CLINICAL STUDY PROTOCOL

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

Investigational Product: Avatrombopag oral tablet
Protocol Number: AVA-ITP-401
NCT Number: 04638829

Sponsor:
Sobi, Inc. (formerly Dova Pharmaceuticals, Inc.)
77 Fourth Ave, 3rd Floor
Waltham, MA 02451
United States
[redacted]

Version Number: 2.0
Date: 28 January 2022
Replaces: Version 1.0 / 24 August 2020

SIGNATURE PAGE

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

I, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature [redacted] **Date** 31 January 2022

[redacted]
Vice President, Global Drug Development
Sobi, Inc.

INVESTIGATOR AGREEMENT

By signing below, I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Sobi, Inc. to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Sobi, Inc. and that it may not be further disclosed to third parties. I understand that the study may be terminated, or enrollment suspended at any time by Sobi, Inc. with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

I agree to conduct this study in full accordance with Institutional Review Board/Ethics Committee Regulations, and International Council for Harmonisation (ICH) Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

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

PROTOCOL VERSION/DATE: V2.0/28 January 2022

PRODUCT: Avatrombopag oral tablet

PHASE: 4

RATIONALE AND BACKGROUND: Chronic ITP is an autoimmune disorder characterized by low platelet counts and the risk of bleeding complications. The clinical management of ITP depends on its severity and the bleeding risk. Treatment is considered when platelet counts fall below 30 to 50×10^9/L with a goal to maintain platelet counts in a target range of 50 to 150-200×10^9/L, so patients can live relatively active lives with a manageable bleeding risk. The standard of care after a failure of 1st line therapy includes the initiation of a thrombopoietin receptor agonist (TPO-RA) (Provan, 2019). Three TPO-RAs (eltrombopag [Promacta®], romiplostim [Nplate®], and avatrombopag [DOPTELET®]) are currently approved in the United States (US) for the treatment of thrombocytopenia in adult patients with chronic ITP who have had an insufficient response to a previous treatment.

Avatrombopag (DOPTELET) was approved in June 2019 for the treatment of thrombocytopenia in adult patients with chronic ITP who have had an insufficient response to a previous treatment. It is an orally administered small molecule that mimics the biological effects of thrombopoietin (TPO) vitro and in vivo. In clinical trials, avatrombopag increased platelet counts within 3-5 days and maintained them in the target range (50 to 150×10^9/L) with chronic dosing (Jurczak, 2018). Further, it has an exposure-adjusted safety profile generally comparable to placebo, no boxed safety warning for hepatotoxicity, and is recommended to be taken with food.

Eltrombopag is taken orally, however, the tablets must be taken on an empty stomach or with a low calcium meal and 2 hours before or 4 hours after any antacids, dairy products, or mineral supplements containing polyvalent cations. Romiplostim requires a weekly subcutaneous injection which is typically administered by the patient's healthcare provider.

The US Prescribing Information (USPI) for eltrombopag, romiplostim, and avatrombopag recommends using the lowest dose needed to achieve and maintain a platelet count $\geq50\times10^9$/L, as necessary, to reduce the risk of bleeding in patients with ITP. Dose adjustment guidelines in the USPI are based on platelet count response and should not exceed a dose of 75 mg once daily, 10 µg/kg once weekly, and 40 mg once daily for eltrombopag, romiplostim, and avatrombopag, respectively; the goal of dose adjustments should not be to normalize platelet counts. Additionally, the USPI recommends discontinuation of the TPO-RA if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks of therapy at the maximum dose.

Observational studies have shown that switching to an alternate TPO-RA may be beneficial if there was an insufficient response to treatment with the initial TPO-RA, which may be due to refractoriness to the previous treatment or non-compliance with the treatment regimen (Kuter, 2015). Although there are now 3 TPO-RA options for adult patients with ITP, data on clinical outcomes, treatment responses, and patient reported outcomes among patients who switch TPO-RAs for the treatment of ITP are limited.

The purpose of this Phase 4 prospective study is to evaluate safety, platelet count, and subject reported treatment satisfaction after receiving avatrombopag for 90 days following treatment with either eltrombopag or romiplostim. The initial dose and dose adjustments of avatrombopag will be determined by the Investigator, per the DOPTELET USPI. There is no protocol-required washout period between treatment with TPO-RAs, 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).

The Treatment Satisfaction Questionnaire for Medication (TSQM) Version 1.4 is a validated 14-item questionnaire designed as a general measure of treatment satisfaction with medication. In order to capture subject reported outcomes after switching from eltrombopag or romiplostim to avatrombopag, the TSQM will be administered at Baseline (before the first dose of avatrombopag), Day 30, and Day 90.

STUDY OBJECTIVES:

Primary Objective: Characterize the safety and tolerability of avatrombopag given for 90 days after stopping treatment with eltrombopag or romiplostim.

Secondary Objectives:

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

STUDY ENDPOINTS:

Primary Endpoint: Occurrence of adverse events (AEs) and serious adverse events (SAEs).

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 $\geq 50\times10^9$/L to $\leq 200\times10^9$/L at Day 15, Day 30, Day 60, and Day 90.

STUDY DESIGN AND DURATION: This Phase 4, prospective, multi-center, open-label study will 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 will be enrolled, 50 (±10) who have received eltrombopag and 50 (±10) who have received romiplostim for at least 90 days prior to study entry.

The initial dose and dose adjustments of avatrombopag will be determined by the Investigator in conjunction with the DOPTELET USPI. There is no protocol-required washout period between treatment with TPO-RAs, 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 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 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, however, the Screening Visit may be combined with the Baseline Visit. 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 visits during the study are the Baseline Visit, 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.

STUDY POPULATION:

Inclusion Criteria

Subjects who meet all of the following criteria will be eligible to participate:

1. Subject is willing and able to provide written informed consent.
2. Male or female aged ≥18 years of age at the Screening Visit/Visit 1.
3. Subject has been undergoing treatment for primary ITP with eltrombopag or romiplostim for at least 90 days prior to the Screening Visit/Visit 1.
4. Subject has had a previous response (at any time) to either eltrombopag or romiplostim, defined as at least 2 platelet counts $\geq 50 \times 10^9$/L.
5. Subject is willing and able to comply with all aspects of the protocol, including completing the self-administered TSQM.

Exclusion Criteria

Subjects who meet any of the following criteria will not be eligible to participate:

1. Subject is currently receiving chemotherapy or radiation for any form of cancer.
2. Subject with conditions that are likely to prevent them from accurately and reliably completing study assessments, including evidence of moderate to severe dementia, and/or severe and progressive medical illness, as determined by the Investigator.
3. Any previous avatrombopag use.
4. Previous participation in this study; a subject may not re-enroll after prior discontinuation or completion.
5. Enrollment in another clinical study with any investigational drug or device within 30 days of Baseline (or 5 half-lives, whichever is longer); however, participation in observational studies within the previous 30 days is permitted.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION: Subjects will receive the avatrombopag 20 mg oral tablet formulation for up to 90 days while enrolled in the study. Avatrombopag dosage will be determined by the Investigator, based on platelet count, in conjunction with the DOPTELET USPI.

STATISTICAL/DATA ANALYSES:

Analysis Populations

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

Analysis of Safety

AEs, SAEs, and Adverse Events of Special Interest (AESIs) will be summarized for all enrolled subjects using counts and percentages. Treatment-emergent AEs and SAEs will be summarized overall, by system organ class, and by preferred term. AESIs will be summarized by event type (thromboembolic events and bleeding events). In addition, treatment-emergent AEs will be summarized by severity and by relationship to study drug.

Bleeding events reported during the study will be summarized by their WHO grade.

Analysis of Platelet Count

Platelet count assessed at Baseline, Day 15, Day 30, Day 60, and Day 90 will be summarized descriptively for all enrolled subjects. Graphic presentations of platelet count over time will be provided.

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

Analysis of TSQM

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 also be summarized descriptively.

The primary interest in the TSQM assessment is the convenience domain score. The hypothesis is that switching from a prior TPO-RA treatment (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.

SAMPLE SIZE DETERMINATION:

Assuming the mean TSQM convenience scores at Baseline and at the end of study are 74 and 82, respectively, with a standard deviation (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 which includes approximately 50 subjects with a prior treatment of eltrombopag and approximately 50 subjects with a prior treatment of romiplostim.

SITES: Approximately 20 centers in the US.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
21 CFR	Title 21 of the Code of Federal Regulations
AE	Adverse event
AESI	Adverse event of special interest
CLD	Chronic liver disease
CRA	Clinical research associate
eCRF	Electronic case report form
EDC	Electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
ITP	Immune thrombocytopenia
SAE	Serious adverse event
SD	Standard deviation
SUSAR	Suspected unexpected serious adverse reaction
TPO	Thrombopoietin
TPO-RA	Thrombopoietin receptor agonist
TSQM	Treatment Satisfaction Questionnaire for Medication
US	United States
USPI	United States Prescribing Information
WHO	World Health Organization

1 INTRODUCTION AND BACKGROUND INFORMATION

1.1 Thrombocytopenia

Platelets originate from megakaryocytes in the bone marrow and are an important component of blood that function to maintain normal hemostasis by helping to control bleeding through aggregating and inducing clot formation in conjunction with blood coagulation factors. In healthy individuals, the average lifespan of platelets is 7 to 10 days, after which they are destroyed and replaced with newly generated platelets from the bone marrow. A normal blood platelet count ranges from 150×10^9/L to 450×10^9/L, and patients who have less than 150×10^9/L have the condition known as thrombocytopenia, which is associated with easy or excessive bruising and mild to severe or potentially fatal bleeding.

Thrombopoietin (TPO), the principal physiologic regulator of platelet production, is produced constitutively in the liver, circulates in the bloodstream, and is delivered to the bone marrow, where it stimulates the early development of multiple hematopoietic lineages leading to megakaryocytopoiesis. This results in the production of new platelets by the bone marrow, a process which is directly correlated with plasma TPO levels.

The circulating platelet count in the blood is determined by the rates of platelet production and platelet destruction. Thrombocytopenia can result from decreased platelet production in the bone marrow, increased platelet destruction in the blood (such as from autoantibodies), sequestration of platelets in the spleen, and/or the dilution of platelets following multiple blood transfusions. There are numerous disease states which cause thrombocytopenia, including immune thrombocytopenia (ITP), chronic liver disease (CLD), and chemotherapy-induced thrombocytopenia (CIT).

1.2 Immune Thrombocytopenia

ITP is an autoimmune disorder characterized by low platelet counts caused by a combination of both impaired platelet production and increased peripheral platelet destruction. It has an incidence of as many as 5 out of every 100,000 people and may be either a primary condition or secondary to other causes, such as bacterial or viral infections. The 2019 International Consensus Report on the Investigation and Management of ITP (Provan, 2019) and the American Society of Hematology Guidelines for ITP (Neunert, 2019) define ITP in 3 distinct subsets in accordance with disease duration, which includes:

- Newly Diagnosed ITP: within 3 months of the diagnosis
- Persistent ITP: within 3 to 12 months of the diagnosis
- Chronic ITP: more than 1 year after the diagnosis

Clinical management of ITP depends primarily on its severity, with initial therapy being indicated when platelet counts fall below 30 to 50×10^9/L with a goal to maintain platelet counts between 50 to 200×10^9/L to reduce the risk of concurrent bleeding symptoms or impact on health-related quality of life (Neunert, 2019; Provan, 2019). The clinical goal of treatment for ITP is not to normalize platelet counts, but to increase platelet counts to a level that enables patients to live relatively normal and active lives with a manageable risk of bleeding. For the treatment of newly diagnosed ITP in patients who have non-life-threatening bleeding, agents that decrease platelet destruction (e.g., corticosteroids or immunoglobulins) are recommended as 1st line treatment. These medications have variable and transient efficacy and significant toxicities.

After the failure of a 1st line therapy, 2nd line treatment options approved in the United States (US) for the treatment of thrombocytopenia in adult patients with chronic ITP who have had an insufficient response to a previous treatment include the TPO receptor agonists (TPO-RAs) avatrombopag (DOPTELET®), eltrombopag (Promacta®), and romiplostim (Nplate®).

The US Prescribing Information (USPI) for avatrombopag, eltrombopag, and romiplostim recommends using the lowest dose needed to achieve and maintain a platelet count $\geq 50 \times 10^9$/L, as necessary, to reduce the risk of bleeding in patients with ITP. Dose adjustment guidelines in the USPIs of TPO-RAs are based on platelet count response and should not exceed a dose of 40 mg once daily, 75 mg once daily, or 10 µg/kg once weekly for avatrombopag, eltrombopag, and romiplostim, respectively; the goal of dose adjustments should not be to normalize platelet counts. Additionally, each of the 3 USPIs recommend discontinuation of the TPO-RA if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks of therapy at the maximum dose.

Avatrombopag is an oral agent which is taken with any type of food. Although eltrombopag is also taken orally, the tablets must be taken with a meal low in calcium (≤50 mg) and 2 hours before or 4 hours after other medications (e.g., antacids), calcium-rich foods (containing >50 mg calcium [e.g., dairy products, calcium-fortified juices, and certain fruits and vegetables]), or supplements containing polyvalent cations, such as iron, calcium, aluminum, magnesium, selenium, and zinc, which may be challenging for patients. Romiplostim requires weekly subcutaneous injections which are typically performed by the patient's healthcare provider (Promacta USPI; Nplate USPI; Neunert, 2019; Provan, 2019).

Observational studies have shown that switching to an alternate TPO-RA may be beneficial if the patient had an insufficient response to treatment with the initial TPO-RA, which may be due to refractoriness to the previous treatment or non-compliance with the treatment regimen (Kuter, 2015). Data also suggests that switching to an alternate TPO-RA in order to improve convenience in patients who are responding to their current TPO-RA therapy may yield continued efficacy (Kuter, 2015). Although there are now 3 approved TPO-RA options for adult patients with ITP, data on clinical outcomes, treatment responses, and patient reported outcomes among patients who switch TPO-RAs for the treatment of ITP are limited.

1.3 Avatrombopag

Avatrombopag maleate is an orally administered, small molecule TPO-receptor (c-Mpl) agonist that mimics the biologic effects of TPO in vitro and in vivo, resulting in a measured increase in platelet counts. Like other TPO receptor agonists, avatrombopag activates the human TPO receptor, but binds to a different site on the receptor than endogenous TPO. After binding, avatrombopag stimulates signal transduction and mimics the biologic effects of TPO, which in turn increases platelet counts. Given its basic mechanism of action, by directly stimulating the normal production of new platelets by the bone marrow, avatrombopag has the potential to be useful for the treatment of thrombocytopenia of any etiology across a variety of indications and patient populations when used in both acute and chronic dosing regimens.

Avatrombopag has been approved by the US Food and Drug Administration (FDA) for the treatment of thrombocytopenia in adult patients with CLD who are scheduled to undergo a procedure and for the treatment of adult patients with chronic ITP who have had an insufficient response to a previous treatment (DOPTELET USPI).

Exposure to avatrombopag across the clinical development program includes chronic and acute dosing from a range of 1 to 100 mg. The total safety subject population from completed studies includes more than 1200 subjects who received avatrombopag and had at least 1 safety assessment. In the Phase 2 and 3 studies conducted in adults with ITP, avatrombopag was administered to 128 subjects for a median duration of 7 months and a maximum duration of 2.3 years. The primary efficacy endpoint in the pivotal Phase 3 ITP study (E5501-G000-302 [Study 302]) the Cumulative Number of Weeks with a platelet count $\geq 50 \times 10^9$/L during 6 months of treatment in the absence of rescue therapy, was a median of 12.4 weeks for avatrombopag versus 0 weeks for placebo ($p<0.0001$). The most common (≥10%) adverse events (AEs) in placebo and avatrombopag-treated subjects from the Phase 2 and 3 ITP studies (pooled data) are presented in Table 1.

Table 1 Adverse Events with a Frequency ≥10% in Subjects with Chronic ITP Treated with DOPTELET – Pooled Data from Clinical Trials[a]

Adverse Event	DOPTELET (N=128)	Placebo (N=22)
Headache	31%	14%
Fatigue	28%	9%
Contusion	26%	18%
Epistaxis	19%	18%
Upper Respiratory Tract Infection	15%	5%
Arthralgia	13%	0%
Gingival Bleeding	13%	0%
Petechiae	11%	9%
Nasopharyngitis	10%	0%

a: DOPTELET USPI

1.4 Study Rationale

The purpose of this Phase 4 prospective study is to evaluate safety, platelet count, and subject reported treatment satisfaction after receiving avatrombopag for 90 days following at least 90 days of treatment with either eltrombopag or romiplostim.

The study will enroll at least 100 adult subjects which will include 50 (±10) subjects who were treated with eltrombopag and 50 (±10) subjects who were treated with romiplostim. Participating subjects must have a diagnosis of chronic ITP and have had a previous response (defined as at least 2 platelet counts $\geq 50 \times 10^9$/L) to either eltrombopag or romiplostim. Once enrolled in the study, subjects will be started on avatrombopag at a dose determined to be appropriate by the Investigator in conjunction with the DOPTELET USPI.

Safety will be collected throughout the 90-day study period. Platelet counts will be collected per protocol at Baseline, Day 15, Day 30, Day 60, and at Day 90. No additional platelet counts are required, however, all platelet counts collected per the subject's standard of care during the study period should be recorded in the electronic case report form (eCRF).

The Treatment Satisfaction Questionnaire for Medication (TSQM) Version 1.4 is a validated 14-item questionnaire designed as a general measure of treatment satisfaction with medication. In order to capture subject reported outcomes after switching from eltrombopag or romiplostim to avatrombopag, the TSQM will be administered at Baseline (before the first dose of avatrombopag), Day 30, and Day 90.

2 STUDY OBJECTIVES

2.1 Primary Objective

Characterize the safety and tolerability of avatrombopag given for 90 days after stopping treatment with eltrombopag or romiplostim.

2.2 Secondary Objectives

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

3 STUDY ENDPOINTS

3.1 Primary Endpoint

Occurrence of AEs and serious adverse events (SAEs).

3.2 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.

4 STUDY DESCRIPTION

4.1 Summary of Study Design

This Phase 4, prospective, multi-center, open-label study will 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 will 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.

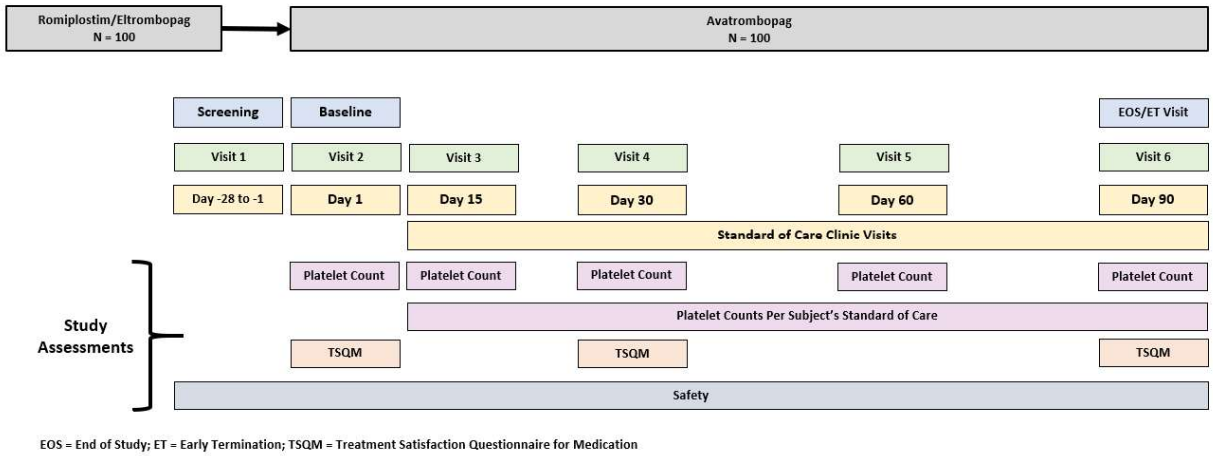
The initial dose and dose adjustments of avatrombopag will be determined by the Investigator in conjunction with the DOPTELET USPI. There is no protocol-required washout period between treatment with TPO-RAs, however avatrombopag should not be administered on the same day as another TPO-RA. The start and stop dates of all prior and concomitant medications should be recorded in the eCRF.

Safety will be evaluated throughout the study. 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 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.

Figure 1 AVA-ITP-401 Study Schematic



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

5 SELECTION AND EARLY TERMINATION OF SUBJECTS

5.1 Inclusion Criteria

Subjects who meet all of the following criteria will be eligible to participate:

1. Subject is willing and able to provide written informed consent.
2. Male or female aged ≥18 years of age at the Screening Visit/Visit 1.
3. Subject has been undergoing treatment for primary ITP with eltrombopag or romiplostim for at least 90 days prior to the Screening Visit/Visit 1.
4. Subject has had a previous response (at any time) to either eltrombopag or romiplostim, defined as at least 2 platelet counts $\geq 50 \times 10^9$/L.
5. Subject is willing and able to comply with all aspects of the protocol, including completing the self-administered TSQM.

5.2 Exclusion Criteria

Subjects who meet any of the following criteria will not be eligible to participate:

1. Subject is currently receiving chemotherapy or radiation for any form of cancer.
2. Subject with conditions that are likely to prevent them from accurately and reliably completing study assessments, including evidence of moderate to severe dementia, and/or severe and progressive medical illness, as determined by the Investigator.
3. Any previous avatrombopag use.
4. Previous participation in this study; a subject may not re-enroll after prior discontinuation or completion.
5. Enrollment in another clinical study with any investigational drug or device within 30 days of Baseline (or 5 half-lives, whichever is longer); however, participation in observational studies within the previous 30 days is permitted.

5.3 Subject and Study Discontinuation

A subject can withdraw from the study, at any time, and for any reason. The standard of care for the subject will not be affected in any way.

If a subject withdraws prematurely from the study, study staff should make every effort to collect the full panel of data scheduled for the Day 90/Early Termination Visit.

The reason for early termination must be documented in the eCRF. Terminated subjects will not be replaced.

5.3.1 Screen Failures

Subjects who sign and date the informed consent form (ICF) but who fail to meet all the inclusion criteria or meet any exclusion criteria are defined as a screen failure.

The following data will be recorded in the eCRF for screen failed subjects:

- ICF signature date
- Demographic information
- AEs that occur after signing the ICF
- Reason for screen failure (e.g., inclusion/exclusion criteria that was not met, etc.)

Subjects may be re-screened with prior approval from the Sponsor.

5.3.2 Early Termination

A subject may be early terminated for any of the following reasons:

- Subject wishes to withdraw consent for any reason.
- Subject non-compliance or unwillingness to comply with the procedures required by the protocol.
- Subject failed to meet inclusion/exclusion criterion.
- Occurrence of any medical condition that exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements of the protocol.
- Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition which indicates to the Investigator that continued participation in the study is not in the best interest of the subject.
- Investigator discretion.
- Sponsor request.
- Termination of the study by the Sponsor or a regulatory agency.

If a subject is early terminated from the study, the Early Termination procedures (Section 7.4.5) should be performed. Subjects early terminated from the study will not be replaced, regardless of the reason for early termination.

6 STUDY TREATMENT

Avatrombopag doses will be determined by the treating physician in conjunction with the FDA-approved package insert.

6.1 Randomization and Blinding

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

6.2 Avatrombopag Supplies

A sufficient supply of commercially available avatrombopag will be provided to the clinical site. Avatrombopag will be provided as film-coated tablets, with each tablet containing avatrombopag maleate (equivalent to 20 mg avatrombopag) and excipients.

6.3 Avatrombopag Dosage and Administration

Avatrombopag doses will be determined by the treating physician in conjunction with the FDA-approved DOPTELET USPI.

At the Baseline Visit/Visit 2, the clinical site will dispense the number of avatrombopag tablets required for dosing each subject at the discretion of the Investigator, per the subject's standard of care.

6.4 Receipt of Supplies

Upon receipt of the avatrombopag supplies, the pharmacist, or designee, will visually inspect the shipment and verify drug information, quantity, and condition of the avatrombopag received.

6.5 Avatrombopag Storage Conditions

Avatrombopag should be stored in a secure location, in its original packaging, at a controlled room temperature of 20°C to 25°C (68°F to 77°F) and protected from light and moisture. Excursions are permitted to 15°C to 30°C (59°F to 86°F). The storage location must be a locked room with limited access, available to appropriate study personnel only.

6.6 Compliance

Compliance with the Investigator-prescribed avatrombopag dosing regimen will be evaluated through the study drug accountability eCRF page and the completion of a Dosing Diary by the subject.

The first dose of avatrombopag will be taken while the subject is at the site during the Baseline Visit/Visit 2. During this visit, subjects will be provided with instructions on appropriate at-home avatrombopag administration. When taking avatrombopag at home, subjects should record the date and time of each dose in the provided Dosing Diary.

6.7 Avatrombopag Accountability

The Sponsor will provide the Investigators with a sufficient amount of avatrombopag to begin enrollment for this study. Sites will be responsible for ordering additional avatrombopag as needed, once subjects have been enrolled, via a website (detailed instructions will be provided). It is the responsibility of the Investigator to ensure that a current record of inventory/drug accountability is maintained. Inventory records must be readily available for inspection by the study Clinical Research Associate (CRA), the Sponsor (or designee), or regulatory authorities.

6.8 Avatrombopag Handling and Returns

Upon completion or termination of the study, and upon written authorization from the Sponsor, or its designee, unused and/or partially used avatrombopag should be returned or destroyed at the investigational site. If avatrombopag will be destroyed by the study site, it is the Investigator's responsibility to ensure that the Sponsor or its designee has provided written authorization for proper disposal of avatrombopag, and that appropriate records of the disposal are documented and maintained. No unused avatrombopag may be disposed of until fully accounted for by the Sponsor, or designee.

7 STUDY PROCEDURES

The only protocol-mandated visits are the Screening Visit/Visit 1, the Baseline Visit/Visit 2 (which may be combined with the Screening Visit/Visit 1), Day 15, Day 30, Day 60, and the Day 90/Early Termination Visit.

Data will be collected from information routinely recorded in a subject's medical record and from laboratory data. Except for the Screening Visit/Visit 1, Baseline Visit/Visit 2, Day 15, Day 30, Day 60, and Day 90/Early Termination Visit, no visits, examinations, laboratory tests, or procedures are mandated or recommended as part of this study. All platelet counts collected per the subject's standard of care while the subject is enrolled in the study should be recorded in the eCRF.

A schedule of events in tabular format is provided in Table 2 in Appendix A.

7.1 Informed Consent

Prior to conducting any study-related data collection, informed consent must be signed and dated by the subject. See Section 12.4 for additional information on informed consent.

7.2 Screening Visit (Visit 1)

The Screening Visit/Visit 1 must be completed within 28 days of the Baseline Visit/Visit 2, however, this visit may also be combined with the Baseline Visit/Visit 2.

The following procedures should be performed at the Screening Visit/Visit 1.

- Collect signed and dated informed consent prior to any other study procedures.
- Review of inclusion/exclusion criteria (Section 5) to confirm study eligibility.
- Record subject demographic information including race/ethnicity, date of birth and gender.
- Record ITP 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 platelet transfusion.
    - Number of previous hospitalizations for ITP.
    - Number of previous significant bleeding events (e.g., blood loss ≥1/2 cup).
    - Most recent dose level and duration of previous treatments with eltrombopag and/or 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.
- Record the reason for switching to avatrombopag from eltrombopag or romiplostim.

- Record subject-reported responses to brief questions (to be provided) regarding the prior administration of eltrombopag or romiplostim.
- Record any data on Additional Safety Information (Section 9.1.1) or (AESIs) (Section 9.5) that have occurred since the subject signed the ICF.
- Record any AEs that have occurred since the subject signed the ICF.
- Record any concomitant medication use, including concomitant ITP medications.
- Instruct subject on when to return for the Baseline Visit/Visit 2 if the Screening Visit/Visit 1 will not be combined with the Baseline Visit/Visit 2.

7.3 Baseline Visit (Visit 2/Day 1)

The Baseline Visit/Visit 2 must be completed within 28 days of the Screening Visit/Visit 1 but may also be combined with the Screening Visit/Visit 1. If the Baseline Visit/Visit 2 will be combined with the Screening Visit/Visit 1, ensure all procedures listed under Section 7.2 are completed.

The following procedures should be performed at the Baseline Visit/Visit 2.

- Review of inclusion/exclusion criteria (Section 5) to confirm continued study eligibility.
- Administer the TSQM Version 1.4 to the subject prior to any other study procedures.
- Perform World Health Organization (WHO) Bleeding Scale Assessment (Appendix B). The Investigator should ask the subject the following question: "Have you had any bleeding or bruising within the last 7 days?". This assessment should be completed after the TSQM has been completed, but prior to other visit assessments.
- Record any changes in ITP history, including changes in:
    - Number of platelet transfusions in the previous 1 year, including date of last platelet transfusion.
    - Number of previous hospitalizations for ITP.
    - Number of previous significant bleeding events (e.g., blood loss ≥1/2 cup).
    - Most recent dose level and duration of previous treatments with eltrombopag and/or 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.
- Record the reason for switching to avatrombopag from eltrombopag or romiplostim.
- Record the date of the last dose of eltrombopag or romiplostim.
- Collect and record platelet count (local lab).
- Determine appropriate dose of avatrombopag, based on instructions in the USPI.

- Administer first dose of avatrombopag, on a full stomach, while the subject is in the clinic and record the date/time of the first dose on the eCRF and on the Dosing Diary.
- Provide instructions to the subject for proper at-home administration of avatrombopag, including completion of the Dosing Diary.
- Dispense avatrombopag and the Dosing Diary to the subject.
- Record any data on Additional Safety Information (Section 9.1.1) or AESIs (Section 9.5) that have occurred since the subject signed the ICF.
- Record any AEs that have occurred since the subject signed the ICF.
- Record any concomitant medication use, including concomitant ITP medications.
- Instruct subject on when to return for the Day 15 Visit.

7.4 Treatment Period (through Day 90)

7.4.1 Day 15 (±2 Days)/Visit 3

- Perform WHO Bleeding Scale Assessment (Appendix B). The Investigator should ask the subject the following question: "Have you had any bleeding or bruising since I saw you last?". This assessment should be completed prior to other visit assessments.
- Collect and record platelet count (local lab).
- Record the occurrence of any platelet transfusion (including the number of units).
- Record whether the subject required any rescue procedure for bleeding.
- Review subject Dosing Diary and record any deviations from prescribed dosing regimen in the eCRF.
- Record any changes in avatrombopag dose and dose frequency.
- Dispense additional avatrombopag to the subject, as needed.
- Record any data on Additional Safety Information (Section 9.1.1) or AESIs (Section 9.5) that have occurred.
- Record any AEs.
- Record any concomitant medication use, including concomitant ITP medications.
- Instruct subject on when to return for the Day 30 Visit.

7.4.2 Day 30 (±2 Days)/Visit 4

- Administer TSQM Version 1.4 to the subject.
- Perform WHO Bleeding Scale Assessment (Appendix B). The Investigator should ask the subject the following question: "Have you had any bleeding or bruising since I saw you last?". This assessment should be completed prior to other visit assessments.
- Collect and record platelet count (local lab).

- Record the occurrence of any platelet transfusion (including the number of units).
- Record whether the subject required any rescue procedure for bleeding.
- Review subject Dosing Diary and record any deviations from prescribed dosing regimen in the eCRF.
- Record any changes in avatrombopag dose and dose frequency.
- Dispense additional avatrombopag to the subject, as needed.
- Record any data on Additional Safety Information (Section 9.1.1) or AESIs (Section 9.5) that have occurred.
- Record any AEs.
- Record any concomitant medication use, including concomitant ITP medications.
- Instruct subject on when to return for the Day 60 visit.

7.4.3 Day 60 (±2 Days)/Visit 5

- Perform WHO Bleeding Scale Assessment (Appendix B). The Investigator should ask the subject the following question: "Have you had any bleeding or bruising since I saw you last?". This assessment should be completed prior to other visit assessments.
- Collect and record platelet count (local lab).
- Record the occurrence of any platelet transfusion (including the number of units).
- Record whether the subject required any rescue procedure for bleeding.
- Review subject Dosing Diary and record any deviations from prescribed dosing regimen in the eCRF.
- Record any changes in avatrombopag dose and dose frequency.
- Dispense additional avatrombopag to the subject, as needed.
- Record any data on Additional Safety Information (Section 9.1.1) or AESIs (Section 9.5) that have occurred.
- Record any AEs.
- Record any concomitant medication use, including concomitant ITP medications.
- Instruct subject on when to return for the Day 90/End of Study Visit.

7.4.4 Standard-of-Care Clinic Visits

If the subject has a clinic visit or laboratory assessment of platelet count that is separate from the protocol-required visits described in Section 7.2 through Section 7.4.3, the following data (if available and collected per the subject's standard-of-care) should be recorded in the eCRF.

- WHO Bleeding Scale Assessment, if collected per the subject's standard-of-care.
- Record any platelet counts that are collected, per the subject's standard of care, while enrolled in the study.

- Record the occurrence of any platelet transfusion (including the number of units).
- Record whether the subject required any rescue procedure for bleeding.
- Record any changes in avatrombopag dose and dose frequency.
- Dispense additional avatrombopag to the subject, as needed.
- Record any data on Additional Safety Information (Section 9.1.1) or AESIs (Section 9.5) that have occurred.
- Record any AEs.
- Record any concomitant medication use, including concomitant ITP medications.

7.4.5 Day 90 (±2 Days)/End of Study/Early Termination Visit/Visit 6

The following procedures should be performed during the Day 90/End of Study/Early Termination Visit.

- Administer TSQM Version 1.4 to the subject.
- Perform WHO Bleeding Scale Assessment (Appendix B). The Investigator should ask the subject the following question: "Have you had any bleeding or bruising since I saw you last?". This assessment should be completed after the TSQM but prior to other visit assessments.
- Collect and record platelet count (local lab).
- Record the occurrence of any platelet transfusion (including the number of units).
- Record whether the subject required any rescue procedure for bleeding.
- Record final avatrombopag dose and dose frequency on the eCRF.
- Review Dosing Diary, record any deviations from prescribe dosing regimen, and collect from the subject.
- Record any data on Additional Safety Information (Section 9.1.1) or AESIs (Section 9.5) that have occurred.
- Record any AEs.
- Record any concomitant medication use, including concomitant ITP medications.
- Discharge subject from the study.

7.5 Early Termination Visit

All subjects who are early terminated from the study prior to the Day 90/End of Study Visit should complete the Day 90/End of Study Visit assessments in Section 7.4.5.

8 STUDY ASSESSMENTS

8.1 Treatment Satisfaction Questionnaire for Medication (TSQM)

The TSQM is a 14-item, validated, self-administered patient reported outcome (PRO) questionnaire that is used to assess treatment satisfaction by analyzing the following 4 domains: effectiveness, side effects, convenience, and global satisfaction (Atkinson, 2004).

The TSQM will be administered to the subject at the Baseline Visit/Visit 2, at Day 30, and at the Day 90/End of Study/Early Termination Visit prior to any study procedures.

8.2 Laboratory Examinations

8.2.1 Platelet Count (Local Lab)

Local laboratory platelet counts will be collected per protocol at the Baseline Visit/Visit 2, Day 15, Day 30, Day 60 and at the Day 90/End of Study/Early Termination Visit. 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.

8.3 World Health Organization Bleeding Scale

Beginning with the Baseline Visit/Visit 2, the Investigator should assess bleeding using the WHO Bleeding Scale (Appendix B) according to verbal response.

During the Baseline Visit/Visit 2, the following question should be asked: "Have you experienced any bruising or bleeding within the last 7 days?".

At each subsequent visit, the following question should be asked: "Have you experienced any bruising or bleeding since I saw you last?".

This assessment should be completed ***after*** the TSQM at the Baseline, Day 30, and the Day 90 Visits.

9 SAFETY ASSESSMENTS

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or an SAE and remain responsible for following up on AEs that are serious, considered related to study procedures, or that caused the subject to discontinue avatrombopag.

9.1 Adverse Events

An AE 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. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

AEs will be monitored and documented from the time of informed consent until study participation is complete. Subjects should be instructed to report any AE that they experience to the Investigator. Beginning with the informed consent signature, Investigators should make an assessment for AEs at each visit and record the event on the appropriate AE eCRF. Events associated with disease progression should not be reported as AEs or SAEs. However, if in the Investigator's opinion the disease progression is manifesting in an unusual or uncharacteristic manner, the associated events should be reported as AEs/SAEs, as appropriate.

Wherever possible, a specific disease or syndrome (i.e., diagnosis) rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the eCRF. Additionally, the condition that led to a medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an AE, not the procedure.

Any medical condition already present at Screening should not be reported as an AE unless the medical condition or signs or symptoms present at Screening change in severity, frequency or seriousness at any time during the study. In this case, it should be reported as an AE.

Clinically significant abnormal laboratory or other examination findings that are detected during the study or are present at Screening and significantly worsen during the study should be reported as AEs. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal finding is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Any abnormal test that is determined to be an error does not require reporting as an AE.

9.1.1 Additional Safety Information

In addition to AEs, there are safety-related situations in which other information must be collected, regardless of whether or not there is an associated AE. These include:

- Use during pregnancy (i.e., drug exposure to a fetus in utero).
- Exposure to a drug during breast-feeding/lactation.

- Overdose (whether intentional, accidental or prescribed; whether symptomatic or not).
    - An overdose is defined as the administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information. When applying this definition, clinical judgment should always be applied.
- Drug abuse or misuse.
- Medication errors (including dispensing errors, accidental exposure, maladministration, etc.).
- Unapproved or off-label use (i.e., intentional medical use of a product not in conjunction with the authorized product information).
- Withdrawal reactions/rebound effects.
- Unusual exacerbation of existing disease.
- Suspected use of counterfeit/falsified medicines/tampering.
- Drug-drug/drug-food interactions.
- Occupational exposure (as a result of one's professional or non-professional occupation).
- Unexpected or unintended benefit/effect.
- Actual or potential transmission via a medicinal product of an infectious agent.

If these above events occur and are serious (see Section 9.2), they should be reported using the SAE Report Form within 24 hours by fax or email. If non-serious, the events should be reported in the eCRF.

9.1.2 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each AE as mild, moderate, or severe, and will also categorize each AE as to its potential relationship to avatrombopag using the categories of yes or no.

9.1.2.1 Severity Assessment

- Mild – A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate – A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe – A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

9.1.2.2 Causality Assessment

The relationship of an AE to the administration of avatrombopag is to be assessed according to the following definitions:

- No (unrelated, not related, no relation) – The time course between the administration of avatrombopag 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 avatrombopag 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.
    - The definition implies a reasonable possibility of a causal relationship between the event and avatrombopag. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from avatrombopag administration-
    - The event should occur after avatrombopag is given. The length of time from avatrombopag exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases-
    - Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant drug(s)-
    - The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of medication-
    - Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses-
    - The exposure to stress might induce adverse changes in the subject and provide a logical and better explanation for the event.
- The pharmacology and PK of avatrombopag-
    - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of avatrombopag should be considered.

9.2 Serious Adverse Events

An AE or adverse reaction 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 AE,
  - NOTE: An AE or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires hospitalization or prolongation of existing hospitalizations,
  - NOTE: Any hospital admission will be considered an inpatient hospitalization, even if admitted and discharged on the same day. An emergency room visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e., no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations. Hospitalization due to expected recovery time for the planned procedure will not be counted as an SAE.
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions,
- A congenital anomaly/birth defect, or
- An important medical event.
  - NOTE: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

9.3 Method of Detecting Adverse Events and Serious Adverse Events

AEs will be reported by the subject (or, when appropriate, by a healthcare provider, caregiver or surrogate). Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

9.4 Serious Adverse Event Reporting − Procedures for Investigators

9.4.1 Initial Reports

All SAEs, regardless of causal assessment, occurring from the time of informed consent until discharge from the study at Day 90 must be reported to the Sponsor as directed on the SAE reporting form within 24 hours of the knowledge of the occurrence (this refers to any AE that meets any of the aforementioned serious criteria). All SAEs that the Investigator considers causally related to avatrombopag occurring after discharge from the study must be reported to the Sponsor.

To report the SAE, complete the appropriate form for the study and submit to the Sponsor or designee as instructed on the form. It is very important that the form be filled out as completely as possible at the time of the initial report. This includes the Investigator's assessment of causality. The Investigator must notify his/her Institutional Review Board (IRB) of the occurrence of the SAE, in writing, if required by their institution. A copy of this communication must be forwarded to the Sponsor to be filed in the Sponsor's Trial Master File.

After discharge from the study, if the Investigator becomes aware of an SAE which, per the Investigator, is attributable to avatrombopag treatment, the event should be reported to the Sponsor within 24 hours of awareness.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

9.4.2 Follow-up Reports

The Investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), the subject is lost to follow-up, or the subject dies.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the Investigator's assessment of causality, this should also be noted on the appropriate SAE follow-up form. Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the Sponsor.

Within 24 hours of receipt of follow-up information, the Investigator must update the appropriate form for the study and submit any supporting documentation (e.g., subject discharge summary or autopsy reports) via fax or e-mail.

9.5 Adverse Events of Special Interest

The Investigator will monitor each subject for clinical and laboratory evidence for pre-defined AESIs throughout their participation in this study. The purpose for specifying these AESI is to enable further characterization of the clinical course and management of these events. An AESI may or may not be the consequence of treatment with avatrombopag.

The AESIs defined in this protocol include:

- Thromboembolic events (any thrombotic or embolic event, whether arterial or venous)
- Bleeding events (any clinically significant blood loss [e.g., WHO Grade 2 or higher]).

These events will be recorded on the AE eCRF page. The Investigator will assess and record any additional information on the AESI in detail on a SAE form (whether or not the event meets seriousness criteria in Section 9.2), to be submitted within 24 hours of awareness of the event. During the course of the study, additional AESIs may be identified by the Sponsor.

9.6 Pregnancy Reporting

If a subject becomes pregnant during the study, the Investigator should report the pregnancy using the Pregnancy Report Form within 24 hours of being notified. Monitoring of the subject should continue until conclusion of the pregnancy, which may involve follow−up after the subject's involvement in the study has ended. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

9.7 Regulatory Reporting Requirements for Serious Adverse Events

Regulatory reporting requirements for SAEs include:

- Prompt notification by the Investigator to the Sponsor, or designee, of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor, or designee, will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB, and Investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy. These safety reports will be forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing a SUSAR or other specific safety information (e.g., summary or listing of SUSARs) from the Sponsor will review the report, file it, and will notify the IRB, if appropriate, according to local requirements.

10 STATISTICS

This section outlines the statistical methodology used for the safety, platelet count, and TSQM assessments. The detailed analyses will be provided in the Statistical Analysis Plan that will be finalized before the database lock.

10.1 Analysis Populations

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

10.2 Statistical Methods

10.2.1 Analysis of Safety

AEs, SAEs, and AESIs will be summarized for all enrolled subjects using counts and percentages. Treatment-emergent AEs and SAEs will be summarized overall, by system organ class, and by preferred term. AESIs will be summarized by event type (thromboembolic events and bleeding events). In addition, treatment-emergent AEs will be summarized by severity and by relationship to study drug.

Bleeding events reported during the study will be summarized by WHO grade.

10.2.2 Analysis of Platelet Count

Platelet count assessed at Baseline, Day 15, Day 30, Day 60, and Day 90 will be summarized descriptively for all enrolled subjects. Graphic presentations of platelet count over time will be provided.

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.

10.2.3 Analysis of the Treatment Satisfaction Questionnaire for Medication

Domain scores of effectiveness, side effects, convenience, and global satisfaction will be computed according to the TSQM manual, Version 1.4. Each domain score ranges from 0 to 100, and a higher score indicates a better outcome. 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.

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.

Additional analyses on platelet count and TSQM may be conducted as appropriate.

10.2.4 Sample Size Determination

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 recieved prior treatment with romiplostim.

11 DATA MANAGEMENT AND RECORD KEEPING

11.1 Data Management

11.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the Sponsor or designee during monitoring visits/calls. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the Electronic Data Capture (EDC) system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for and reconciliation between other databases (e.g., safety) is complete.

11.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

11.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure username and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR) Part 11 and other appropriate international regulations. All passwords will be strictly confidential.

11.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

- Medical Dictionary for Regulatory Activities (MedDRA) for medical history and AEs, and
- WHO Drug Dictionary for prior and concomitant medications.

11.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

11.2 Record Keeping

Records of subjects, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

12 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

12.1 Ethical Conduct of the Study

This study will be conducted in compliance with the protocol and all regulatory requirements, in accordance with Good Clinical Practice (GCP), including International Council for Harmonisation (ICH) guidelines, and in general conformity with the most recent version of the Declaration of Helsinki. Sobi Quality Assurance or designee may verify adherence to these practices and procedures through audit and inspection.

12.2 Institutional Review Board

The IRB will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of subjects. The study will only be conducted at sites where IRB approval has been obtained. The protocol, ICF, advertisements (if applicable), written information given to the subjects, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the Investigator.

The Investigator is obligated to keep the IRB informed of any unanticipated problems. This may include notification to the IRB of Investigational New Drug (IND) Safety Reports.

Federal regulations and ICH guidelines require that approval be obtained from an IRB prior to participation of subjects in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, or advertisements to be used for subject recruitment, and any other written information regarding this study to be provided to a subject must be approved by the IRB.

The study will only start in the respective sites once the IRB's written approval has been given. No drug will be released to the site for dosing until written IRB authorization has been received by the Sponsor.

It is the responsibility of the Sponsor, or their designee, to obtain the approval of the responsible IRB according to national regulations.

12.3 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigator by the Sponsor or designee. All protocol amendments will undergo the same review and approval process as the original protocol. Substantial amendments must be approved as per local regulations prior to enrolling subjects. A protocol amendment may be implemented after it has been approved by the IRB, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IRB within 5 working days.

12.4 Informed Consent

The ICF and any changes made during the course of the study, must be agreed to by the Sponsor or designee and the IRB prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the subject has been informed of his/her rights to privacy. The Investigator will obtain informed consent from each subject before any study-specific activity is performed and should document in

the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by the Sponsor, their representatives, auditors, the IRB, and/or regulatory agencies. A copy of the signed ICF will be given to the subject.

12.5 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Declaration of Helsinki, ICH GCP, and applicable regulatory requirements, and that valid data are entered into the eCRFs.

To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized and easily retrievable data. Before the enrollment of any subject in this study, the Sponsor or their designee will review with the Investigator and site personnel the following documents: protocol, USPI, eCRFs and procedures for their completion, ICF process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits/calls, information recorded on the eCRFs may be verified against source documents and requests for clarification or correction may be made. After the eCRF data is entered by the site, the monitor will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities, including visits and calls, will be reported and archived. In addition, on-site monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

12.6 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB as appropriate. Subjects or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

The subject's medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

12.7 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating subjects (sufficient information to link records, e.g., eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, forms for SAEs, source documents, and detailed records of treatment. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

12.8 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

12.9 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR Part 54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

12.10 Insurance and Indemnity

In accordance with the relevant national regulations, the Sponsor has taken out subject liability insurance for all subjects who have given their consent to the clinical study. This coverage is designed for the event that a fatality, physical injury, or damage to health occurs during the clinical study’s execution.

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APPENDIX A: Schedule of Events

Table 2 AVA-ITP-401 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

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.

[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.

	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**
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

[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.

APPENDIX B: 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

a: Fogarty, 2012; Miller, 1981

APPENDIX C: PROTOCOL AMENDMENTS

Protocol Amendment 1 (protocol v2.0) updates the sponsor name to Sobi, Inc. Dova Pharmaceuticals, Inc. (the initial study sponsor) and Sobi, Inc. are affiliates that have a common ownership, Swedish Orphan Biovitrum AB (publ) (Sobi). Each is a wholly owned subsidiary of Sobi. Dova Pharmaceuticals, Inc. will soon cease to exist as a legal entity, and Sobi, Inc. will be the sponsor going forward.

Summary of Changes:

- The Sponsor name and address have been updated throughout the protocol.
- The National Clinical Trial (NCT) identifier from clinicaltrials.gov has been added to the cover page.
- The estimated number of sites has been modified to 20.
- A small number of typographical and editorial errors have been corrected in background text; these spelling and wording corrections have no impact on any protocol definitions or procedures.

Revisions to individual sentences due to these administrative updates and non-substantive corrections are not presented.