listing will designate whether a medication is considered prior or concomitant. A separate listing will also be produced for concomitant medications taken as rescue for a bleeding event.

An overall listing of procedures will also be provided with procedure name, start and end dates, a flag for prior/concomitant procedure, and details about reason for the procedure (indication).

8. Efficacy/Effectiveness Evaluation

8.1 Treatment Satisfaction Questionnaire for Medication (TSQM)

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The domain scores of effectiveness, side effects, convenience, and global satisfaction will be computed according to the Treatment Satisfaction Questionnaire for Medication (TSQM) User Manual (IQVIA, Version 1.6: 04 March 2020). Each domain score ranges from 0 to 100, and a higher score indicates a better outcome. The TSQM will be administered at Baseline (before the first dose of avatrombopag), Day 30, and Day 90.

The scoring algorithms are as follows:

If more than one item score is missing, the scale score should not be computed and set to missing. If a subject answers "No" to Item 4, the side effects scale score will not be computed.

Effectiveness

Effectiveness scale score = [(Item 1 + Item 2 + Item 3 – 3)/18] x 100

If one item is missing:

Effectiveness scale score = [(Item 1? + Item 2? + Item 3? -2)/12] x 100

Side Effects

If Question 4 is answered 'No' then score = 100

Else:

Side effects scale score = [(Item 5 + Item 6 + Item 7 + Item 8 – 4)/16] x 100

If one item is missing:

Side effects scale score = [(Item 5? + Item 6? + Item 7? + Item 8? – 3)/12] x 100

Convenience

Convenience scale score = [(Item 9 + Item 10 + Item 11 – 3)/18] x 100

If one item is missing:

Convenience scale score = [(Item 9? + Item 10? + Item 11? – 2)/12] x 100

Global Satisfaction

Global satisfaction scale score = [(Item 12 + Item 13 + Item 14 – 3)/14] x 100

If Item 12 or 13 is missing

([(Sum(the two completed items)) – 2] divided by 10) * 100

If Item 14 is missing

([(Sum(Item 12 and Item 13)) – 2] divided by 8) * 100

Descriptive statistics will be summarized for each domain score and each visit. The change from Baseline and percent change in each mean domain score will be

summarized descriptively by prior TPO-RA (eltrombopag vs romiplostim) and overall.

The primary interest in the TSQM assessment is the convenience domain score. The hypothesis is that switching from a prior TPO-RA treatment (e.g., eltrombopag or romiplostim) to avatrombopag results in an improvement in the convenience domain score. Change from Baseline to Day 90 (or End of Study) in the convenience domain score will be tested using paired t-tests, by prior TPO-RA treatment (eltrombopag vs romiplostim) and overall. As a part of the secondary endpoint analyses, this paired t-test analysis will also be performed to examine the global satisfaction, effectiveness, and side effects domain score by prior TPO-RA treatment (eltrombopag vs romiplostim) and overall.

A listing of TSQM scores will be provided.

8.2 Analysis of Platelet Count

Platelet count (local lab) assessed at Baseline, Day 15, Day 30, Day 60, and Day 90 will be summarized descriptively for all enrolled subjects. A graphical presentation of platelet count over time will be provided by prior TPO-RA (romiplostim and eltrombopag) and overall.

The proportion of subjects who have a platelet count $\geq 50\times10^9$/L and $\leq 200\times10^9$/L will be tabulated using count and percentage for Baseline, Day 15, Day 30, Day 60, and Day 90.

A listing will provide details of local lab platelet counts by visit.

9. Safety Evaluation

Safety and tolerability will be assessed by examining exposure, treatment compliance, and adverse events by prior TPO-RA (romiplostim and eltrombopag) and overall of all enrolled subjects.

9.1 Exposure and Treatment Compliance

Exposure and treatment compliance will be summarized for all enrolled subjects by prior TPO-RA and overall.

Duration of exposure (in days) will be calculated as (Last dose date – First dose Date +1).

Number of tablets taken will be calculated as (total number of tablets dispensed – total number of tablets returned).

Number of tablets expected to take will be calculated as sum of (regimen end date – regimen start date +1)*prescribed treatment regimen of each regimen period.

Treatment compliance will be calculated as (number of tablets taken/number of tablets expected to take)*100. The treatment compliance will be summarized descriptively and also presented categorically (e.g. number and percentage of subjects with <80%, 80-100%, and >100-110%).

Data listings will provide details of subject exposure including treatment regimen, regimen start and end dates, regimen adjustments, number of tablets dispensed

[redacted]

[redacted]

and returned according to the Drug Accountability eCRF page, and compliance as assessed by the Drug Regimen Adjustments eCRF page.

Duration of exposure, number of tablets taken, number of tables expected to take, and treatment compliance of each subject will be listed as well.

9.2 Adverse Events

Adverse events (AEs) will be coded using MedDRA version 26.1 or later. The coding may be updated according to newly released versions of the dictionary.

Severity of AEs is categorized according to the following categories as entered in the eCRF: Mild, Moderate, Severe.

For investigator determined relationship to study drug, AEs are classified as "Related" or "Not Related".

AEs leading to discontinuation of avatrombopag are AEs where action taken is designated as "Drug Withdrawn" in the eCRF.

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:

1. Thromboembolic events - Any thrombotic or embolic event, whether arterial or venous – SMQ = Embolic and thrombotic events
2. 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)

TEAEs are defined as AEs occurring on or after the first dose of study treatment. TEAE will be tabulated by System Organ Class (SOC) and Preferred Term (PT) by prior TPO-RA (romiplostim and eltrombopag) and overall. TEAESI will be tabulated by AESI category and PT. Subjects with more than one TEAE in a SOC or PT will only be counted once per SOC or PT.

An overview summary table will include the number and percentage of all enrolled subjects with at least one:

- TEAE
- Serious TEAE
- TEAE of special interest (thromboembolic events and bleeding events)
- TEAE related to avatrombopag
- Severe TEAEs
- TEAE leading to study drug discontinuation

Summary tables of TEAEs will be provided for:

- TEAE (by SOC and PT)
- Serious TEAE (by SOC and PT)
- TEAE of special interest (by AESI category and PT)
- TEAE related to avatrombopag (by SOC and PT)

[redacted]

[redacted]

- Severe TEAEs (by SOC and PT)
- TEAE leading to study drug discontinuation (by SOC and PT)

Summary tables will also include number of events for each AE by SOC and by PT.

Listings of all adverse events reported after the consent form is signed (both TEAE and non-TEAE) will be provided and will include information such as the patient identifier, SOC, PT, reported term, date of onset/stop, duration of the event, TEAE, seriousness, severity, action taken, outcome, causality and relationship. A flag will be included in the listings to designate whether an adverse event is treatment-emergent.

Listings of adverse events will be provided for the following categories:

- All Adverse Events
- Serious AEs
- AEs of special interest (thromboembolic events and bleeding events)
- AEs related to avatrombopag
- Severe AEs
- AE leading to study drug discontinuation

9.3 Other Safety Measures

9.3.1 Platelet Transfusions

A summary table will be created by prior TPO-RA (romiplostim and eltrombopag) and overall to display the frequency and percentage of enrolled subjects who have platelet transfusions (yes/no). The total number of platelet transfusions, and the reasons for transfusion (Thrombocytopenia, Bleeding Event, Adverse Event other than Bleeding Event, Other) will be summarized by category (subjects may appear in more than one category). The total number of packs/units received per transfusion will be summarized as a continuous variable.

Details of platelet transfusions occurring during the study will be presented in a listing.

9.3.2 World Health Organization Bleeding Scale

Bleeding will be assessed using the WHO Bleeding Scale according to verbal response. This assessment will be completed after the TSQM at the Baseline, Day 30, and Day 90 Visits. The Baseline WHO Bleeding Scale Assessment evaluates the severity of any bruising or bleeding the subject experienced within the 7 days prior to the Baseline Visit on Day 1. WHO Bleeding Scale assessed on Day 15, Day 30, Day 60, and Day 90 evaluates the severity of any bruising or bleeding the subject experienced since the previous visit.

The baseline assessment will be summarized in a table of baseline characteristics according to Section 6.1. A separate table will summarize WHO Bleeding Scale assessed on Day 15, Day 30, Day 60, and Day 90 which evaluates the highest severity of any bruising or bleeding the subject experienced since the previous visit (exclusive) including unscheduled visits up to the planned study visit. Bleeding for overall study period will also be presented which will include all schedule and unscheduled visits bleeding assessments and subjects are counted at the highest

[redacted]

[redacted]

grade for the overall study period. A listing will be provided with details of the WHO Bleeding Scale assessment at all visits. The summary will be presented by prior TPO-RA (romiplostim and eltrombopag) and overall.

9.3.3 COVID-19 Impact

The eCRF includes a page for collecting the extent to which study visits may have been affected by the COVID-19 global pandemic. This page collects a Yes/No answer of whether there was any impact. If the answer was yes, additional data as to the type of impact (Visit not done, Visit delay, Study drug not taken as planned, Study discontinuation, Lab sample collection, Study procedures, Other), visit impacted, and description of impact were collected.

The details of the COVID-19 Impact will be presented in a listing.

10. References

International Conference on Harmonization (ICH) guideline "Statistical principles for Clinical trials": E9, 1998.

IQVIA User Manual for the Treatment Satisfaction Questionnaire for Medication (TSQM): Version 1.6, 04 March 2020.

11. List of Tables, Listings, and Figures

A separate document will detail the list of the planned tables, listings, and figures for the final statistical analysis. The document will also include the mock tables, listings, and figures.

[redacted]

12. APPENDIX A: Schedule of Events

	Screening[a]	Baseline[a]	Day 15	Day 30	Day 60	Standard of Care Clinic Visits[b]	Day 90/End of Study/ Early Termination
Visit	**1**	**2**	**3**	**4**	**5**	**-**	**6**
Day (Window)	**-28 to -1**	**1**	**15 (±2 Days)**	**30 (±2 Days)**	**60 (±2 Days)**	**-**	**90 (±2 Days)**
Informed Consent	X						
Inclusion/Exclusion Criteria Review	X	X					
Demographics	X						
ITP History[c]	X	X[d]					
Record Subject Response to Questions Regarding Administration of Prior TPO-RA	X						
Administer TSQM		X		X			X
WHO Bleeding Scale[e]		X	X	X	X	X	X
Assess Platelet Transfusions			X	X	X	X	X
Assess Rescue Procedures			X	X	X	X	X
Platelet Count[f]		X[g]	X	X	X	X	X
Dispense Avatrombopag[h]		X	X	X	X	X	
Dispense Dosing Diary		X					
Record Prescribed Avatrombopag Dose Regimen in eCRF		X	X	X	X	X	X
Review Subject Dosing Diary		X[i]	X	X	X		X
Retrieve Unused Avatrombopag, if Applicable			X	X	X		X
Retrieve Dosing Diary							X
Record Adverse Events[j]	X	X	X	X	X	X	X
Record Concomitant Medications[k]	X	X	X	X	X	X	X

TPO-RA = thrombopoietin receptor agonist; TSQM = Treatment Satisfaction Questionnaire for Medication; WHO = World Health Organization

[a]The Screening Visit may be combined with the Baseline Visit if the subject's platelet count can be obtained prior to dosing with avatrombopag.

[b]Additional study visits are not required, per the protocol, however, if a subject has a scheduled clinic visit according to their standard of care, the information included in this column, if available, should be recorded in the electronic case report form (eCRF). In addition, avatrombopag should be dispensed and the Dosing Diary reviewed, as needed, during these visits.

[redacted]

[redacted]

[c]Record ITP (immune thrombocytopenia) history that is available in the subject's medical record, including date of ITP diagnosis, number of platelet transfusions in the previous 1 year (including date of last transfusion), number of previous hospitalizations for ITP, number of previous significant bleeding events (e.g., blood loss ≥1/2 cup), dose and duration of previous treatments with eltrombopag and romiplostim (including qualifying eltrombopag/romiplostim treatment over the 90 days prior to study entry), other previous treatments for ITP (including duration), history of splenectomy (yes/no), history of thromboembolic events and reason for switching to avatrombopag.
[d]Update the eCRF with any ITP history changes since Screening.
[e]The following question should be asked of the subject during the Baseline Visit: "Have you experienced any bruising or bleeding within the last 7 days?" while the following question should be asked of the subject during each subsequent protocol specified visit: "Have you experienced any bruising or bleeding since I saw you last?". The WHO Bleeding Scale should be performed after the TSQM at the Baseline Visit, Visit Days 15, 30, 60, and at the Day 90 Visit and prior to any other visit procedures.
[f]Only local lab results will be used.
[g]Any platelet count measured within the previous 7 days will be accepted.
[h]Dispense avatrombopag, based on the subject's current dosage regimen, per the DOPTELET Unites States Prescribing Information (USPI)
[i]During the Baseline Visit/Visit 2, the study team should review with the subject instructions for completion of the Dosing Diary.
[j]Adverse events, including AESIs, will be collected from the time of informed consent.
[k]Including concomitant ITP medications.