CLINICAL STUDY PROTOCOL

A Phase 3b, Multi-center, Randomized, Double-blind, Placebo-controlled, Parallel-group Trial with an Open-label Extension Phase to Evaluate the Efficacy and Safety of Avatrombopag for the Treatment of Thrombocytopenia in Pediatric Subjects with Immune Thrombocytopenia for ≥6 Months

Investigational Product: Avatrombopag
Protocol Number: AVA-PED-301
EudraCT Number 2020-003232-24
NCT Number 04516967

Sponsor:
Sobi, Inc. (formerly Dova Pharmaceuticals, Inc.)
890 Winter Street, Suite 200
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Version Number: 3.0 / Amendment 2
Date: 02 November 2021
Replaces: Version 2.0 / 17 December 2020

SIGNATURE PAGE

STUDY TITLE: (AVA-PED-301) A Phase 3b, Multi-center, Randomized, Double-blind, Placebo-controlled, Parallel-group Trial with an Open-label Extension Phase to Evaluate the Efficacy and Safety of Avatrombopag for the Treatment of Thrombocytopenia in Pediatric Subjects with Immune Thrombocytopenia for ≥6 Months

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

Signature **Date**

[redacted] 02 NOV 2021

[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: A Phase 3b, Multi-center, Randomized, Double-blind, Placebo-controlled, Parallel-group Trial with an Open-label Extension Phase to Evaluate the Efficacy and Safety of Avatrombopag for the Treatment of Thrombocytopenia in Pediatric Subjects with Immune Thrombocytopenia for ≥6 Months

PROTOCOL NUMBER: AVA-PED-301

PROTOCOL VERSION/DATE: Version 3.0; 02 November 2021

INVESTIGATIONAL PRODUCT: Avatrombopag

PHASE: 3b

RATIONALE AND BACKGROUND: Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by low platelet counts caused from 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.

ITP resolves on its own in 74% of children <1 year of age, 67% of children between 1-6 years of age, and 62% of those between 10-20 years of age, however, it may become chronic and symptomatic in a proportion of children affected. Current guidelines recommend observation (or watchful waiting) in children with newly diagnosed ITP who have no or only minor bleeding, rather than treatment with corticosteroids or intravenous immune globulin (IVIg). For the treatment of newly diagnosed ITP in children who have non-life-threatening bleeding, agents that decrease platelet destruction (e.g., corticosteroids or immunoglobulins) are recommended as first line treatment. Second-line treatment options in children include rituximab and thrombopoietin (TPO) receptor agonists (TPO-RAs) such as eltrombopag (PROMACTA®/REVOLADE®) and romiplostim (NPLATE®). There remains an important unmet medical need for new treatment options for pediatric patients with ITP, given the difficult administration requirements and the variable, transient response, frequent relapse, and associated toxicities of the available treatments.

Avatrombopag maleate (DOPTELET®) 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. Avatrombopag has been authorized by the European Commission for the treatment of severe thrombocytopenia in patients with chronic liver disease (CLD) who are scheduled to undergo an invasive procedure. It has also been approved by the United States (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.

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 reactions in placebo and avatrombopag-treated subjects from the Phase 2 and 3 ITP studies (pooled data) were headache, fatigue, contusion, epistaxis, upper respiratory tract infection, arthralgia, gingival bleeding, petechiae, and nasopharyngitis.

This Phase 3b, multi-center, randomized, double-blind, placebo-controlled, parallel-group study in pediatric subjects who have had a diagnosis of ITP for ≥6 months, includes a 12 week Core Phase followed by a 2 year open-label Extension Phase. It is designed to evaluate the efficacy, safety, tolerability, and pharmacokinetic (PK)/pharmacodynamic (PD) profile of avatrombopag, as well as provide data on palatability/acceptability, dosing parameters, and response to treatment.

PRIMARY OBJECTIVE: To demonstrate that the efficacy of avatrombopag is superior to placebo for the treatment of pediatric subjects with ITP of ≥6 months duration who have had an insufficient response to a previous treatment.

SECONDARY OBJECTIVES:

- To evaluate the safety and tolerability of avatrombopag
- To evaluate the PK and PD of avatrombopag

EXPLORATORY OBJECTIVE: To provide data on the palatability and parent/caregiver reported acceptability of the avatrombopag powder for oral suspension.

EFFICACY ENDPOINTS:

In order to satisfy the primary endpoint requirements of different regulatory agencies, 2 separate Statistical Analysis Plans (SAPs) will be developed for this study. In the first SAP, the endpoint described below as "Primary Efficacy Endpoint" will be assessed as the primary efficacy endpoint, and the endpoint described below as the "Alternative Primary Efficacy Endpoint" will be assessed as the first secondary efficacy endpoint. In the second SAP, the endpoint described below as "Alternative Primary Efficacy Endpoint" will be assessed as the primary efficacy endpoint, and the endpoint described below as the "Primary Efficacy Endpoint" will be assessed as the first secondary efficacy endpoint. Both SAPs will evaluate the additional secondary efficacy endpoints.

Primary Efficacy Endpoint: Durable platelet response as defined by the proportion of subjects achieving at least 6 out of 8 weekly platelet counts $\geq 50 \times 10^9$/L during the last 8 weeks of the 12 week Treatment Period in the Core Phase in the absence of rescue medication.

Alternative Primary Efficacy Endpoint: Platelet response as defined by the proportion of subjects for whom at least 2 consecutive platelet assessments are $\geq 50 \times 10^9$/L over the 12 week Treatment Period in the Core Phase in the absence of rescue medication.

Additional Secondary Efficacy Endpoints:

- The percentage of weeks subjects have a platelet count $\geq 50\times10^9$/L during 12 weeks of treatment in the Core Phase, in the absence of rescue therapy.
- Platelet response at Day 8 (defined by the proportion of subjects with a platelet count $\geq 50\times10^9$/L at Day 8, in the absence of rescue therapy).
- The percentage of weeks subjects have a platelet count between $\geq 50\times10^9$/L and $\leq 150\times10^9$/L, during 12 weeks of treatment in the Core Phase, in the absence of rescue therapy.
- The proportion of subjects who require rescue medications during 12 weeks of treatment in the Core Phase of the study.
- Incidence and severity of bleeding symptoms associated with ITP measured using the World Health Organization (WHO) Bleeding Scale.

SAFETY ENDPOINTS:

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

PHARMACOKINETIC/PHARMACODYNAMIC ENDPOINTS:

- Individual PK parameters will be derived from the final population PK model. Effects of intrinsic factors, including age and weight, and extrinsic factors, including formulation, on the PK parameters may be evaluated.
- Effects of covariates on PD parameters may be evaluated.

EXPLORATORY ENDPOINTS:

- Platelet count assessments and platelet response during the Extension Phase.
- Subject reported palatability and parent/caregiver reported acceptability assessed by a palatability/acceptability questionnaire administered after the first dose of the powder for oral suspension.

POPULATION:

Inclusion and Exclusion Criteria for the Core Phase:

Inclusion Criteria:

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

1. Male or female subjects ≥1 and <18 years of age at Screening and Baseline.
2. Subject and/or subject's legally authorized representative (LAR) must be able to provide informed consent and/or assent, as applicable.

3. Subject has a confirmed diagnosis of primary ITP according to the International Consensus Report on the Investigation and Management of Primary ITP (Provan, 2019) for ≥6 months duration and has had an insufficient response to a previous treatment, in the opinion of the Investigator.
4. Subject has an average of 2 platelet counts $<30\times10^9$/L with no single count $>35\times10^9$/L.

   The platelet count obtained at the Screening Visit/Visit 1 and 1 other platelet count taken within 28 days on either side of the Screening Visit (may use a historical value collected per standard of care if within 28 days of Screening) will be averaged to obtain the study eligibility platelet count value, which must be $<30\times10^9$/L. The 2 samples must be obtained ≥24 hours and ≤28 days apart and the results must be available prior to randomization.
5. Subjects being treated chronically with corticosteroids or azathioprine/6-mercaptopurine must be receiving a stable dose for at least 30 days prior to Day 1/Visit 2 or must have completed these therapies more than 30 days prior to Day 1/Visit 2.
6. Subjects being treated with mycophenolate mofetil (MMF), cyclosporine (CsA), sirolimus, or danazol must be receiving a stable dose for at least 90 days prior to Day 1/Visit 2 or must have completed these therapies more than 30 days prior to Day 1/Visit 2.
7. Previous therapy for ITP with immunoglobulins (IVIg and anti-D) or corticosteroid rescue therapy must have been completed at least 14 days prior to Day 1/Visit 2.
8. Cyclophosphamide and vinca alkaloid regimens must have been completed at least 30 days prior to Day 1/Visit 2.
9. Splenectomy and rituximab must have been completed at least 90 days prior to Day 1/ Visit 2.
10. Previous therapy with any other TPO-RAs (e.g., eltrombopag or romiplostim) or recombinant human TPO must have been completed 28 days prior to Day 1/Visit 2.
11. Previous therapy with vitamin K antagonists, antifibrinolytic agents, recombinant activated factor VII, heparin, factor Xa inhibitors, direct thrombin inhibitors, desmopressin, or chronic antiplatelet therapy must have been completed within 7 days of Day 1/Visit 2.
12. Previous therapy with moderate or strong dual inducers or moderate or strong dual inhibitors of cytochrome P450 (CYP)2C9 and CYP3A4 must have been completed within 7 days of Day1/Visit 2.
13. Platelet transfusion, or receipt of blood products containing platelets must have been completed within 7 days of Day 1/Visit 2. Packed red blood cells (RBCs) are permitted.
14. Females of childbearing potential must have a negative urine or serum pregnancy test at Screening and Day 1/Visit 2 and must not be breastfeeding.
15. Female subjects of childbearing potential and who are sexually active and male subjects who are sexually active must agree to use highly effective methods of contraception.
16. Subject and/or subject's LAR is willing and able to comply with all aspects of the protocol.

Exclusion Criteria:

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

1. Known secondary ITP.
2. Body Mass Index (BMI) >30 kg/m^2 or >95% for age.
3. Any history of arterial or venous thrombosis, including partial or complete thrombosis.
4. Subjects with known inherited thrombocytopenia (e.g., MYH-9 disorders).
5. History of myelodysplastic syndrome (MDS).
6. Known history of congenital heart abnormalities or arrhythmias.
7. History of hepatitis B (HBV), hepatitis C (HCV), or human immunodeficiency virus (HIV).
8. Known history of disseminated intravascular coagulation (DIC), hemolytic uremic syndrome (HUS), or thrombotic thrombocytopenic purpura (TTP).
9. Subjects with Evans syndrome.
10. Concurrent malignant disease or previous history of myeloid hematologic malignancies.
11. Hemoglobin (Hgb) levels ≤9 g/dL in ages ≥1 year to <6 years and ≤8 g/dL in ages ≥6 to <18 years.
12. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2.
13. Serum total bilirubin >1.5× the upper limit of normal (ULN) for age, alanine transaminase (ALT) and aspartate aminotransferase (AST) >3× the ULN for age.
14. Known allergy to avatrombopag or any of its excipients.
15. Subject is unable to take oral medication, has a malabsorption syndrome, or has known hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption or any other uncontrolled gastrointestinal condition.
16. Enrollment in another clinical study with any investigational drug or device within 30 days of Day 1/Visit 2 (or 5 half-lives, whichever is longer); however, participation in observational studies within the previous 30 days is permitted.
17. Any clinically relevant abnormality which makes the subject unsuitable for participation in the study, in the opinion of the Investigator.
18. Considered unable or unwilling to comply with the study protocol requirements.

Inclusion and Exclusion Criteria for the Extension Phase

Inclusion Criteria:

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

1. Subject and/or the LAR must provide consent and/or assent, as applicable, to continue into the open-label Extension Phase. The consent for the Extension Phase will be part of the consent for the Core Phase.
2. Completed 12 weeks of treatment in the Core Phase or discontinued the Core Phase early due to lack of treatment effects.

3. Female subjects of childbearing potential and who are sexually active and male subjects who are sexually active must agree to use highly effective methods of contraception.
4. Subject and/or the subject's LAR is willing and able to comply with all aspects of the protocol.

Exclusion Criteria:

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

1. Significant safety or tolerability concerns with the subject's participation, in the opinion of the Investigator.
2. Subjects requiring the following drugs or procedures at the time of enrollment into the Extension Phase:
    - Rituximab
    - Other TPO-RAs
    - Splenectomy
    - Moderate or strong dual inducers or moderate or strong dual inhibitors of CYP2C9 and CYP3A4.

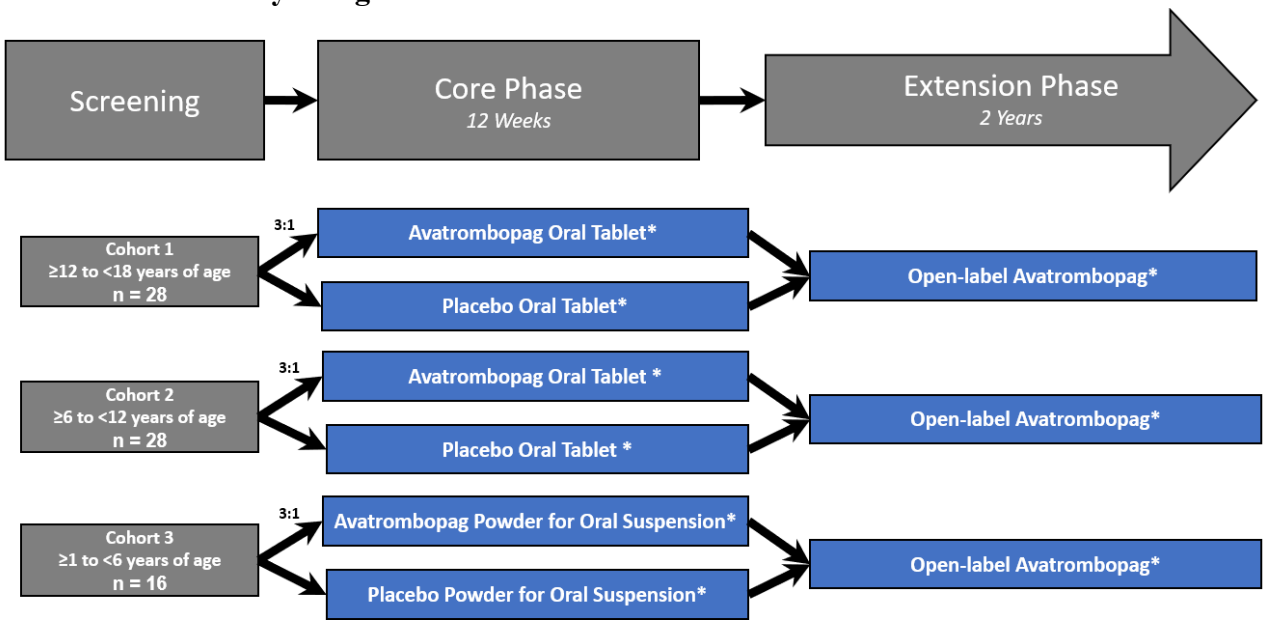
STUDY DESIGN AND DURATION:

The study will enroll at least 72 pediatric subjects, aged ≥1 to <18 years. Participating subjects must have a diagnosis of primary ITP for ≥6 months, an average of 2 platelet counts $<30\times10^9$/L with no single count $>35\times10^9$/L, and an insufficient response to a previous ITP treatment. Subjects will be randomized to blinded therapy of either avatrombopag or placebo (in a 3:1 ratio) and will also be assigned to age cohorts in a 2:2:1 ratio (subject age at the time of randomization will be used). Cohort 1 and Cohort 2 will each enroll more subjects than will be enrolled in Cohort 3 in order to minimize exposure of the youngest age group to placebo. Randomization will be stratified by age cohort. Subjects will also be stratified by a Baseline platelet count of $\leq15\times10^9$/L or $>15\times10^9$/L to $<30\times10^9$/L in order to ensure treatment groups are approximately balanced.

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

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

AVA-PED-301 Study Design



*Dose titration based on platelet count.

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

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

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

Lack of treatment effect will be defined as:

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

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

Subjects who complete the 12 week Core Phase of the study, or who meet the stopping criteria and are discontinued from the Core Phase, will be eligible to enter the open-label Extension Phase, if they continue to meet the inclusion criteria and do not meet any exclusion criteria for this phase of the study. Subjects and/or the subject's LAR must complete informed consent/assent in order to participate in the Extension Phase of the study. The Extension Phase of the study will last 2 years during which time the subject will have monthly clinic visits. Subjects may be early terminated from the Extension Phase if they have a platelet count $>250\times10^9$/L after 2 weeks of once weekly dosing for any age cohort or $<30\times10^9$/L after 3 weeks of once daily dosing at the cohort defined maximum dose.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION: In the Core Phase of the study, subjects will receive avatrombopag or placebo as either the film-coated oral tablet (20 mg per tablet) or as a capsule containing a powder for oral suspension (10 mg per capsule) which can be opened to sprinkle the contents into an appropriate vehicle. Subjects in Cohort 1 (aged ≥12 to <18 years) and Cohort 2 (aged ≥6 to <12 years) will receive the oral tablet and subjects in Cohort 3 (aged ≥1 to <6 years) will receive the powder for suspension in a capsule.

In the Extension Phase of the study, subjects will receive open-label avatrombopag as either the film-coated oral tablet (20 mg per tablet) or as the capsule containing a powder for oral suspension (10 mg per capsule).

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

Analysis Populations:

- **Full Analysis Set (FAS):** The FAS will include all randomized subjects.
- **Per Protocol Analysis Set (PPS):** The PPS will include the subset of subjects from the FAS who do not meet the criteria that would confound the evaluation of the efficacy endpoints. A full list of the criteria will be finalized prior to database lock and unblinding.

- **Safety Analysis Set:** The Safety Analysis Set will include all subjects who receive at least 1 dose of study drug.

All efficacy analyses will be conducted using the FAS, unless otherwise specified.

Primary Efficacy Endpoint: The primary efficacy endpoint will be tested between avatrombopag and placebo using the Cochran-Mantel-Haenszel 2-sided test at α=0.05, adjusting for age cohort and Baseline platelet count ($\leq 15\times 10^9$/L vs $>15\times 10^9$/L), or the Fisher's exact test, when data is sparse. In addition, the numbers and percentages of responders in each treatment group, the associated 95% confidence intervals (CI), and the 95% CI for the difference between avatrombopag and placebo will be summarized.

Alternative Primary Efficacy Endpoint: The alternative primary efficacy endpoint will be tested between avatrombopag and placebo using the Cochran-Mantel-Haenszel 2-sided test at α=0.05, adjusting for age cohort and Baseline platelet count ($\leq 15\times 10^9$/L vs $>15\times 10^9$/L), or the Fisher's exact test, when data is sparse. In addition, the numbers and percentages of responders in each treatment group, the associated 95% CI, and the 95% CI for the difference between avatrombopag and placebo will be summarized.

Safety Analysis: Safety assessments for this study include the incidence of AEs, SAEs, AESI, clinical laboratory tests, and vital signs. The safety assessments will be summarized descriptively by treatment group for the Safety Analysis Set.

Pharmacokinetic/Pharmacodynamic Analysis: Population PK modeling will be conducted to estimate PK parameters. Effects of intrinsic factors, including age and weight, and extrinsic factors, including formulation, on the PK parameters may be evaluated.

SAMPLE SIZE DETERMINATION: With the 3:1 ratio of avatrombopag to placebo, a total of 72 subjects (54 avatrombopag and 18 placebo) will provide at least 90% power to detect the treatment difference of 37.9% in durable response at α=0.05, based on the Fisher's exact test.

In addition, with the 3:1 ratio of avatrombopag to placebo, a total of 72 subjects (54 avatrombopag and 18 placebo) will provide ≥99% power to detect the treatment difference of 80% in proportion of subjects achieving a platelet count $\geq 50\times 10^9$/L for 2 consecutive weeks at α=0.05, based on the Fisher's exact test.

SITES: Approximately 50 sites globally

SPONSOR:

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
21 CFR	Title 21 of the Code of Federal Regulations
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine transaminase
AST	Aspartate aminotransferase
AUC	The area under the plot of plasma concentration of drug against time after drug administration
BMI	Body mass index
CI	Confidence interval
CIT	Chemotherapy-induced thrombocytopenia
CLD	Chronic liver disease
CL/F	Apparent total body clearance after extravascular administration, calculated as Dose/$AUC_{0-\infty}$
C_{max}	Maximum measured plasma concentration
CRA	Clinical research associate
CsA	Cyclosporine
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Hgb	Hemoglobin
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive response technology
ITP	Immune thrombocytopenia
IVIg	Intravenous immune globulin
LAR	Legally authorized representative
MDRD	Modification of Diet in Renal Disease Study
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
MMF	Mycophenolate mofetil
PD	Pharmacodynamic
PE	Physical exam
PK	Pharmacokinetic
PPS	Per-protocol analysis set
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SmPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Half life
TPO	Thrombopoietin
TPO-RA	Thrombopoietin receptor agonist
ULN	Upper limit of normal
US	United States
USPI	United States Prescribing Information
V_z/F	Apparent volume of distribution based on the terminal elimination phase after extravascular administration calculated as $Dose/AUC_{0-\infty}/\lambda_z$
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 by clumping 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 in both adults and children 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.

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).

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.

1.2 Immune Thrombocytopenia in Adults and Pediatrics

ITP is an autoimmune disorder characterized by low platelet counts caused from 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 (adults or children) 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 to 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

The rates of spontaneous remission in adults are much lower than those seen in pediatrics. ITP resolves on its own in 74% of children <1 year of age, 67% of children between 1-6 years of age, and 62% of those between 10-20 years of age, however, it may become chronic and symptomatic in a proportion of children affected (Neunert, 2019). Bleeding events can range from minor events such as bruising and petechiae to more severe events such as hematuria or intracranial hemorrhage which occurs in up to 0.4% of children with ITP; severe bleeding is reported in up to 20% of children. In general, 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 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. Current guidelines recommend observation (or watchful waiting) in children with newly diagnosed ITP who have no or only minor bleeding, rather than treatment with corticosteroids or intravenous immune globulin (IVIg). For the treatment of newly diagnosed ITP in children who have non-life-threatening bleeding, agents that decrease platelet destruction (e.g., corticosteroids or immunoglobulins) are recommended as first line treatment. However, these drugs have variable and transient efficacy and significant toxicities.

Second-line treatment options in children include rituximab (an immune suppressing agent) and the TPO receptor agonists (TPO-RAs) eltrombopag (PROMACTA®/REVOLADE®) and romiplostim (NPLATE®). Rituximab has effects on the immune system that may last longer than the disease course and can also be associated with infusion-related side effects and persistent hypogammaglobulinemia. Eltrombopag must be taken 2 hours before or 4 hours after any antacids, dairy products, or mineral supplements containing polyvalent cations and must also be taken on an empty stomach, 1 hour prior to eating or 2 hours after eating, which may be challenging for children. Romiplostim requires weekly subcutaneous injections which are typically performed by the patient's healthcare provider. Finally, splenectomy is discouraged in children due to the high rates of spontaneous remission in this population as well as the short and long-term risks of asplenia (PROMACTA® United States Prescribing Information [USPI]/REVOLADE® Summary of Product Characteristics [SmPC]; NPLATE® USPI; NPLATE® SmPC; Neunert, 2019; Provan, 2019).

There remains an important unmet medical need for new treatment options for pediatric patients with ITP, given the difficult administration requirements and the variable, transient response, frequent relapse, and associated toxicities of the available treatments.

1.3 Avatrombopag

Avatrombopag maleate (DOPTELET®) 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 authorized by the European Commission for the treatment of severe thrombocytopenia in patients with CLD who are scheduled to undergo an invasive procedure (DOPTELET® SmPC). It has also been approved by the United States (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 greater 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 ≥50×10^9/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 included in Table 1.

Table 1 Adverse Events with a Frequency ≥10% in Patients 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

1.4.1 Study Design

This Phase 3b, multi-center, randomized, double-blind, placebo-controlled, parallel-group study in pediatric subjects includes a 12 week Core Phase followed by an open-label Extension Phase and will evaluate the efficacy, safety, tolerability, and pharmacokinetic (PK)/pharmacodynamic (PD) profile of avatrombopag, as well as provide data on palatability/acceptability, dosing parameters, and response to treatment. In order to satisfy the primary endpoint requirements of different regulatory agencies, 2 separate statistical analysis plans (SAPs) will be developed for this study to accommodate the primary endpoint and the alternative primary endpoint discussed in Section 3.1 and Section 3.2.

The study will enroll at least 72 pediatric subjects, aged ≥1 to <18 years. Participating subjects must have a diagnosis of primary ITP (as defined in Provan, 2019) for ≥6 months, an average of 2 platelet counts <30×10^9/L with no single count >35×10^9/L, and an insufficient response to a previous ITP treatment. The platelet count obtained at the Screening Visit/Visit 1 and 1 other platelet count taken within 28 days on either side of the Screening Visit (may use a historical value collected per standard of care if within 28 days of the Screening Visit) will be averaged to obtain the study eligibility platelet count value. The 2 samples must be obtained ≥24 hours and ≤28 days apart and the results must be available prior to randomization. This population is consistent with the populations studied in other TPO-RA pediatric ITP trials (Bussel, 2015; Tarantino, 2016).

Subjects will be randomized to blinded therapy of either avatrombopag or placebo (in a 3:1 ratio) and will also be assigned to age cohorts in a 2:2:1 ratio. Cohort 1 and Cohort 2 will each enroll more subjects than will be enrolled in Cohort 3 in order to minimize exposure of the youngest age group to placebo (Figure 1). Randomization will be stratified by age cohort. Subjects will also be stratified

by a Baseline platelet count of $\leq 15\times10^9$/L or $>15\times10^9$/L to $<30\times10^9$/L in order to ensure treatment groups are approximately balanced.

Core Phase Cohort Enrollment (subject age at the time of randomization will be used):

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

The dose of study drug will be titrated based on the subject's individual responses to study drug (Table 4). The overall goal of dose modification will be to maintain the peripheral platelet count $\geq 50\times10^9$/L and $\leq 150\times10^9$/L. The upper limit of 150×10^9/L was chosen in order to be consistent with the upper limit used in the adult pivotal Phase 3 ITP study (Study 302).

Enrollment into the 12 week Core Phase will be staggered by descending age cohort. Prior to opening Cohort 2 or Cohort 3 for enrollment, PK, PD, and safety data will be reviewed after the first 10 subjects in the previous cohort have completed Visit 12 (Week 10). The pediatric PK/PD model will be updated after each age cohort is fully enrolled. Additional details regarding this ongoing data review are in Section 5.1.

After the 12 week Core Phase, subjects may enter the 2-year open-label Extension Phase where all subjects will receive open-label avatrombopag and monthly study visits will be conducted to assess platelet count and to collect data on avatrombopag safety, dose, and dosing frequency (Figure 1). In addition, subjects enrolled in the Core Phase who are not showing a platelet response (i.e., a lack of treatment effect) at the highest dose of study drug based on the subject's Cohort (Table 3) may be terminated from the Core Phase and directly enrolled into the open-label Extension Phase (Section 5.3). Subjects may be early terminated from the Extension Phase if they have a platelet count $>250\times10^9$/L after 2 weeks of once weekly dosing for any age cohort or $<30\times10^9$/L after 3 weeks of once daily dosing at the cohort defined maximum dose.

Bleeding severity will be captured using the World Health Organization (WHO) bleeding scale (Appendix C). Although an ITP Bleeding Scale (IBLS) is available, the WHO bleeding scale has a simple and easily applicable definition, it was used in the adult avatrombopag ITP studies as well as other TPO-RA trials, and thus will enable direct comparisons. (Section 9.4) (Fogarty, 2012).

Additional information regarding the study design of AVA-PED-301 is in Section 4.

1.4.2 Pharmacokinetic Sampling Schedule

In order to minimize the number of blood draws subjects are subjected to, blood samples for *serial* PK assessments will be collected only during Visit 4 (Week 2) and Visit 12 (Week 10) of the 12 week Core Phase. Regardless of the subject's current treatment regimen (once daily, three times a week, etc.) Visit 4 and Visit 12 must fall on a day the subject is scheduled to take their dose of study drug. Serial PK sampling may need to occur at a visit later than Visit 4 or Visit 12 if study drug was held or if the dose changed; see Section 9.6. During these visits, subjects ≥6 years of age (Cohort 1 and Cohort 2) will have a blood sample drawn before dosing with study drug on that day (pre-dose) and between 2 to 4 hours, 6 to 8 hours, and 10 to 12 hours post-dose (there will be 4 PK samples drawn at each visit, 2 mL each). Subjects <6 years of age (Cohort 3) will also have a blood sample drawn pre-dose and at 2 to 4 hours post-dose but will be randomized in a 1:1 ratio, stratified by treatment group, to either the 6 to 8 hour or the 10 to 12 hour post-dose timepoint at Visit 4 (Week

2). The timepoint not drawn at Visit 4 (Week 2) will be drawn at Visit 12 (Week 10) (there will be 3 PK samples drawn at each visit, 2 mL each).

For all age groups, blood samples for *sparse* PK assessments (2 mL each) will be collected while the subject is at the clinic during Visit 3 (Week 1) and at each weekly visit during the period from Visit 5 (Week 3) to Visit 11 (Week 9) (there will be 8 total PK samples drawn across these visits, 2 mL each). This frequency of sparse and serial PK blood sampling will allow for a comparison of PK values between pediatric and adult ITP patients and to confirm the appropriate dose of avatrombopag prior to opening the next cohort for enrollment. Blood draws for clinical laboratory samples and for PK samples may be drawn on the same blood draw in order to further minimize the number of needle sticks for the subject. Additional details on the PK sampling schedule are included in Figure 3 and Section 9.6.

1.5 Pediatric Formulation and Dosing Regimen

During efforts to develop a pediatric formulation of avatrombopag, a Phase 1 formulation bridging study (AVA-PED-101) was completed which compared the relative bioavailability of the avatrombopag tablet for oral suspension to the commercially available film-coated oral tablet, administered as a single 20 mg dose, under the fed condition, in healthy adult subjects.

The results of this study showed that the tablet for oral suspension demonstrated suitable PK properties when compared with the film-coated oral tablet and confirmed that administration with food decreases the PK variability of the tablet for oral suspension. All treatment-emergent AEs (TEAEs) were mild and resolved by the end of the study; none were considered by the Investigator to be related to avatrombopag. There were no serious AEs (SAEs) or deaths.

The palatability of the tablet for oral suspension, after dispersion in 8 oz of water, was assessed as an exploratory endpoint. The palatability was considered by most adult subjects to be "Neither Good nor Bad". "Very Bad" was not selected by any subject for any palatability measure. In addition, most adult subjects selected "No Taste" when asked to describe different taste characteristics of the tablet for oral suspension after dispersion in water (e.g., sweet, salty, bitter, etc.).

1.5.1 Powder for Oral Suspension in a Capsule

The tablet for oral suspension used in AVA-PED-101 is no longer being pursued by the Sponsor due to its slow dispersion properties in water and the Sponsor has selected a powder for oral suspension in a capsule for this pediatric study. The excipient composition of the powder for oral suspension is identical to the tablet for oral suspension studied in AVA-PED-101, with the only difference being that rather than compressing the formulation into a tablet, the formulation is placed in a capsule which can be opened and the contents suspended in water, or other appropriate vehicles, prior to administration. More information on the administration of avatrombopag is in Section 7.

The results of the palatability assessment of the tablet for oral suspension in the Phase 1 AVA-PED-101 study (Section 1.5), demonstrated that it was sufficient to disperse the avatrombopag tablet for oral suspension in water prior to dosing, with no taste masking agent required.

Child reported palatability and parent/caregiver reported acceptability of the powder for oral suspension will be assessed after the first dose of study drug in the Core Phase of this study for subjects in Cohort 3 (see questionnaire in Appendix B).

1.5.2 Dose Modeling and Simulation

A population PK model was previously established for avatrombopag exposure in adult healthy subjects as well as adult ITP patients dosed with avatrombopag. In addition, a population PK/PD model was established for platelet response in adult ITP patients dosed with avatrombopag. The population PK model established for adults was used to predict avatrombopag exposure in pediatric ITP patients taking into consideration weight differences in adults and children. The final PK/PD model for platelet response remained the same between adult and pediatrics, except that Baseline age was added as a covariate based on the population PK/PD model for eltrombopag ITP patients aged ≥1 to <18 years. This modification is appropriate because platelet maturation is a physiological process that differs between adults and pediatrics, and is not drug dependent (Wire, 2018).

Simulations were performed assuming the Baseline platelet count was $<30\times10^9$/L with a goal to increase the platelet count to $\geq50\times10^9$/L to $\leq150\times10^9$/L with avatrombopag treatment. No drug-drug-interaction perpetrators (i.e., moderate or strong dual inducers or moderate or strong dual inhibitors of cytochrome P450 (CYP)2C9 and CYP3A4) were included.

1.5.3 Core Phase Dosing Regimen

The simulations described above suggested that the doses of avatrombopag listed in Table 4 were the most appropriate starting doses to maximize the percentage of subjects achieving the target platelet count range of $\geq50\times10^9$/L to $\leq150\times10^9$/L for each age group. The appropriate starting doses of avatrombopag will be confirmed in the Core Phase of the study when PK, platelet count, and safety data will be reviewed after the first 10 subjects in each cohort complete Visit 12 (Week 10) and before opening enrollment to subsequent cohorts (Figure 2).

In the Core Phase of the study, subjects will receive avatrombopag or placebo as either the film-coated oral tablet (20 mg per tablet) or as a capsule containing a powder for oral suspension (10 mg per capsule) which can be opened to sprinkle the contents into an appropriate vehicle. Subjects in Cohort 1 (aged ≥12 to <18 years) and Cohort 2 (aged ≥6 to <12 years) will receive the oral tablet and subjects in Cohort 3 (aged ≥1 to <6 years) will receive the powder for oral suspension in a capsule.

On Day 1/Visit 2, Cohort 1 (≥12 to <18 years of age) will have a starting dose of avatrombopag, or matching placebo, of 20 mg once daily, administered as an oral tablet, consistent with the approved adult dosing. The starting dose for Cohort 2 (≥6 to <12 years of age) will also be 20 mg once daily administered as an oral tablet, and the starting dose for Cohort 3 (≥1 to <6 years of age) will be 10 mg once daily administered as a powder for oral suspension in a capsule (Table 2). The dose of study drug may be titrated up or down based on the subject's platelet count in order to maintain a platelet count between ≥50 to $\leq150\times10^9$/L during the 12 week Core Phase (Table 4).

If subjects in Cohort 3 require higher doses of avatrombopag than what is listed in Dose Level 6 in order to maintain a platelet count $\geq50\times10^9$/L, the appropriate dose may be discussed with the Sponsor Medical Monitor (Table 4). However, across all age cohorts, the maximum allowable dose of study drug is 40 mg daily and the dose should not be increased beyond what is in Dose Level 6 in Table 4 for Cohort 3 without approval from the Sponsor Medical Monitor. If two subjects in Cohort 3 require escalation above Dose Level 6, a protocol amendment must be implemented before any additional subjects will be permitted to escalate above Dose Level 6.

Table 2 Study Drug Starting Dose by Age Cohort[a] in the Core Phase and Extension Phase

Age Range (Years)	Study Drug Starting Dose (mg)	Formulation
Cohort 1		
≥12 to <18	20 mg Once Daily	Oral Tablet
Cohort 2		
≥6 to <12	20 mg Once Daily	Oral Tablet
Cohort 3		
≥1 to <6	10 mg Once Daily	Capsule

a: Subject age at the time of randomization will be used. The starting dose of study drug may be revised after scheduled PK/PD and safety reviews (Section 5.1).

Table 3 Study Drug Dose Adjustments in the Core Phase and Extension Phase

Platelet Count ($\times 10^9$/L)	Dose Adjustment or Action
<50×10^9/L after at least 2 weeks of dosing.	• Increase 1 Dose Level per Table 4. • Wait 2 weeks to assess the effects of this regimen and any subsequent dose adjustments.
>150×10^9/L to ≤250×10^9/L	• Decrease 1 Dose Level per Table 4. • Wait 2 weeks to assess the effects of this regimen and any subsequent dose adjustments.
>250 ×10^9/L	• Stop study drug. • Increase platelet monitoring to twice weekly. • When platelet count is ≤100×10^9/L, decrease 1 Dose Level per Table 4.
<30×10^9/L after 3 weeks of once daily dosing at the cohort defined maximum dose per Table 4. *Also see protocol stopping criteria in Section 5.3 and early termination criteria in Section 6.1.6.*	Discontinue study drug.
>250×10^9/L after 2 weeks of once weekly dosing for any age cohort	Discontinue study drug.

Table 4 Study Drug Dose Level Titration (Core and Extension)

Dose	Dose Level
Cohort 1 (≥12 to <18 Years) and Cohort 2 (≥6 to <12 Years) Dosed with Oral Tablet	
40 mg Once Daily	6
40 mg Three Times a Week *AND* 20 mg on the Four Remaining Days of Each Week	5
20 mg Once Daily[a]	**4**
20 mg Three Times a Week	3
20 mg Twice a Week	2
20 mg Once Weekly	1
Cohort 3 (≥1 to <6 Years) Dosed with Powder for Oral Suspension	
20 mg Once Daily	6
20 mg Three Times a Week *AND* 10 mg on the Four Remaining Days of Each Week	5
10 mg Once Daily[a]	**4**
10 mg Three Times a Week	3
10 mg Twice a Week	2
10 mg Once Weekly	1

a: Subject age at the time of randomization will be used. Initial dose regimen based on modeling and simulation. Actual initial dose in Cohort 2 and Cohort 3 may be modified after modeling is completed using data from the previous cohort.

To ensure accuracy of the predictions, PK, platelet response, and safety data will be reviewed by the Sponsor, or the Sponsor's unblinded designee, as described in Section 5.1 and if necessary, adjustments of the dose level may be made following these data reviews.

1.5.4 Extension Phase Dosing Regimen

Subjects who complete the 12 week Core Phase of the study, or who meet the stopping criteria as defined in Section 5.3 and are discontinued from the Core Phase, will be eligible to enter the open-label Extension Phase, if they continue to meet the inclusion criteria and do not meet any exclusion criteria for this phase of the study (Section 4.1.2).

In the Extension Phase of the study, subjects will receive open-label avatrombopag as either the film-coated oral tablet (20 mg per tablet) or as a capsule containing a powder for oral suspension (10 mg per capsule) which can be opened to sprinkle the contents into an appropriate vehicle. The formulation received should be recorded in the electronic case report form (eCRF). The appropriate Extension Phase starting dose of open-label avatrombopag should be determined based on the instructions below.

- If a subject entering the Extension Phase has a platelet count within the target range of $\geq 50\times10^9$/L to $\leq 150\times10^9$/L on their current dose of study drug, they may continue that dose of open-label avatrombopag when entering the Extension Phase.
- If a subject entering the Extension Phase has a platelet count $<50\times10^9$/L when entering the Extension Phase, the subject should be started on the dose of open-label avatrombopag listed in Table 2, based on the subject's age cohort.
- If a subject entering the Extension Phase has a platelet count $>150\times10^9$/L when entering the Extension Phase, the initial dose of open-label avatrombopag in the Extension Phase should be titrated down per the instructions in Table 4, based on the subject's platelet count, in order to maintain a platelet count between ≥ 50 to $\leq 150\times10^9$/L.

Throughout the Extension Phase, the dose of open-label avatrombopag may be titrated up or down per the instructions in Table 4, based on the subject's platelet count, in order to maintain a platelet count between ≥ 50 to $\leq 150\times10^9$/L.

If subjects in Cohort 3 require higher doses of avatrombopag than what is listed in Dose Level 6 in order to maintain a platelet count $\geq 50\times10^9$/L, the appropriate dose may be discussed with the Sponsor Medical Monitor (Table 4). However, across all age cohorts, the maximum allowable dose of study drug is 40 mg daily and the dose should not be increased beyond what is in Dose Level 6 in Table 4 for Cohort 3 without approval from the Sponsor Medical Monitor. If two subjects in Cohort 3 require escalation above Dose Level 6, a protocol amendment must be implemented before any additional subjects will be permitted to escalate above Dose Level 6.

2 STUDY OBJECTIVES

2.1 Primary Objective

To demonstrate that the efficacy of avatrombopag is superior to placebo for the treatment of pediatric subjects with ITP of ≥6 months duration who have had an insufficient response to a previous treatment.

2.2 Secondary Objectives

- To evaluate the safety and tolerability of avatrombopag
- To evaluate the PK and PD of avatrombopag

2.3 Exploratory Objective

To provide data on the palatability and parent/caregiver reported acceptability of the avatrombopag powder for oral suspension.

3 STUDY ENDPOINTS

In order to satisfy the primary endpoint requirements of different regulatory agencies, 2 separate SAPs will be developed for this study. In the first SAP, the endpoint described as "Primary Efficacy Endpoint" in Section 3.1 will be assessed as the primary efficacy endpoint, and the endpoint described as the "Alternative Primary Efficacy Endpoint" in Section 3.2 will be assessed as the first secondary efficacy endpoint. In the second SAP, the endpoint described as "Alternative Primary Efficacy Endpoint" in Section 3.2 will be assessed as the primary efficacy endpoint, and the endpoint described as the "Primary Efficacy Endpoint" in Section 3.1 will be assessed as the first secondary efficacy endpoint. Both SAPs will evaluate the additional secondary efficacy endpoints described in Section 3.3.

3.1 Primary Efficacy Endpoint

Durable platelet response as defined by the proportion of subjects achieving at least 6 out of 8 weekly platelet counts $\geq 50 \times 10^9$/L during the last 8 weeks of the 12 week Treatment Period in the Core Phase in the absence of rescue medication.

3.2 Alternative Primary Efficacy Endpoint

Platelet response as defined by the proportion of subjects for whom at least 2 consecutive platelet assessments are $\geq 50 \times 10^9$/L over the 12 week Treatment Period in the Core Phase in the absence of rescue medication.

3.3 Additional Secondary Efficacy Endpoints

- The percentage of weeks subjects have a platelet count $\geq 50 \times 10^9$/L during 12 weeks of treatment in the Core Phase, in the absence of rescue therapy.
- Platelet response at Day 8 (defined by the proportion of subjects with a platelet count $\geq 50 \times 10^9$/L at Day 8, in the absence of rescue therapy).

- The percentage of weeks subjects have a platelet count between $\geq 50 \times 10^9$/L and $\leq 150 \times 10^9$/L, during 12 weeks of treatment in the Core Phase, in the absence of rescue therapy.
- The proportion of subjects who require rescue medications during 12 weeks of treatment in the Core Phase of the study.
- Incidence and severity of bleeding symptoms associated with ITP measured using the WHO Bleeding Scale.

3.4 Safety Endpoints

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

3.5 Pharmacokinetic and Pharmacodynamic Endpoints

- Individual PK parameters will be derived from the final population PK model. Effects of intrinsic factors, including age and weight, and extrinsic factors, including formulation, on the PK parameters may be evaluated.
- Effects of covariates on PD parameters may be evaluated.

3.6 Exploratory Endpoints

- Platelet count assessments and platelet response during the Extension Phase.
- Subject reported palatability and parent/caregiver reported acceptability assessed by a palatability/acceptability questionnaire administered after the first dose of the powder for oral suspension.

4 STUDY DESCRIPTION

4.1 Summary of Study Design

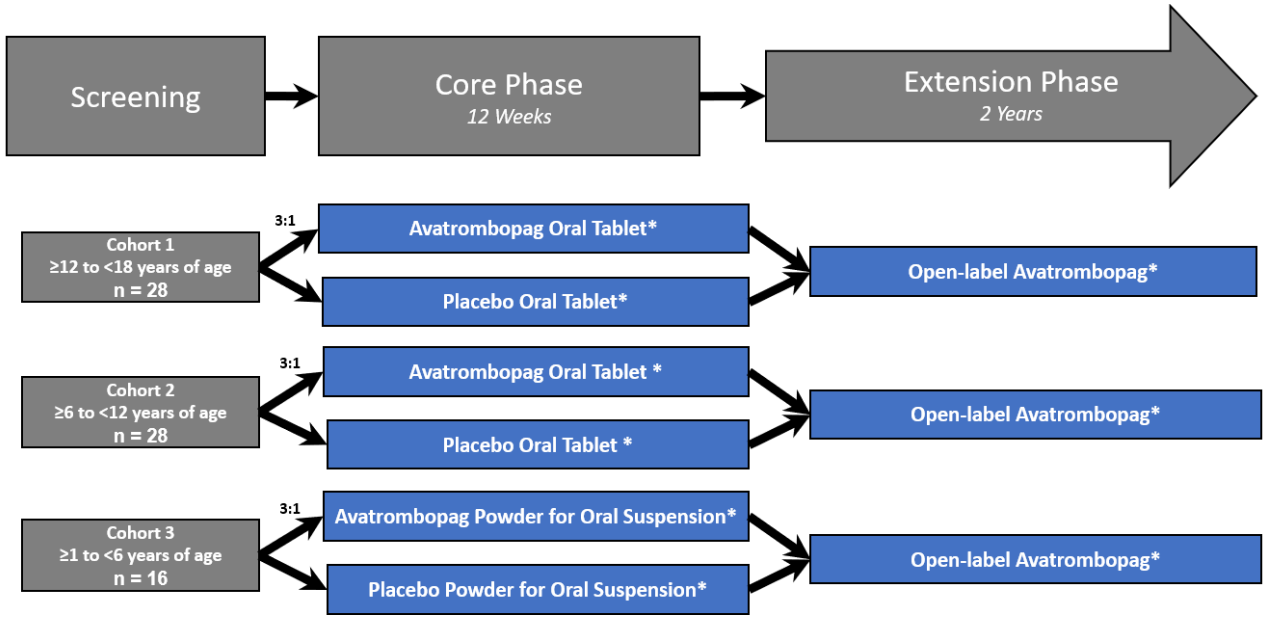
AVA-PED-301 is a multi-center, randomized, double-blind, placebo-controlled, parallel-group study in pediatric subjects with a 12 week Core Phase followed by an open-label Extension Phase to evaluate the efficacy, safety, tolerability, and PK/PD profile of avatrombopag, as well as provide data on palatability/acceptability,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

The study will enroll at least 72 pediatric subjects, aged ≥1 to <18 years (Figure 1). Subjects will be assigned to 3 age cohorts in a 2:2:1 ratio and subjects will be randomized within each cohort in a 3:1 ratio to receive either avatrombopag or placebo. Subject age at the time of randomization will be used. Cohort 1 and Cohort 2 will each enroll more subjects than will be enrolled in Cohort 3 in order to minimize the exposure of the youngest age group to placebo.

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

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

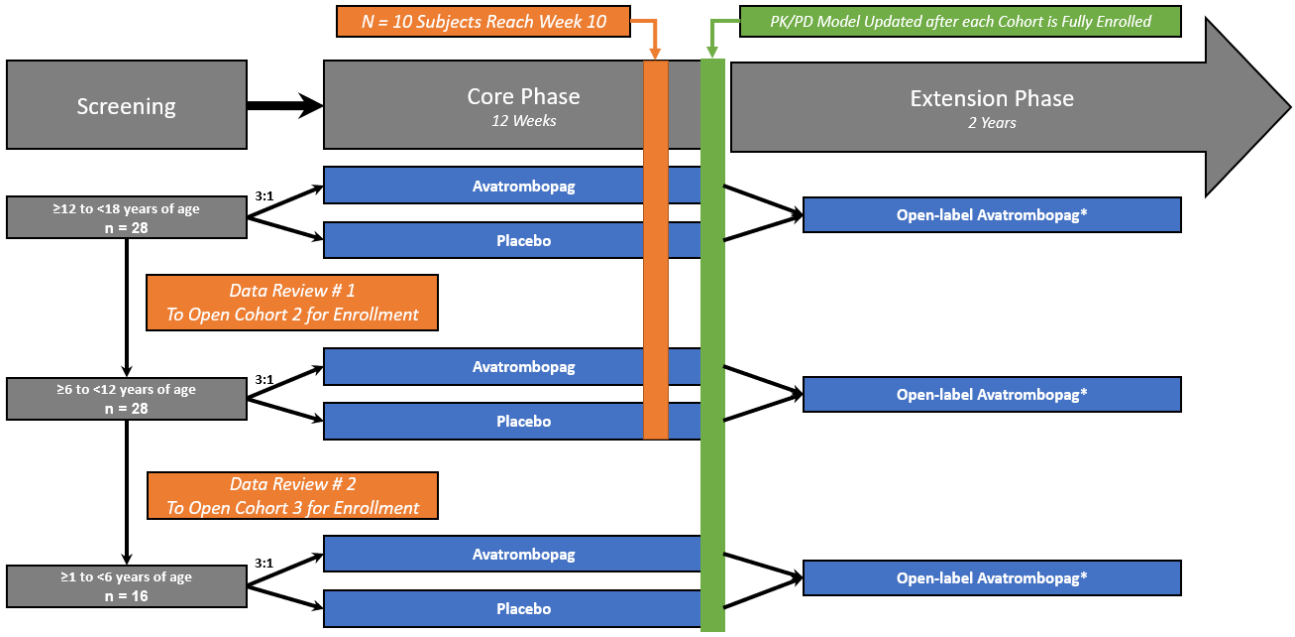
Figure 1 AVA-PED-301 Study Design



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

The dose of avatrombopag may be modified during the study based on results of the PK and safety data review. In addition, safety data will be reviewed on an ongoing basis and new enrollment may be paused for any serious unexpected and related AEs that occur (Figure 2).

Figure 2 AVA-PED-301 Enrollment and Data Review Plan



PK = pharmacokinetic; PD = pharmacodynamic

Enrollment will not stop in the current cohort for the data review after Week 10, or for the data review after each cohort is fully enrolled.

Subjects who are not showing a platelet response (i.e., a lack of treatment effect) at the highest dose of study drug based on the subject's age cohort may be terminated from the Core Phase and directly enrolled into the open-label Extension Phase (Section 5.3).

Lack of treatment effect will be defined as:

- Platelet count remains $<30\times10^9$/L after more than 3 weeks at the maximum dose of study drug per Table 4. Subjects may also be terminated from the Core Phase and directly enrolled into the Extension Phase after 7 days of therapy at the maximum dose if they have dangerously low platelet counts (in the opinion of the Investigator), or

- Subjects who require rescue therapy more than 3 times or continuous rescue therapy for more than 3 weeks (Section 8.6).

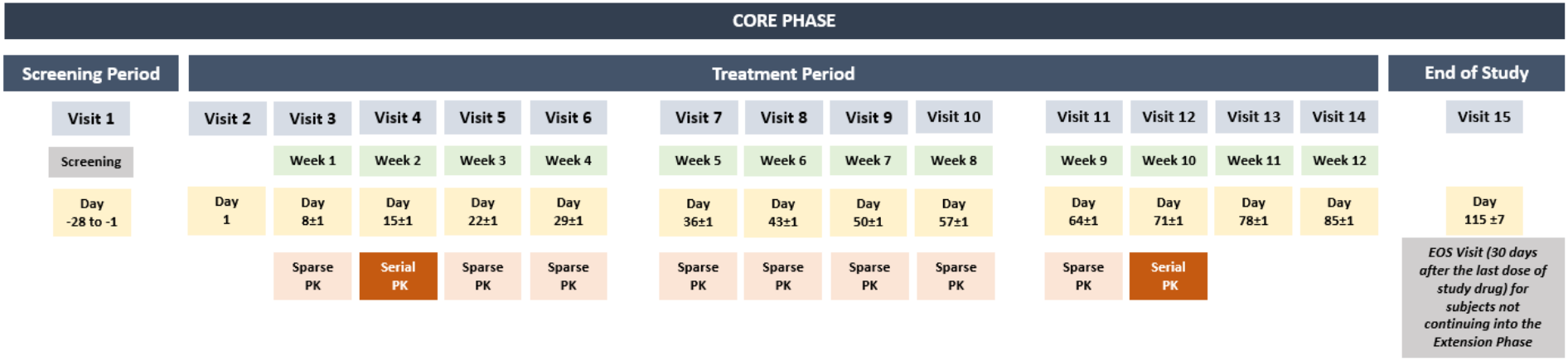
4.1.1 Core Phase

The Core Phase of AVA-PED-301 is designed to assess the efficacy, safety, and tolerability of avatrombopag in pediatric subjects with ITP.

In order to participate in the Core Phase of the study, informed consent/assent must be completed by the subject and/or the subject's Legally Authorized Representative (LAR).

Subjects who participate in the Core Phase will enter a Screening Period followed by a 12 week Treatment Period after which they may either complete the study with an End of Study Visit that will occur 30 days after the last dose of study drug or continue into the open-label Extension Phase. The Core Phase of the study will last 12 weeks (approximately 84 days), which does not include the 4 week Follow-up Period, with study visits occurring once weekly through the end of Week 12 (Figure 3).

Figure 3 AVA-PED-301: Core Phase Study Schematic



4.1.1.1 Screening Period

The Screening Visit (Visit 1) will be completed within 28 days prior to Baseline (Day 1/Visit 2).

4.1.1.2 Treatment Period (Visit 2 Through Visit 14)

Enrollment will begin with Cohort 1 (ages ≥12 to <18 years). Enrollment into Cohort 2 (ages ≥6 to <12 years) and Cohort 3 (ages ≥1 to <6 years) will begin after notification from the Sponsor as described in Section 4.1 and Figure 2. Subject age at the time of randomization will be used.

At Day 1/Visit 2 eligible subjects will be randomized 3:1 to receive either avatrombopag or placebo at the starting dose determined by the PK/PD modeling described in Section 1.1.5. Throughout the Treatment Period, the dose of avatrombopag may be titrated up or down by the Investigator, based on platelet count (Table 4).

Subjects may be removed from the Core Phase and directly enrolled into the open-label Extension Phase due to a lack of treatment effect (Section 5.3).

Blood samples for *serial* PK assessments will be collected during Visit 4 (Week 2) and Visit 12 (Week 10) of the Core Phase. During these visits, subjects ≥6 years of age will have a blood sample drawn pre-dose and between 2 to 4 hours, 6 to 8 hours, and 10 to 12 hours post-dose (4 samples drawn at each visit, 2 mL each). Subjects <6 years of age will have a blood sample drawn pre-dose and at 2 to 4 hours post-dose but will be randomized in a 1:1 ratio, stratified by treatment group, to either the 6 to 8 hour or the 10 to 12 hour post-dose timepoint at Visit 4 (Week 2). The timepoint not drawn at Visit 4 (Week 2) will be drawn at Visit 12 (Week 10) (3 samples drawn at each visit, 2 mL each). For all age groups, blood samples for *sparse* PK assessments (2 mL each) will be collected while the subject is at the clinic during Visit 3 (Week 1) and at each visit during Visit 5 to Visit 11 (Week 3 to Week 9; 8 samples, 2 mL each) (Section 9.6).

After Visit 14 (Week 12), the subject may enter the 2-year open-label Extension Phase (Section 9.2). If the subject does not enter the Extension Phase, an End of Study Visit (Section 9.1.16) must be completed approximately 30 days after the last dose of study drug, prior to discharging the subject from the study. Visit 14 will serve as the last visit of the Core Phase and the first visit of the Extension Phase (Visit E-1).

4.1.1.3 End of Study Visit (for Subjects *not* Continuing into the Extension Phase)

Subjects who are not continuing into the 2-year open-label Extension Phase will be followed for 30 days (±7 days) following the last dose of study drug in the Core Phase. Once the End of Study Visit (Section 9.1.16; Table 7) has been completed, the subject may be discharged from the study.

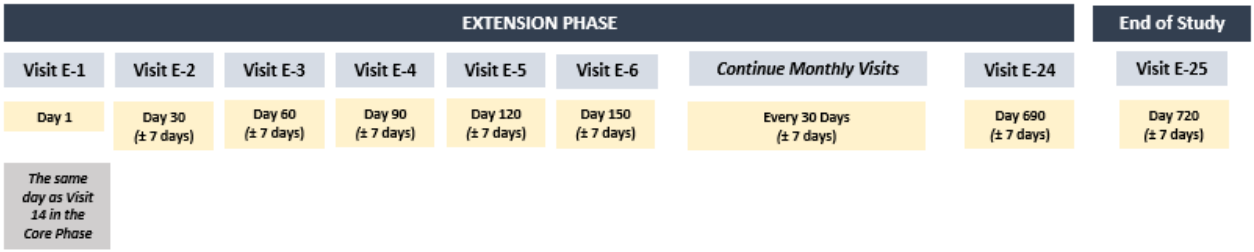
4.1.2 Extension Phase

Subjects who complete the 12 week Core Phase of the study, or who meet the stopping criteria as defined in Section 5.3 and are discontinued from the Core Phase, will be eligible to enter the open-label Extension Phase, if they continue to meet the inclusion criteria and do not meet any exclusion criteria for this phase of the study. Subjects and/or the subject's LAR must complete informed consent/assent in order to participate in the Extension Phase of the study.

Until the last subject completes the Core Phase and the database is locked, the Sponsor, all subjects, and all Investigators will remain blinded to treatment received in the Core Phase. Dosing of open-label avatrombopag during the Extension Phase is described in Section 1.1.6.

Study visits will begin with Visit E-1/Month 1 which will be the same day as Visit 14 in the Core Phase. After dosing with open-label avatrombopag has been initiated during Visit E-1/Day 1, the subject should have weekly platelet counts drawn until it is determined that the subject is receiving a stable dose of avatrombopag. Otherwise, during the Extension Phase, visits will occur every 30 days for 24 months through Visit E-24/Month 24 (Figure 4).

Figure 4 AVA-PED-301: Extension Phase Study Schematic



4.1.2.1 End of Study Visit

9.1.20; Table 8) has been completed, the subject may be discharged from the study.

5 PHARMACOKINETIC AND SAFETY DATA REVIEW

5.1 Ongoing Data Review

All available PK and safety data through Week 10 of the study will be reviewed by the Sponsor and/or the Sponsor's designee (e.g., for unblinded PK data) for the first 10 subjects enrolled into Cohort 1 prior to opening enrollment into the Core Phase for subjects in Cohort 2. Likewise, all available PK and safety data through Week 10 will be reviewed by the Sponsor and/or the Sponsor's designee (e.g., for unblinded PK data) for the first 10 subjects enrolled into Cohort 2, prior to opening enrollment into the Core Phase for Cohort 3. Enrollment will not stop during this data review period.

As the study progresses and data become available, the pediatric PK/PD model will be updated with emerging data in order to confirm the appropriate dose of avatrombopag in each cohort. The PK/PD model will be updated after each age cohort is fully enrolled, but without stopping enrollment for remaining cohorts. The dose of avatrombopag may be modified during the study based on results of the PK and safety data review.

Safety data will be reviewed on an ongoing basis and new enrollment may be paused for any serious unexpected and related AEs that occur (Figure 2).

The exact doses of avatrombopag may be modified during the study based on PK/PD analysis of emerging PK/PD and safety data.

The Sponsor and the project team will remain blinded during the ongoing safety data review. Interim PK/PD analyses will be conducted by an unblinded designee.

5.2 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will assess the overall status of the study and the safety of subjects. An IDMC charter will be developed to govern IDMC activities which will pre-specify the rules for safety reporting and safety analyses to be presented to the IDMC. The IDMC will make formal recommendations about the conduct of the study and safety of study participants following each IDMC meeting.

In general, it is anticipated that the IDMC will be asked to perform a safety review in the case of thromboembolic events or serious unexpected adverse reactions occurring in ≥2 subjects in any single Cohort in the Core Phase.

5.3 Stopping Criteria

Subjects may be removed from the Core Phase and directly enrolled into the open-label Extension Phase due to a lack of treatment effect.

A lack of treatment effect will be defined as:

- Platelet count remains $<30\times10^9$/L after more than 3 weeks at the maximum dose of study drug per Table 4. Subjects may also be terminated from the Core Phase and directly enrolled into the Extension Phase after 7 days of therapy at the maximum dose if they have dangerously low platelet counts (in the opinion of the Investigator), or
- Subjects who require rescue therapy more than 3 times or continuous rescue therapy for more than 3 weeks (Section 8.6).

6 SELECTION AND EARLY TERMINATION OF SUBJECTS

The following criteria for enrollment must be met to be eligible for the study. The Investigator or other study site personnel must document in the source documents that the informed consent form (ICF) and/or assent form, as required by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), was signed and dated prior to any study procedures being performed. The date informed consent/assent was obtained will also be recorded in the eCRF.

6.1 Inclusion and Exclusion Criteria for the Core Phase

6.1.1 Inclusion Criteria

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

1. Male or female subjects ≥1 and <18 years of age at Screening and Baseline.
2. Subject and/or subject's LAR must be able to provide informed consent and/or assent, as applicable.
3. Subject has a confirmed diagnosis of primary ITP according to the International Consensus Report on the Investigation and Management of Primary ITP (Provan, 2019) for ≥6 months duration and has had an insufficient response to a previous treatment, in the opinion of the Investigator.
4. Subject has an average of 2 platelet counts $<30\times10^9$/L with no single count $>35\times10^9$/L.

   The platelet count obtained at the Screening Visit/Visit 1 and 1 other platelet count taken within 28 days on either side of the Screening Visit (may use a historical value collected per standard of care if within 28 days of Screening) will be averaged to obtain the study eligibility platelet count value, which must be $<30\times10^9$/L. The 2 samples must be obtained ≥24 hours and ≤28 days apart and the results must be available prior to randomization.
5. Subjects being treated chronically with corticosteroids or azathioprine/6-mercaptopurine must be receiving a stable dose for at least 30 days prior to Day 1/Visit 2 or must have completed these therapies more than 30 days prior to Day 1/Visit 2.
6. Subjects being treated with mycophenolate mofetil (MMF), cyclosporine (CsA), sirolimus, or danazol must be receiving a stable dose for at least 90 days prior to Day 1/Visit 2 or must have completed these therapies more than 30 days prior to Day 1/Visit 2.
7. Previous therapy for ITP with immunoglobulins (IVIg and anti-D) or corticosteroid rescue therapy must have been completed at least 14 days prior to Day 1/Visit 2.
8. Cyclophosphamide and vinca alkaloid regimens must have been completed at least 30 days prior to Day 1/Visit 2.
9. Splenectomy and rituximab must have been completed at least 90 days prior to Day 1/ Visit 2.
10. Previous therapy with any other TPO-RAs (e.g., eltrombopag or romiplostim) or recombinant human TPO must have been completed 28 days prior to Day 1/Visit 2.
11. Previous therapy with vitamin K antagonists, antifibrinolytic agents, recombinant activated factor VII, heparin, factor Xa inhibitors, direct thrombin inhibitors, desmopressin, or chronic antiplatelet therapy must have been completed within 7 days of Day 1/Visit 2.

12. Previous therapy with moderate or strong dual inducers or moderate or strong dual inhibitors of CYP2C9 and CYP3A4 must have been completed within 7 days of Day1/Visit 2 (Appendix D).
13. Platelet transfusion, or receipt of blood products containing platelets must have been completed within 7 days of Day 1/Visit 2. Packed red blood cells (RBCs) are permitted.
14. Females of childbearing potential must have a negative urine or serum pregnancy test at Screening and Day 1/Visit 2 and must not be breastfeeding.
15. Female subjects of childbearing potential and who are sexually active and male subjects who are sexually active must agree to use highly effective methods of contraception.
16. Subject and/or subject's LAR is willing and able to comply with all aspects of the protocol.

6.1.2 Exclusion Criteria

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

1. Known secondary ITP.
2. Body Mass Index (BMI) >30 kg/m^2 or >95% for age.
3. Any history of arterial or venous thrombosis, including partial or complete thrombosis.
4. Subjects with known inherited thrombocytopenia (e.g., MYH-9 disorders).
5. History of myelodysplastic syndrome (MDS).
6. Known history of congenital heart abnormalities or arrhythmias.
7. History of hepatitis B (HBV), hepatitis C (HCV), or human immunodeficiency virus (HIV).
8. Known history of disseminated intravascular coagulation (DIC), hemolytic uremic syndrome (HUS), or thrombotic thrombocytopenic purpura (TTP).
9. Subjects with Evans syndrome.
10. Concurrent malignant disease or previous history of myeloid hematologic malignancies.
11. Hemoglobin (Hgb) levels ≤9 g/dL in ages ≥1 year to <6 years and ≤8 g/dL in ages ≥6 to <18 years.
12. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2.
13. Serum total bilirubin >1.5× the upper limit of normal (ULN) for age, alanine transaminase (ALT) and aspartate aminotransferase (AST) >3× the ULN for age.
14. Known allergy to avatrombopag or any of its excipients.
15. Subject is unable to take oral medication, has a malabsorption syndrome, or has known hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption or any other uncontrolled gastrointestinal condition.
16. Enrollment in another clinical study with any investigational drug or device within 30 days of Day 1/Visit 2 (or 5 half-lives, whichever is longer); however, participation in observational studies within the previous 30 days is permitted.

17. Any clinically relevant abnormality which makes the subject unsuitable for participation in the study, in the opinion of the Investigator.
18. Considered unable or unwilling to comply with the study protocol requirements.

6.2 Inclusion and Exclusion Criteria for the Extension Phase

6.2.1 Inclusion Criteria

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

1. Subject and/or the LAR must provide consent and/or assent, as applicable, to continue into the open-label Extension Phase. The consent for the Extension Phase will be part of the consent for the Core Phase.
2. Completed 12 weeks of treatment in the Core Phase or discontinued the Core Phase early due to lack of treatment effects (see definition of lack of treatment effect in Section 5.3).
3. Female subjects of childbearing potential and who are sexually active and male subjects who are sexually active must agree to use highly effective methods of contraception (see Section 8.2).
4. Subject and/or the subject's LAR is willing and able to comply with all aspects of the protocol.

6.2.2 Exclusion Criteria

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

1. Significant safety or tolerability concerns with the subject's participation, in the opinion of the Investigator.
2. Subjects requiring the following drugs or procedures at the time of enrollment into the Extension Phase:
    - Rituximab
    - Other TPO-RAs
    - Splenectomy
    - Moderate or strong dual inducers or moderate or strong dual inhibitors of CYP2C9 and CYP3A4 (Appendix D).

6.3 Subject and Study Discontinuation

6.3.1 Screen Failures

Subjects and/or their LAR, as applicable, who sign and date the ICF and/or assent form, but who fail to meet all the inclusion criteria or meet any exclusion criteria for the Core Phase, are defined as a screen failure.

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

- ICF and/or assent form signature date

- Demographic information
- AEs that occur after signing the ICF and/or assent
- 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.

6.3.2 Early Termination

A subject may be early terminated from the Core Phase or the Extension Phase for any of the following reasons:

- A platelet count >250×10^9/L after 2 weeks of once weekly dosing for any age cohort.
- Subject or the subject's LAR, as applicable, wishes to withdraw consent/assent for any reason.
- Subject non-compliance or unwillingness to comply with the procedures required by the protocol.
- 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.
- Pregnancy.
- Requirement of a prohibited concomitant medication (Section 8).
- Investigator discretion.
- Sponsor request.
- Termination of the study by the Sponsor or a regulatory agency.

In addition, a subject may be early terminated from the Extension Phase if they have a platelet count <30×10^9/L after 3 weeks of once daily dosing at the cohort defined maximum dose.

Every effort should be made during the conduct of the study to limit the extent of missing data. Except for subjects who are being withdrawn from the Core Phase due to a lack of treatment effect (Section 5.3), subjects who prematurely discontinue the study drug should remain in the study for collection of data, unless the subject withdraws consent. If a subject is early terminated from the Core Phase of the study after the first dose of study drug, but prior to the end of the PK blood collection (Visit 12/Week 10), consideration should be given to collecting all remaining PK blood draws, if possible.

If a subject is early terminated from the study after randomization, the Early Termination procedures (Section 9.3) should be performed. Subjects withdrawn from the study after randomization will not be replaced, regardless of the reason for withdrawal.

7 STUDY TREATMENTS

7.1 Treatment Groups

The 12 week Core Phase of this Phase 3b study is randomized, double-blind, and placebo-controlled. At Day 1/Visit 2, subjects will be randomized in a 3:1 ratio to receive either avatrombopag or matching placebo.

The Extension Phase of this study is open-label therefore all subjects will receive avatrombopag.

7.2 Randomization and Blinding

During Day 1/Visit 2 of the Core Phase, after study eligibility has been confirmed, randomization assignment will be performed using interactive response technology (IRT). Randomization will be stratified by age cohort. Subjects will also be stratified by a Baseline platelet count of $\leq 15\times10^9$/L or $>15\times10^9$/L to $<30\times10^9$/L in order to ensure treatment groups are approximately balanced. Following randomization, study drug will be dispensed in a double-blind manner. The Sponsor, the subject, and the clinical site personnel will be blinded to the treatment assignment.

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

7.3 Breaking the Blind

At the initiation of the study, the Investigator will be instructed on the method for breaking the blind during the Core Phase. The blind is not to be broken during the study unless considered necessary by the Investigator for emergency situations and/or for reasons of subject safety. Unblinding at the clinical site for any other reason will be considered a major protocol deviation. The Investigator should contact the Medical Monitor before breaking the blind, if possible. The reason for breaking the blind should be fully documented.

7.4 Drug Supplies

7.4.1 Labels and Packaging

7.4.1.1 Avatrombopag Film-Coated Oral Tablets or Matching Placebo

A sufficient supply of avatrombopag or placebo oral tablets 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 of avatrombopag) and excipients. Matching placebo tablets will also be provided for the Core Phase.

During the Extension Phase, avatrombopag film-coated oral tablets will be packaged in open-label packages.

The clinical site will dispense the number of tablets required for dosing each subject for a 30 day period (e.g., a monthly supply of thirty 20 mg tablets for a 20 mg daily dose).

7.4.1.2 Avatrombopag Powder for Oral Suspension in a Capsule or Matching Placebo

A sufficient supply of avatrombopag or placebo capsules, which can be opened to sprinkle the contents into an appropriate vehicle, will be provided to the clinical site. Each avatrombopag capsule

will contain avatrombopag maleate (equivalent to 10 mg avatrombopag) and excipients. Matching placebo capsules, containing the same excipients as the active capsules, will also be provided for the Core Phase.

During the Extension Phase, avatrombopag capsules will be packaged in open-label packages.

The clinical site will dispense the number of capsules required for dosing each subject for a 30 day period (e.g., a monthly supply of sixty 10 mg capsules for a 20 mg daily dose).

7.5 Avatrombopag Administration

Subjects will receive avatrombopag, or matching placebo, in the Core Phase, as either the film-coated oral tablet or the powder for oral suspension in a capsule that can be opened to sprinkle the powder for oral suspension into an appropriate vehicle. No partial dosing from the capsule is allowed; the entire contents of the capsule should be used.

During the Core Phase, subjects in Cohort 1 (aged ≥12 to <18 years) and Cohort 2 (aged ≥6 to <12 years) will receive the oral tablet and subjects in Cohort 3 (aged ≥1 to <6 years) will receive the powder for suspension in a capsule. The formulation received should be recorded in the eCRF.

Study drug will be taken by mouth, with food, and the first dose will be administered by the study team while the subject is at the site for Day 1/Visit 2 during the Core Phase. Palatability and acceptability of the powder for oral suspension will be assessed after the first dose of study drug during the Core Phase in subjects in Cohort 3 (Table 7; Appendix B).

Instructions for administration of the oral tablet and the powder for oral suspension in a capsule will be provided in a separate document.

The date and time of administration of each dose of study drug (administered at home or in-clinic) should be recorded by the subject, or the subject's LAR, on the provided Dosing Diary.

7.6 Receipt of Supplies

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

7.7 Study Drug Storage Conditions

Study drug should be stored in a secure location at a controlled room temperature of 20°C to 25°C (68°F to 77°F) and protected from light and moisture. The storage location must be a locked room with limited access, available to appropriate study personnel only.

7.8 Treatment Compliance

The first dose of study drug will be taken while the subject is at the site during Day 1/Visit 2. During this visit, subjects and/or their caregiver, as applicable, will be provided with instructions on appropriate at-home study drug administration.

Regardless of the subject's current treatment regimen (once daily, three times a week, etc.) Visit 4 and Visit 12 must fall on a day the subject is scheduled to take their dose of study drug. During Visit 4 (Week 2) and Visit 12 (Week 10) subjects will receive the dose of study drug while at the site after

the pre-dose PK sample has been collected (Section 9.6). Administration date and time, including the vehicle and the volume of the vehicle used with the powder for oral suspension, will be documented in the eCRF.

When taking study drug at home, subjects and/or the subject's LAR should record the date and time of each dose of study drug, as well as the vehicle and volume of vehicle used for ingestion of the powder for oral suspension, as applicable, in the provided Dosing Diary.

Study personnel should review the Dosing Diary at applicable visits (Appendix A) to ensure accuracy of the entries on the diary.

7.9 Study Drug Accountability

The Sponsor will provide the Investigators with sufficient amounts of study drug for this study. 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. The study team should perform a count of unused study drug returned from the subject at the frequency defined in the Core Phase and the Extension Phase Schedule of Events in Table 7 and Table 8.

7.10 Study Drug 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 study drug should be returned or destroyed at the investigational site. It is the Investigator's responsibility to ensure that the Sponsor or its designee has provided written authorization for proper disposal of study drug, and that appropriate records of the disposal are documented and maintained. No unused study drug may be disposed of until fully accounted for by the Sponsor, or designee.

8 PRIOR AND CONCOMITANT MEDICATIONS AND/OR PROCEDURES

8.1 Documentation of Prior and Concomitant Medications

All concomitant medications (including concurrent therapies and concurrent procedures) will be documented from the time of informed consent/assent through study discharge in the source documents and the eCRF. Dose, frequency, indication for administration, and dates of medication administration will be captured for all medications taken within 90 days of Screening.

8.2 Contraception Requirements

For this study, a woman is considered of childbearing potential, i.e. fertile, following menarche unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

- Females of childbearing potential who are sexually active must agree to use highly effective methods of birth control (i.e., oral or injectable contraceptive in combination with a second method, contraceptive implant, indwelling intrauterine device (IUD), or a vasectomized partner) while participating in the study and for 30 days after the last dose of study drug.
- Males who are sexually active must agree that their female partner has had a bilateral tubular occlusion or agree to use a male condom plus spermicide combined with female diaphragm plus spermicide while participating in the study and for 30 days after the last dose of study drug.
- Sexual abstinence is acceptable as an effective method of birth control only as true abstinence: when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

8.3 Permitted ITP Concomitant Background Medications

The following medications are permitted as concomitant background medications as long as they are taken at a stable dose for the specified amount of time prior to Day 1/Visit 2. The dose/frequency as well as any dose changes must be recorded in the eCRF.

- Corticosteroids or azathioprine/6-mercaptopurine taken at a stable dose for at least 30 days before Day 1/Visit 2.
- MMF, CsA, sirolimus, or danazol taken at a stable dose for at least 90 days before Day 1/ Visit 2.

8.4 Concomitant ITP Medication Dose Reduction

Any permitted concomitant ITP medications taken at Day 1/Visit 2 by the subject during the Core Phase may be down titrated in order to maintain the subject's platelet count between $\geq 50\times10^9$/L and $\leq 150\times10^9$/L. Downward concomitant ITP medication titration will be at the discretion of the Investigator, all dose changes must be recorded in the eCRF.

8.5 Prohibited Medications and/or Procedures

The following medications and/or procedures are prohibited:

- Immunoglobulins (IVIg and anti-D) are prohibited during the study unless needed as a rescue therapy (Section 8.6). Immunoglobulins must have been completed at least 14 days prior to Day 1/Visit 2.
- Platelet transfusion, or receipt of blood products containing platelets, within 7 days of Day 1/Visit 2 and during the study unless needed as a rescue therapy (Section 8.6). Packed RBCs are permitted.
- Cyclophosphamide and vinca alkaloid regimens must have been completed at least 30 days prior to Day 1/Visit 2.
- Splenectomy and rituximab must have been completed at least 90 days prior to Day 1/ Visit 2.
- Use of other TPO-RAs (e.g., eltrombopag or romiplostim) or recombinant human TPO within 28 days prior to Day 1/Visit 2 and during the study.
- Use of vitamin K antagonists, antifibrinolytic agents, recombinant activated factor VII, heparin, factor Xa inhibitors, direct thrombin inhibitors, desmopressin, or chronic antiplatelet therapy (>30 days) during the study.
- Previous therapy with moderate or strong dual inducers or moderate or strong dual inhibitors of CYP2C9 and CYP3A4 must have been completed within 7 days of Day 1/Visit 2 (Appendix D).
- Enrollment in another clinical study with any investigational drug or device within 30 days of Screening or during the study; however, participation in observational studies within the previous 30 days is permitted.

8.6 Rescue Therapies

Subjects may receive rescue therapy at the discretion of the Investigator if there is an urgent need to increase platelet count, such as in the case of life-threatening thrombocytopenia, in the opinion of the Investigator, clinical signs and symptoms suggesting a potential bleed (e.g., wet purpura) or a major bleed. All rescue medications, including dose and frequency, must be recorded on the eCRF.

Rescue therapy may include:

- The addition of any ***new*** ITP medication or medication to treat thrombocytopenia, such as:
  - Corticosteroids
  - IVIg
  - Anti-D
  - Platelet transfusion
- Any ***increase in the Day 1/Visit 2 dose*** of a concomitant ITP medication.
- TPO-RAs are not allowed as rescue therapy.

9 STUDY ASSESSMENTS AND PROCEDURES

A schedule of events in tabular format is provided for the Core Phase in Table 7 and for the Extension Phase in Table 8 in Appendix A.

9.1 Core Phase

9.1.1 Informed Consent/Assent

As AVA-PED-301 is enrolling adolescents and children as subjects, the study site should follow the guidelines from their respective IRB/IEC to determine the requirements for parental/LAR consent and child assent.

The ICF/assent form must be signed and dated prior to the initiation of study-related assessments, and prior to administration of study drug. The original signed ICF/assent form for each participating subject will be filed with records kept by the Investigator. A copy of the ICF/assent form must be provided to the subject and/or the subject's LAR, as applicable.

9.1.2 Screening (Visit 1/Day -28 to -1)

The Screening Visit must be completed within 28 days of Day 1/Visit 2.

The following procedures will be performed at the Screening Visit.

- Collect signed and dated informed consent/assent prior to any study procedures.
- Review of inclusion/exclusion criteria (Section 6.1) to confirm study eligibility.
- Record subject demographic information.
- Record medical/medication/surgical history to include all past significant illnesses and/or surgeries (in the opinion of the Investigator) and all medications taken (including non-prescription medications, vitamins, dietary supplements, and herbal products) within the past 90 days.
- Record ITP history, including date of diagnosis and any concomitant ITP medications.
- Collect height and weight to determine BMI (calculated by eCRF).
- Perform abbreviated physical exam (PE). The abbreviated PE will consist of the following: general appearance, head, neck, eyes, ears, nose, throat, chest, lungs, heart, abdomen, extremities, joints, lymph nodes, and neurology.
- Collect vital signs (blood pressure, heart rate, and temperature). Vital signs should be taken after sitting for 5 minutes, whenever possible, and prior to any blood draws.
- Collect blood for clinical laboratory tests to assess study eligibility as outlined in Section 6 (see details in Section 9.5 and Core Phase Schedule of Events, Table 7).
    - Local laboratories may be used to confirm study eligibility, however, for study analysis and reporting purposes, only values determined at a central laboratory will be used with the exception of platelet count (Section 9.5).
- Collect blood for platelet count (local laboratory).

- The platelet count obtained at the Screening Visit/Visit 1 and 1 other platelet count taken within 28 days on either side of the Screening Visit (may use a historical value collected per standard of care if within 28 days of Screening) will be averaged to obtain the study eligibility platelet count value, which must be $<30\times10^9$/L. The 2 samples must be obtained ≥24 hours and ≤28 days apart and the results must be available prior to randomization.

- Perform urine or serum pregnancy test for female subjects of childbearing potential. The pregnancy test may be performed locally.
- Review and record AEs that may have occurred after signing informed consent/assent.
- Discharge subject from clinic with instructions for when to return for Day 1/Visit 2.

9.1.3 Baseline (Visit 2 [Day 1])

Visit 2 should take place within 28 days of the Screening Visit. The first dose of study drug will be administered in clinic during this visit.

The following procedures will be performed at Day 1/Visit 2:

Prior to Dosing with Study Drug:

- Review of inclusion/exclusion criteria (Section 6.1) to confirm continued study eligibility.
- Perform WHO Bleeding Scale Assessment (Appendix C). The Investigator should ask the subject and/or the subject's parent/caregiver the following question: "Have you had any bleeding or bruising within the last 7 days?". This assessment should be completed prior to other visit assessments.
- Update subject demographic information, including age, if applicable.
- Review and document in the eCRF any changes since Screening to medical/medication/surgical history (including non-prescription medications, vitamins, dietary supplements, and herbal products).
- Review and document in the eCRF any changes since Screening to ITP history, including concomitant ITP medications.
- Collect weight to determine BMI (calculated by eCRF).
- Perform abbreviated PE. The abbreviated PE will consist of the following: general appearance, head, neck, eyes, ears, nose, throat, chest, lungs, heart, abdomen, extremities, joints, lymph nodes, and neurology.
- Collect vital signs (blood pressure, heart rate, and temperature). Vital signs should be taken after sitting for 5 minutes, whenever possible, and prior to any blood draws.
- Collect blood for clinical laboratory tests to assess study eligibility as outlined in Section 6.1 (see details in Section 9.5 and Schedule of Events, Table 7).
- Collect blood for platelet count (local laboratory).
    - The platelet count obtained at the Screening Visit/Visit 1 and 1 other platelet count taken within 28 days on either side of the Screening Visit (may use a historical value collected per standard of care if within 28 days of Screening) will be averaged to

obtain the study eligibility platelet count value, which must be $<30\times10^9$/L. The 2 samples must be obtained ≥24 hours and ≤28 days apart and the results must be available prior to randomization.

- If the Visit 2 platelet count will not be 1 of the 2 platelet counts used to determine study eligibility, it should still be collected and the result recorded in the eCRF.

- Perform urine or serum pregnancy test for female subjects of childbearing potential. The pregnancy test may be performed locally.
- Randomize subject in the IRT system.
- If subject is in Cohort 3, randomize in the IRT system to the PK timepoint to be drawn at Visit 4 (Week 2) and Visit 12 (Week 10).
- After all previous assessments have been completed, administer study drug in the clinic, with food, at the dose and formulation described in Section 1.1.5.

After Dosing with Study Drug:

- Record date and time of the dose of study drug as well as the vehicle (including volume) used with the powder for oral suspension, if applicable, on the Dosing Diary.
- Administer Palatability Questionnaire within 2 minutes after the dose of study drug (Appendix B) to subjects in Cohort 3 who received the powder for oral suspension formulation and the Acceptability Questionnaire to their parent/caregiver.
- Collect vital signs (blood pressure, heart rate, and temperature) 30 minutes (±15 minutes) after dosing with study drug. Vital signs should be taken after sitting for 5 minutes, whenever possible, and prior to any blood draws.
- Dispense remaining 1-month supply of study drug for the subject to take at-home with instructions for administration.
- Dispense new Dosing Diary for the subject to take home with instructions for completion.
- Record any AEs.
- Review and record any concomitant medications, including any modifications to or new concomitant ITP medications.
- Discharge subject from clinic with instructions for when to return for Visit 3.

9.1.4 Visit 3 (Week 1; Day 8 ±1 Day)

The following assessments will be performed during Visit 3:

- Perform WHO Bleeding Scale Assessment (Appendix C). The Investigator should ask the subject and/or the subject's parent/caregiver 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 vital signs (blood pressure, heart rate, and temperature). Vital signs should be taken after sitting for 5 minutes, whenever possible, and prior to any blood draws
- Collect blood for platelet count (local laboratory).

- Collect blood for sparse PK sample (Section 9.6) and record date/time of the last dose of study drug in the eCRF.
- Review study drug administration and Dosing Diary completion with the subject and/or the subject's caregiver.
- Record any AEs.
- Review and record any concomitant medications, including any modifications to or new concomitant ITP medications.
- Discharge subject from clinic with instructions for when to return for Visit 4.

9.1.5 Visit 4 (Week 2; Day 15 ±1 Day)

Regardless of the subject's current treatment regimen (once daily, three times weekly, etc.) Visit 4 must fall on a day the subject is scheduled to take their dose of study drug. **Note:** serial PK sampling may need to occur at a visit later than Visit 4 if study drug was held or if the dose changed; see Section 9.6. Study drug will be administered in the clinic during this visit and subjects in Cohort 1 and Cohort 2 should plan to remain in the clinic for 10 to 12 hours after study drug administration to allow for collection of the serial PK blood samples. Subjects in Cohort 3 should plan to remain in the clinic for 6 to 8 hours or 10 to 12 hours, depending on the timepoint they were randomized to during Day 1/Visit 2.

The following procedures will be performed during Visit 4:

Prior to Dosing with Study Drug:

- Perform WHO Bleeding Scale Assessment (Appendix C). The Investigator should ask the subject and/or the subject's parent/caregiver 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 vital signs (blood pressure, heart rate, and temperature). Vital signs should be taken after sitting for 5 minutes, whenever possible, and prior to any blood draws.
- Collect blood for platelet count (local laboratory) and assess need for study drug dose titration per Table 3.
- Collect blood for the pre-dose serial PK sample (Section 9.6). Record date/time of the last dose of study drug in the eCRF.
- After all previous assessments are completed, administer study drug in the clinic, with food, at the dose and formulation described in Section 1.1.5.

After Dosing with Study Drug:

- Record date and time of the dose of study drug as well as the vehicle (including volume) used with the powder for oral suspension, if applicable, on the Dosing Diary.
- Collect blood for the post-dose serial PK sample at 2 to 4 hours, 6 to 8 hours (if applicable based on the subject's Cohort), and 10 to 12 hours (if applicable based on the subject's Cohort) (Section 9.6).

- Review study drug administration and Dosing Diary completion with the subject and/or the subject's caregiver.
- Record any AEs.
- Review and record any concomitant medications, including any modifications to or new concomitant ITP medications.
- Discharge subject from clinic with instructions for when to return for Visit 5.

9.1.6 Visit 5 (Week 3; Day 22 ±1 Day)

- Perform WHO Bleeding Scale Assessment (Appendix C). The Investigator should ask the subject and/or the subject's parent/caregiver 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 vital signs (blood pressure, heart rate, and temperature). Vital signs should be taken after sitting for 5 minutes, whenever possible, and prior to any blood draws.
- Collect blood for platelet count (local laboratory) and assess need for study drug dose titration per Table 3.
- Collect blood for sparse PK sample (Section 9.6) and record date/time of the last dose of study drug in the eCRF.
- Review study drug administration and Dosing Diary completion with the subject and/or the subject's caregiver.
- Record any AEs.
- Review and record any concomitant medications, including any modifications to or new concomitant ITP medications.
- Discharge subject from clinic with instructions for when to return for Visit 6.

9.1.7 Visit 6 (Week 4; Day 29 ±1 Day)

The following assessments will be performed during Visit 6:

- Perform WHO Bleeding Scale Assessment (Appendix C). The Investigator should ask the subject and/or the subject's parent/caregiver 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 weight.
- Perform abbreviated PE. The abbreviated PE will consist of the following: general appearance, head, neck, eyes, ears, nose, throat, chest, lungs, heart, abdomen, extremities, joints, lymph nodes, and neurology
- Collect vital signs (blood pressure, heart rate, and temperature). Vital signs should be taken after sitting for 5 minutes, whenever possible, and prior to any blood draws.
- Collect blood for clinical laboratory tests (e.g., serum chemistry, hematology [Table 7]).

- Collect blood for platelet count (local laboratory) and assess need for study drug dose titration per Table 3.
- Collect blood for sparse PK sample (Section 9.6) and record date/time of the last dose of study drug in the eCRF.
- Perform urine or serum pregnancy test for female subjects of childbearing potential. The pregnancy test may be performed locally.
- Retrieve unused study drug and record compliance in the eCRF.
- Review study drug administration and Dosing Diary completion with the subject and/or the subject's caregiver.
- Dispense new Dosing Diary for the subject to take home with instructions for completion.
- Dispense 1-month supply of study drug for the subject to take at-home with instructions for administration.
- Record any AEs.
- Review and record any concomitant medications, including any modifications to or new concomitant ITP medications.
- Discharge subject from clinic with instructions for when to return for Visit 7.

9.1.8 Visit 7 (Week 5; Day 36 ± 1 Day)

The following assessments will be performed during Visit 7:

- Perform WHO Bleeding Scale Assessment (Appendix C). The Investigator should ask the subject and/or the subject's parent/caregiver 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 blood for platelet count (local laboratory) and assess need for study drug dose titration per Table 3.
- Collect blood for sparse PK sample (Section 9.6) and record date/time of the last dose of study drug in the eCRF.
- Review study drug administration and Dosing Diary completion with the subject and/or the subject's caregiver.
- Record any AEs.
- Review and record any concomitant medications, including any modifications to or new concomitant ITP medications.
- Discharge subject from clinic with instructions for when to return for Visit 8.

9.1.9 Visit 8 (Week 6; Day 43 ± 1 Day)

The following assessments will be performed during Visit 8:

- Perform WHO Bleeding Scale Assessment (Appendix C). The Investigator should ask the subject and/or the subject's parent/caregiver 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 vital signs (blood pressure, heart rate, and temperature). Vital signs should be taken after sitting for 5 minutes, whenever possible, and prior to any blood draws.
- Collect blood for platelet count (local laboratory) and assess need for study drug dose titration per Table 3.
- Collect blood for sparse PK sample (Section 9.6) and record date/time of the last dose of study drug in the eCRF.
- Review study drug administration and Dosing Diary completion with the subject and/or the subject's caregiver.
- Record any AEs.
- Review and record any concomitant medications, including any modifications to or new concomitant ITP medications.
- Discharge subject from clinic with instructions for when to return for Visit 9.

9.1.10 Visit 9 (Week 7; Day 50 ± 1 Day)

The following assessments will be performed during Visit 9:

- Perform WHO Bleeding Scale Assessment (Appendix C). The Investigator should ask the subject and/or the subject's parent/caregiver 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 blood for platelet count (local laboratory) and assess need for study drug dose titration per Table 3.
- Collect blood for sparse PK sample (Section 9.6) and record date/time of the last dose of study drug in the eCRF.
- Review study drug administration and Dosing Diary completion with the subject and/or the subject's caregiver.
- Record any AEs.
- Review and record any concomitant medications, including any modifications to ore new concomitant ITP medications.
- Discharge subject from clinic with instructions for when to return for Visit 10.

9.1.11 Visit 10 (Week 8; Day 57 ± 1 Day)

The following assessments will be performed during Visit 10:

- Perform WHO Bleeding Scale Assessment (Appendix C). The Investigator should ask the subject and/or the subject's parent/caregiver 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 weight.

- Perform abbreviated PE. The abbreviated PE will consist of the following: general appearance, head, neck, eyes, ears, nose, throat, chest, lungs, heart, abdomen, extremities, joints, lymph nodes, and neurology
- Collect vital signs (blood pressure, heart rate, and temperature). Vital signs should be taken after sitting for 5 minutes, whenever possible, and prior to any blood draws.
- Collect blood for clinical laboratory tests (e.g., serum chemistry, hematology [Table 7]).
- Collect blood for platelet count (local laboratory) and assess need for study drug dose titration per Table 3.
- Collect blood for sparse PK sample (Section 9.6) and record date/time of the last dose of study drug in the eCRF.
- Perform urine or serum pregnancy test for female subjects of childbearing potential. The pregnancy test may be performed locally.
- Retrieve unused study drug and record compliance in the eCRF.
- Review study drug administration and Dosing Diary completion with the subject and/or the subject's caregiver.
- Dispense new Dosing Diary for the subject to take home with instructions for completion.
- Dispense 1-month supply of study drug for the subject to take at-home with instructions for administration.
- Record any AEs.
- Review and record any concomitant medications, including any modifications to or new concomitant ITP medications.
- Discharge subject from clinic with instructions for when to return for Visit 11.

9.1.12 Visit 11 (Week 9; Day 64 ± 1 Day)

The following assessments will be performed during Visit 11:

- Perform WHO Bleeding Scale Assessment (Appendix C). The Investigator should ask the subject and/or the subject's parent/caregiver 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 blood for platelet count (local laboratory) and assess need for study drug dose titration per Table 3.
- Collect blood for sparse PK sample (Section 9.6) and record date/time of the last dose of study drug in the eCRF.
- Review study drug administration and Dosing Diary completion with the subject and/or the subject's caregiver.
- Record any AEs.
- Review and record any concomitant medications, including any modifications to or new concomitant ITP medications.

- Discharge subject from clinic with instructions for when to return for Visit 12.

9.1.13 Visit 12 (Week 10; Day 71 ± 1 Day)

Regardless of the subject's current treatment regimen (once daily, three times weekly, etc.) Visit 12 must fall on a day the subject is scheduled to take their dose of study drug. **Note:** serial PK sampling may need to occur at a visit later than Visit 12 if study drug was held or if the dose changed; see Section 9.6. Study drug will be administered in the clinic during Visit 12. Subjects in Cohort 1 and Cohort 2 should plan to remain in the clinic for 10 to 12 hours after study drug administration to allow for collection of the serial PK blood samples. Subjects in Cohort 3 should plan to remain in the clinic for 6 to 8 hours or 10 to 12 hours, depending on the timepoint they were randomized to during Day 1/Visit 2.

The following procedures will be performed during Visit 12:

Prior to Dosing with Study Drug:

- Perform WHO Bleeding Scale Assessment (Appendix C). The Investigator should ask the subject and/or the subject's parent/caregiver 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 vital signs (blood pressure, heart rate, and temperature). Vital signs should be taken after sitting for 5 minutes, whenever possible, and prior to any blood draws.
- Collect blood for platelet count (local laboratory) and assess need for study drug dose titration per Table 3.
- Collect blood for the pre-dose serial PK sample (Section 9.6). Record date/time of the last dose of study drug in the eCRF.
- After all previous assessments are completed, administer study drug in the clinic, with food, at the dose and formulation listed Section 1.1.5.

After Dosing with Study Drug:

- Record date and time of the dose of study drug as well as the vehicle (including volume) used with the powder for oral suspension, if applicable, on the Dosing Diary.
- Collect blood for the post-dose serial PK sample at 2 to 4 hours, 6 to 8 hours (if applicable based on the subject's Cohort), and 10 to 12 hours (if applicable based on the subject's Cohort) (Section 9.6).
- Review study drug administration and Dosing Diary completion with the subject and/or the subject's caregiver.
- Record any AEs.
- Review and record any concomitant medications, including any modifications to or new concomitant ITP medications.
- Discharge subject from clinic with instructions for when to return for Visit 13.

9.1.14 Visit 13 (Week 11; Day 78 ± 1 Day)

The following assessments will be performed during Visit 13:

- Perform WHO Bleeding Scale Assessment (Appendix C). The Investigator should ask the subject and/or the subject's parent/caregiver 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 blood for platelet count (local laboratory) and assess need for study drug dose titration per Table 3.
- Review study drug administration and Dosing Diary completion with the subject and/or the subject's caregiver.
- Record any AEs.
- Review and record any concomitant medications, including any modifications to concomitant ITP medications.
- Discharge subject from clinic with instructions for when to return for Visit 14.

9.1.15 Visit 14 (Core Phase - Week 12; Day 85 ± 1 Day)/Visit E-1 (Extension Phase)

For subjects who **are** continuing into the Extension Phase, Visit 14 will serve as the last visit in the Core Phase as well as the first visit in the Extension Phase (Visit E-1).

Procedures to Complete during Visit 14/Visit E-1 if the Subject is Continuing into the Open-label Extension Phase:

- Collect signed and dated informed consent/assent for the Extension Phase prior to any study procedures. The ICF/assent for the Extension Phase may be part of the ICF/assent for the Core Phase.
- Review of inclusion/exclusion criteria (Section 6.2) to confirm continued study eligibility.
- Perform WHO Bleeding Scale Assessment (Appendix C). The Investigator should ask the subject and/or the subject's parent/caregiver 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 height and weight to determine BMI (calculated by eCRF).
- Perform abbreviated PE. The abbreviated PE will consist of the following: general appearance, head, neck, eyes, ears, nose, throat, chest, lungs, heart, abdomen, extremities, joints, lymph nodes, and neurology.
- Collect vital signs (blood pressure, heart rate, and temperature). Vital signs should be taken after sitting for 5 minutes, whenever possible, and prior to any blood draws.
- Perform urine or serum pregnancy test for female subjects of childbearing potential. The pregnancy test may be performed locally.
- Collect blood for clinical laboratory tests (e.g., serum chemistry, hematology [Table 7]).
- Collect blood for platelet count (local laboratory).
- Determine appropriate Extension Phase starting dose of open-label avatrombopag per the instructions in Section 1.1.6.

- Retrieve unused study drug from the Core Phase and record compliance in the eCRF.
- Dispense new Dosing Diary for the subject to take home with instructions for completion.
- Dispense 1-month supply of open-label avatrombopag for the subject to take at-home with instructions for administration.
- Review study drug administration and Dosing Diary completion with the subject and/or the subject's caregiver.
- Record any AEs.
- Review and record any concomitant medications, including any modifications to or new concomitant ITP medications.
- Discharge subject from clinic with instructions for when to return for Visit E-2/Month 2 (Section 9.1.19).

For subjects who are **not** continuing into the Extension Phase, Visit 14 should be completed and Visit 15 (Section 9.1.16) will be the last study visit.

Procedures to Complete during Visit 14/Visit E-1 if the Subject is NOT Continuing into the Open-label Extension Phase:

- Perform WHO Bleeding Scale Assessment (Appendix C). The Investigator should ask the subject and/or the subject's parent/caregiver 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.
- Perform abbreviated PE. The abbreviated PE will consist of the following: general appearance, head, neck, eyes, ears, nose, throat, chest, lungs, heart, abdomen, extremities, joints, lymph nodes, and neurology.
- Collect height and weight to determine BMI (calculated by eCRF).
- Collect vital signs (blood pressure, heart rate, and temperature). Vital signs should be taken after sitting for 5 minutes, whenever possible, and prior to any blood draws.
- Collect blood for clinical laboratory tests (e.g., serum chemistry, hematology [Table 7]).
- Collect blood for platelet count (local laboratory).
- Perform urine or serum pregnancy test for female subjects of childbearing potential. The pregnancy test may be performed locally.
- Retrieve unused study drug and record compliance in the eCRF.
- Record any AEs.
- Review and record any concomitant medications, including any modifications to or new concomitant ITP medications.
- Discharge subject from clinic with instructions for when to return for Visit 15.

9.1.16 Visit 15/End of Study – Core Phase

The End of Study Visit/Visit 15 will be conducted 30 days (± 7 days) after Visit 14 and should only be completed by subjects who are **not** continuing into the Extension Phase.

The following assessments will be performed during Visit 15:

- Perform WHO Bleeding Scale Assessment (Appendix C). The Investigator should ask the subject and/or the subject's parent/caregiver 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.
- Perform abbreviated PE. The abbreviated PE will consist of the following: general appearance, head, neck, eyes, ears, nose, throat, chest, lungs, heart, abdomen, extremities, joints, lymph nodes, and neurology.
- Collect vital signs (blood pressure, heart rate, and temperature). Vital signs should be taken after sitting for 5 minutes, whenever possible, and prior to any blood draws.
- Collect blood for clinical laboratory tests (e.g., serum chemistry, hematology [Table 7]).
- Collect blood for platelet count (local laboratory).
- Perform urine or serum pregnancy test for female subjects of childbearing potential. The pregnancy test may be performed locally.
- Record any AEs.
- Review and record any concomitant medications, including any modifications to concomitant ITP medications.
- Discharge subject from the study.

9.2 Extension Phase

9.2.1 Informed Consent/Assent

An ICF/assent form for the Extension Phase of the study must be signed and dated prior to the initiation of study-related assessments, and prior to administration of avatrombopag in the Extension Phase. The original signed ICF/assent form for each participating subject will be filed with records kept by the Investigator. A copy of the ICF/assent form must be provided to the subject and/or the subject's LAR, as applicable. The ICF/assent form for the Extension Phase may be part of the ICF/assent form for the Core Phase.

9.2.2 Visit E-1

For subjects who are participating in the Extension Phase, Visit E-1 will serve as the first visit of the Extension Phase and the last Visit of the Core Phase (Visit 14). See Section 9.1.15 for procedures that are to be completed during Visit E-1 of the Extension Phase.

9.2.3 Visit E-2 through Visit E-24

Remaining monthly visits during the Extension Phase (Visit E-2 through Visit E-24) should be conducted approximately every 30 days (±7 days).

The following assessments will be performed during each monthly visit, unless otherwise noted:

- Perform WHO Bleeding Scale Assessment (Appendix C). 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 weight.
- Perform abbreviated PE. The abbreviated PE will consist of the following: general appearance, head, neck, eyes, ears, nose, throat, chest, lungs, heart, abdomen, extremities, joints, lymph nodes, and neurology. *The abbreviated PE should occur every 3 months while the subject is enrolled in the Extension Phase (e.g., during Visit E-4, Visit E-7, Visit E-10, Visit E-13, Visit E-16, Visit E-19, and Visit E-22).*
- Collect blood for platelet count (local laboratory) and assess need for study drug dose titration per Table 3. **Note: Platelet counts are to be assessed weekly during the Extension Phase until the subject is determined to be on a stable dose of avatrombopag. Record weekly visits, dose changes, and platelet counts on the eCRF.**
- Perform urine or serum pregnancy test for female subjects of childbearing potential. The pregnancy test may be performed locally and only needs to be performed every 3 months. *The pregnancy test should occur only during Visit E-3, Visit E-6, Visit E-9, Visit E-12, Visit E-15, Visit E-18, Visit E-21, and Visit E-24.*
- Retrieve unused study drug and record compliance in the eCRF.
- Dispense Dosing Diary for the subject to take home with instructions for completion.
- Review study drug administration with the subject and/or the subject's caregiver. *Administer study drug in clinic during Visit E-6, Visit E-12, and Visit E-18 in order to confirm proper administration technique.*
- Dispense 1-month supply of study drug for the subject to take at-home with instructions for administration during Visit E-2 through Visit E-24.
- Record any AEs.
- Review and record any concomitant medications, including any modifications to concomitant ITP medications.
- Discharge subject from clinic with instructions for when to return for the next clinic visit.

9.2.4 Visit E-25/End of Study Visit – Extension Phase

The Extension Phase End of Study Visit should be performed 30 days (±7 days) after Visit E-24.

The following assessments will be performed during the Extension Phase End of Study Visit.

- Perform WHO Bleeding Scale Assessment (Appendix C). 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.
- Perform abbreviated PE. The abbreviated PE will consist of the following: general appearance, head, neck, eyes, ears, nose, throat, chest, lungs, heart, abdomen, extremities, joints, lymph nodes, and neurology.

- Collect vital signs (blood pressure, heart rate, and temperature). Vital signs should be taken after sitting for 5 minutes, whenever possible, and prior to any blood draws.
- Collect blood for platelet count (local laboratory).
- Perform urine or serum pregnancy test for female subjects of childbearing potential. The pregnancy test may be performed locally.
- Retrieve unused study drug and record compliance in the eCRF.
- Record any AEs.
- Review and record any concomitant medications, including any modifications to concomitant ITP medications.
- Discharge subject from the study.

9.3 Early Termination Assessments

Should the subject early terminate from the study, the following assessments should be performed if possible.

- Perform WHO Bleeding Scale Assessment (Appendix C). The Investigator should ask the subject the following question: "Have you had any bleeding or bruising since I saw you last?".
- Perform abbreviated PE. The abbreviated PE will consist of the following: general appearance, head, neck, eyes, ears, nose, throat, chest, lungs, heart, abdomen, extremities, joints, lymph nodes, and neurology.
- Collect vital signs (blood pressure, heart rate, respiratory rate, and temperature). Vital signs should be taken after sitting for 5 minutes whenever possible and prior to any blood draw.
- Collect blood and urine for clinical laboratory tests (e.g., serum chemistry, hematology, and urine pregnancy test).
- Collect blood for platelet count (local laboratory).
- If a subject is early terminated from the study prior to the end of the PK blood draw collection in Visit 10 of the Core Phase, consideration should be given to collecting all remaining PK blood draws prior to discharging from the study.
- Record any AEs.
- Review and record any concomitant medications.
- Collect unused study drug and completed Dosing Diary.
- Discharge subject from study.

9.4 World Health Organization Bleeding Scale

Beginning with Visit 2 in the Core Phase, the Investigator should assess bleeding using the WHO Bleeding Scale (Appendix C) according to verbal responses and PE.

During Day 1/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?”.

9.5 Laboratory Examinations

Local laboratories may be used to determine study eligibility; however, for study analysis and reporting purposes, only values determined at a central laboratory will be used with the exception of platelet count. Platelet count analyses and pregnancy tests will be performed using local laboratory results. Local laboratories may also be used if immediate results are clinically needed.

With the exception of the above, all protocol-required laboratory assessments for the Core Phase and the Extension Phases of the study, as defined in Table 5, will be performed by a central laboratory and must be conducted in accordance with the central laboratory manual and the Schedule of Events in Table 7 and Table 8.

Repeat laboratory evaluations are allowed in cases where abnormal results are noted that are believed to be related to a potential laboratory error or a transient and/or reversible condition (e.g., clumped platelets or hemolyzed sample).

If serum chemistry, hematology, and PK blood draws are drawn from a single venous puncture, a total of 19 study-related blood draws over an approximately 90 day period are expected in the Core Phase, and 24 study-related blood draws over a 24 month period are expected in the Extension Phase.

Table 5 Clinical Laboratory Tests

Category	Parameters
Hematology	
Complete Blood Count	
Chemistry	
Electrolytes	Bicarbonate Chloride Potassium Sodium
Liver Function Tests	ALT AST Alkaline Phosphatase Total Bilirubin
Renal Function Tests	Blood Urea Nitrogen (BUN) eGFR
Other	Glucose
Females of Child-bearing Potential Only	
	Urine or Serum Pregnancy Test

9.5.1 Platelet Counts

Platelet count will be assessed in all subjects at all visits in the Core Phase and the Extension Phase of the study (Table 7 and Table 8). In order to be eligible for the Core Phase of the study, the subject must have an average of 2 platelet counts $<30\times10^9$/L with no single count $>35\times10^9$/L. The platelet count obtained at the Screening Visit/Visit 1 and 1 other platelet count taken within 28 days on either

side of the Screening Visit (may use a historical value collected per standard of care if within 28 days of Screening) will be averaged to obtain the study eligibility platelet count value, which must be $<30\times10^9$/L. The 2 samples must be obtained ≥24 hours and ≤28 days apart and the results must be available prior to randomization.

As subjects may continue from the Core Phase to the Extension Phase, there are no minimum platelet count requirements for the Extension Phase.

9.6 Pharmacokinetic Sampling

Plasma concentrations of avatrombopag during the Core Phase will be measured using a validated bioanalytical assay. Blood samples for the measurement of avatrombopag plasma concentrations will be collected as shown in Table 6.

Regardless of the subject's current treatment regimen (once daily, three times a week, etc.) the serial PK sampling at Visit 4 and Visit 12 must occur on a day the subject is scheduled to take their dose of study drug. If study drug has been held or the dosing regimen has changed within the past week, the serial PK samples should be collected at a visit later than Visit 4 or Visit 12. This is to ensure that serial PK samples will be obtained when the subject has been on a stable dose for at least 1 week.

Blood samples for serial PK assessments will be collected during Week 2 (Visit 4) and Week 10 (Visit 12) of the Core Phase. During these visits, subjects ≥6 years of age (Cohort 1 and Cohort 2) will have a blood sample drawn pre-dose and between 2 to 4 hours, 6 to 8 hours, and 10 to 12 hours post-dose (4 samples drawn at each visit, 2 mL each). Subjects <6 years of age (Cohort 3) will have a blood sample drawn pre-dose and at 2 to 4 hours post-dose but will be randomized in a 1:1 ratio, stratified by treatment group, to either the 6 to 8 hour or the 10 to 12 hour post-dose timepoint at Visit 4 (Week 2). The timepoint not drawn at Visit 4 (Week 2) will be drawn at Visit 12 (Week 10) (3 samples will be drawn at each visit, 2 mL each). For all age groups, blood samples for sparse PK assessments (2 mL each) will be collected while the subject is at the clinic during Visit 3 (Week 1) and at each visit during Visit 5 to Visit 11 (Week 3 to Week 9; 8 samples, 2 mL each). The date and time of each PK sample as well as the date and time of the previous dose of study drug will be recorded on the eCRF.

Table 6 Pharmacokinetic Sampling Schedule

Study Day	Sparse/Serial	Sampling Times
Visit 3/Week 1	Sparse	During clinic visit
Visit 4/Week 2	**Serial**	• **Pre-dose** • **Between 2 to 4 hours post-dose[a]** • **Between 6 to 8 hours post-dose[a]** • **Between 10 to 12 hours post-dose[a]**
Visit 5/Week 3	Sparse	During clinic visit
Visit 6/Week 4	Sparse	During clinic visit
Visit 7/Week 5	Sparse	During clinic visit
Visit 8/Week 6	Sparse	During clinic visit
Visit 9/Week 7	Sparse	During clinic visit
Visit 10/Week 8	Sparse	During clinic visit
Visit 11/Week 9	Sparse	During clinic visit
Visit 12/Week 10	**Serial**	• **Pre-dose** • **Between 2 to 4 hours post-dose[a]** • **Between 6 to 8 hours post-dose[a]** • **Between 10 to 12 hours post-dose[a]**

a: During Day 1/Visit 2, subjects in Cohort 3 (aged 1 to <6 years) will be randomized in a 1:1 ratio, stratified by treatment group, to either the 6 to 8-hour post-dose PK timepoint or the 10 to 12-hour post-dose PK timepoint during Visit 4/Week 2 and Visit 12/Week 10, to minimize the number of blood draws required during these visits. The timepoint not drawn during Visit 4/Week 2 will be drawn during Visit 12/Week 10.

10 SAFETY ASSESSMENTS

Safety assessments will include monitoring and recording of all AEs and SAEs, laboratory tests, vital signs, and physical examinations during the Core Phase and Extension Phase of the study.

10.1 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, whether or not related to the investigational medicinal product. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

AEs, which include clinical laboratory test variables, will be monitored and documented from the time of informed consent/assent until study participation is complete. Subjects should be instructed to report any AE that they experience to the Investigator. Beginning with the informed consent/assent 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/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 laboratory finding, or other abnormal assessment 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.

Clinically significant abnormal findings in PEs subsequent to study drug administration will be reported as AEs.

10.1.1 Method of Detecting Adverse Events and Serious Adverse Events

AEs will be reported by the subject (or, when appropriate, by a healthcare provider, caregiver, surrogate, or the subject's LAR). 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.

10.1.2 Assessment of Adverse Events by the Investigator

10.1.2.1 Severity

The severity of all AEs should be graded according to the Common Terminology Criteria for Adverse Events (CTCAE). Any AEs which are life-threatening or fatal meet the definition of SAEs (Section 10.3). For those AEs not listed in the CTCAE, the following grading system should be used:

- Mild (CTCAE Grade 1): Transient symptoms, awareness of sign/symptom, but easily tolerated and no interference with subject's daily activities.
- Moderate (CTCAE Grade 2): Marked signs/symptoms that interfere with subject's usual activities, but still acceptable.
- Severe (CTCAE Grade 3): Incapacitating signs/symptoms which cause considerable interference with the subject's daily activities, unacceptable.

10.1.2.2 Causality

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

- No (unrelated, not related, no relation) – The time course between the administration of study drug and the occurrence or worsening of the AE rules out a causal relationship and another cause (e.g., concomitant drugs, therapies, complications, etc.) is suspected.
- Yes (related) – The time course between the administration of study drug and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause (e.g., concomitant drugs, therapies, complications, etc.) can be identified.
    - The definition implies a reasonable possibility of a causal relationship between the event and the study drug. 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 study drug administration-
    - The event should occur after the study drug is given. The length of time from study drug 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 study drug-
    - 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 recipient and provide a logical and better explanation for the event.
- The pharmacology and PK of the study drug-
    - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

10.2 Adverse Events of Special Interest

The purpose for specifying AESI is to enable further characterization of the clinical course and management of specific events. The Investigator will monitor each subject for clinical and laboratory evidence of pre-defined AESIs throughout their participation in the study, and will report all AESIs listed below within the same timeframe as an SAE (Section 10.4). An AESI may or may not be the consequence of treatment with avatrombopag.

The AESI 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 10.3), to be submitted within 24 hours of awareness of the event. During the course of the study, additional AESI may be identified and communicated by the Sponsor.

10.3 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/assent. 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.

10.4 Serious Adverse Event Reporting − Procedures for Investigators

10.4.1 Initial Reports

All SAEs, regardless of causal assessment, occurring from the time of informed consent/assent until discharge from the study 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 study drug 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 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 IRB/IEC 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.

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

10.4.2 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.

10.5 Pregnancy Reporting

If the subject becomes pregnant during the study or within 30 days of discontinuing study drug, the Investigator should report the pregnancy to the Sponsor on the Pregnancy Report Form within 24 hours of being notified.

A subject becoming pregnant while on study drug will immediately be withdrawn from the study and early termination study procedures will be performed.

The subject should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify Sobi Pharmacovigilance, or its agent, by completing and forwarding the Pregnancy Report Form with the updated information within 24 hours of being notified. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE and also update the Pregnancy Report Form.

10.6 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/IEC, 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 as SUSAR or other specific safety information (e.g., summary or listing or SUSARs) from the Sponsor will review the report and file it along with the Investigator's Brochure (IB) and will notify the IRB/IEC, if appropriate, according to local requirements.

11 STATISTICS

This section outlines the statistical analysis methodology for this study. Further details of the statistical analyses will be described in the SAP that will be finalized prior to the database lock and unblinding. Statistical analysis will be performed using SAS® software version 9.4 or above and other validated statistical software as needed. All clinical data will be summarized using descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum for continuous measurements, and counts and percentages for categorical measurements).

11.1 Analysis Population

- **Full Analysis Set (FAS):** The FAS will include all randomized subjects.
- **Per-protocol Analysis Set (PPS):** The PPS will include the subset of subjects from the FAS who do not meet the criteria that would confound the evaluation of the efficacy endpoints. A full list of the criteria will be finalized prior to database lock and unblinding.
- **Safety Analysis Set:** The Safety Analysis Set will include all subjects who receive at least 1 dose of study drug.

11.2 Statistical Methods

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

11.2.1 Disposition, Demographics, and Baseline Characteristics

Subject disposition will be summarized overall and by treatment group. In addition, the number of subjects screened, the number of subjects who failed screening, and the reasons for screen failure will be summarized. Demographic and Baseline characteristics will be summarized overall and by treatment group. Medical history and prior and concomitant medications will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and WHODrug dictionaries and summarized overall and by treatment group.

11.2.2 Efficacy Analysis

All efficacy analyses will be conducted using the FAS, unless otherwise specified.

In order to satisfy the primary endpoint requirements of different regulatory agencies, 2 primary efficacy endpoints will be evaluated. Two separate SAPs will be developed to describe the statistical methodology for the analysis of each primary efficacy endpoint. In the first SAP, the endpoint described as “Primary Efficacy Endpoint” in Section 3.1 will be assessed as the primary efficacy endpoint, and the endpoint described as the “Alternative Primary Efficacy Endpoint” in Section 3.2 will be assessed as the first secondary efficacy endpoint. In the second SAP, the endpoint described as “Alternative Primary Efficacy Endpoint” in Section 3.2 will be assessed as the primary efficacy endpoint, and the endpoint described as the “Primary Efficacy Endpoint” in Section 3.1 will be

assessed as the first secondary efficacy endpoint. Both SAPs will evaluate the additional secondary efficacy endpoints described in Section 3.3.

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

Primary Efficacy Endpoint:

The primary efficacy endpoint is the durable platelet response as defined by the proportion of subjects achieving at least 6 out of 8 weekly platelet counts $\geq 50\times10^9$/L during the last 8 weeks of the 12 week Treatment Period in the Core Phase, in the absence of rescue medication. The null hypothesis is that the treatment effect of avatrombopag is the same as that of placebo. The alternative hypothesis is that the treatment effect of avatrombopag is different than that of placebo.

The primary efficacy endpoint will be tested between avatrombopag and placebo using the Cochran-Mantel-Haenszel 2-sided test at $\alpha=0.05$, adjusting for age cohort and Baseline platelet count ($\leq 15\times 10^9$/L vs $>15\times10^9$/L), or the Fisher's exact test, when data is sparse. In addition, the numbers and percentages of responders in each treatment group, the associated 95% confidence intervals (CI), and the 95% CI for the difference between avatrombopag and placebo will be summarized. The primary analysis will be performed based on the FAS and repeated on the PPS as a supportive analysis. Other sensitivity analyses of the primary efficacy endpoint may be performed as appropriate.

Subjects without sufficient data for the determination of response status (i.e., responder versus non-responder) will be treated as non-responders in the analysis. Every effort should be made during the conduct of the study to limit the extent of missing data. Subjects who prematurely discontinue the study drug should remain in the study for collection of data, unless the subject withdraws consent.

Alternative Primary Efficacy Endpoint:

The alternative primary efficacy endpoint is platelet response as defined by the proportion of subjects for whom at least 2 consecutive platelet assessments are $\geq 50\times10^9$/L over the 12-week Treatment Period in the Core Phase in the absence of rescue medication. The null hypothesis is that the treatment effect of avatrombopag is the same as that of placebo. The alternative hypothesis is that the treatment effect of avatrombopag is different than that of placebo.

The alternative primary efficacy endpoint will be tested between avatrombopag and placebo using the Cochran-Mantel-Haenszel 2-sided test at $\alpha=0.05$, adjusting for age cohort and Baseline platelet count ($\leq 15\times 10^9$/L vs $>15\times10^9$/L), or the Fisher's exact test, when data is sparse. In addition, the numbers and percentages of responders in each treatment group, the associated 95% CI, and the 95% CI for the difference between avatrombopag and placebo will be summarized. The primary analysis will be performed based on the FAS and repeated on the PPS as a supportive analysis. Other sensitivity analyses of the alternative primary efficacy endpoint may be performed as appropriate.

11.2.2.1 Secondary Efficacy Analysis

The secondary efficacy endpoints for this study are:

- The percentage of weeks subjects have a platelet count $\geq 50\times10^9$/L during 12 weeks of treatment in the Core Phase, in the absence of rescue therapy.
- Platelet response at Day 8 (defined by the proportion of subjects with a platelet count $\geq 50\times10^9$/L at Day 8, in the absence of rescue therapy).
- The percentage of weeks subjects have a platelet count between $\geq 50\times10^9$/L and $\leq 150\times10^9$/L, during 12 weeks of treatment in the Core Phase, in the absence of rescue therapy.
- The proportion of subjects who require rescue medications during 12 weeks of treatment in the Core Phase of the study.
- Incidence and severity of bleeding symptoms associated with ITP measured using the WHO Bleeding Scale.

The categorical variables (e.g., proportion) will be summarized and analyzed in the same manner as the primary efficacy endpoint. The continuous variables (e.g., percentage of weeks subjects have a platelet count $\geq 50\times10^9$/L) will be analyzed using nonparametric Wilcoxon Rank Sum tests.

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

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

The efficacy variables collected during the Extension Phase will be summarized descriptively. Additional efficacy analyses will be performed if deemed necessary. The details of the analyses will be described in the SAP that will be finalized prior to database lock.

11.2.3 Safety Analysis

Safety assessments for this study include the incidence of AEs, SAEs, AESI, clinical laboratory tests, and vital signs. The safety assessments will be summarized descriptively by treatment group for the Safety Analysis Set.

11.2.4 Interim Analysis

No formal interim analysis is planned for this study. An IDMC will be convened for this study, primarily to monitor safety at regular intervals. An IDMC charter, detailing all aspects of the IDMC's scope of review and procedures will be described in a separate document. In addition, ongoing safety data will be reviewed by the Sponsor in a blinded fashion for each age cohort. Interim PK/PD data will be analyzed by an unblinded designee (Section 5.1).

11.2.5 Pharmacokinetic/Pharmacodynamic Analyses

Population PK modeling will be conducted to estimate PK parameters (e.g., C_{max}, AUC, $t_{1/2}$, CL/F and Vz/F). Effects of intrinsic factors, including age and weight, and extrinsic factors, including formulation, on the PK parameters may be evaluated.

The exposure and platelet count data will be used to establish a population PK/PD model. Covariates on the PD parameters, such as Baseline platelet count and age, may be evaluated. If the dose for any permitted concomitant ITP medications taken at Baseline by the subject has changed during the Core Phase, the platelet count data after the change will not be included in the analysis. The adult data may be combined with the pediatric data to provide more robust evaluation. The PK parameters and PK/PD relationship in the pediatric population may be compared to those in the adult population.

Enrollment in subsequent cohorts will be staggered and the exact doses may be modified during the study based on PK/PD analysis (e.g., PK/PD modeling) of emerging data or safety data. If unanticipated exposure and platelet counts are observed, the doses may be modified to best match exposure-response relationships observed in adults.

11.3 Sample Size Estimation

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

Based on the eltrombopag PETIT2 study conducted in pediatric patients with chronic ITP, the durable response rates were 41.3% and 3.4% for eltrombopag and placebo, respectively (Grainger, 2015). It is reasonable to assume that the treatment effect of avatrombopag will be very similar to that of eltrombopag, due to both drugs being in the same class, having similar mechanisms of action, and treating similar patient populations (e.g., patients aged ≥1 to <18 years with relapsed or refractory disease after 1 or more previous treatments for ITP and a Baseline platelet count $<30\times10^9$/L). With the 3:1 ratio of avatrombopag to placebo, a total of 72 subjects (54 avatrombopag and 18 placebo) will provide at least 90% power to detect the treatment difference of 37.9% in durable response at α=0.05, based on the Fisher's exact test.

In addition, a 12 week study of romiplostim in treating pediatric ITP patients showed that 88% of romiplostim treated subjects achieved a platelet count $\geq50\times10^9$/L for 2 consecutive weeks (alternative primary endpoint for this study), whereas none of the placebo treated subjects achieved the same endpoint (Bussel, 2011). With the 3:1 ratio of avatrombopag to placebo, a total of 72 subjects (54 avatrombopag and 18 placebo) will provide ≥99% power to detect the treatment difference of 80% in proportion of subjects achieving a platelet count $\geq50\times10^9$/L for 2 consecutive weeks at α=0.05, based on the Fisher's exact test.

12 DATA MANAGEMENT AND RECORD KEEPING

12.1 Data Management

12.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the CRA on an ongoing basis and during monitoring visits. The CRA will verify data recorded in the electronic data capture (EDC) system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the 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.

12.1.2 Computer Systems

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

12.1.3 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.

12.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

- MedDRA for medical history and AEs, and
- WHODrug Dictionary for prior and concomitant medications.

12.1.5 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.

12.2 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.

13 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

13.1 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.

13.2 Institutional Review Board/Independent Ethics Committee

The IRB/IEC 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/IEC approval has been obtained. The protocol, IB, ICF/assent, 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/IEC by the Investigator.

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

Federal regulations and ICH guidelines require that approval be obtained from an IRB/IEC prior to participation of subjects in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, assent forms, 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/IEC.

The study will only start in the respective sites once the IRB's/IEC's written approval has been given. No study drug will be released to the site for dosing until written IRB/IEC 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/IEC according to national regulations.

13.3 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/IEC, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IRB/IEC within 5 working days.

13.4 Informed Consent/Assent

The ICF and/or assent, and any changes to the ICF and/or assent made during the course of the study, must be agreed to by the Sponsor or designee and the IRB/IEC 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 and/or subject's LAR, as applicable, is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the subject and/or the subject's LAR, as applicable, has been informed of his/her rights to privacy. The Investigator will obtain written informed consent and/or assent, as applicable, from each subject and/or the subject's LAR, as applicable, 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/assent must be maintained by the Investigator and is subject to inspection by the Sponsor, their representatives, auditors, the IRB/IEC, and/or regulatory agencies. A copy of the signed ICF/assent will be given to the subject and/or the subject's LAR, as applicable.

13.5 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, Directive 2001/20/EC(European Commission), and applicable regulatory requirements, and that valid data are entered into the eCRFs.

To achieve this objective, the CRA'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, IB, eCRFs and procedures for their completion, informed consent/assent 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, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data is entered by the site, the CRA 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 CRA and provide any missing information, whenever possible.

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

13.6 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/IEC 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.

13.7 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 and assent forms, copies of all eCRFs, forms for SAEs, source documents, and detailed records of treatment disposition. 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.

13.8 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.

13.9 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.

13.10 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 7 AVA-PED-301 – Core Phase Schedule of Events

Period	Screening[a]	Treatment													End of Study/ Early Termination[b]
Visit	1	2 Baseline	3	4	5	6	7	8	9	10	11	12	13	14[c]	Visit 15
Day	-28 to -1	1	8±1	15±1	22±1	29±1	36±1	43±1	50±1	57±1	64±1	71±1	78±1	85±1	30 Days (±7 days) after the last dose of study drug
Week (# is the End of Week)	-4	/	1	2	3	4	5	6	7	8	9	10	11	12	/
Informed Consent/Assent	X													X[d]	
Inclusion/Exclusion Criteria Review	X	X[o]												X[e]	
Demographics[f]	X	X[g,o]													
Medical/Medication/ Surgical History	X	X[g,o]													
ITP History	X	X[h,o]													
WHO Bleeding Scale[i]		X[o]	X	X[o]	X	X	X	X	X	X	X	X[o]	X	X	X
Height, Weight, BMI	X	X[j,o]				X[k]				X[k]				X	
Abbreviated Physical Exam[l]	X	X[o]				X				X				X	X

ITP = Immune Thrombocytopenia
WHO = World Health Organization.
[a] The Screening Visit will occur within 28 days prior to Day 1/Visit 2.
[b] If the subject is not continuing into the Extension Phase, perform the End of Study Visit (Visit 15) 30 days after the last dose of study drug (should fall 1 day before Visit 14).
[c] For subjects who are participating in the Extension Phase, Visit 14 will be the last visit during the Core Phase and the first visit during the Extension Phase (Visit E-1).
[d] Signed and dated informed consent/assent for the Extension Phase must be completed prior to any Extension Phase study procedures.
[e] Review Extension Phase inclusion/exclusion criteria to confirm continued study eligibility for subjects who are continuing into the Extension Phase.
[f] Including age.
[g] Update the electronic case report form (eCRF) with any demographic/medical history/surgical history changes since Screening.
[h] Update the eCRF with any ITP history changes since Screening.
[i] The following question should be asked of the subject during Day 1/Visit 2: "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 visit: "Have you experienced any bruising or bleeding since I saw you last?".
[j] Weight and Body Mass Index (BMI) only. The WHO Bleeding Scale should be performed prior to any other visit procedures.
[k] Weight only.
[l] The abbreviated physical exam (PE) will consist of the following: general appearance, head, neck, eyes, ears, nose, throat, chest, lungs, heart, abdomen, extremities, joints, lymph nodes, and neurology.

Period	Screening[a]	Treatment													End of Study/ Early Termination[b]
Visit	1	2 Baseline	3	4	5	6	7	8	9	10	11	12	13	14[c]	Visit 15
Day	-28 to -1	1	8±1	15±1	22±1	29±1	36±1	43±1	50±1	57±1	64±1	71±1	78±1	85±1	30 Days (±7 days) after the last dose of study drug
Week (# is the End of Week)	-4	/	1	2	3	4	5	6	7	8	9	10	11	12	/
Vital Signs[m]	X	X[n]	X	X[o]	X	X		X		X		X[o]		X	X
Serum Chemistry/Hematology (Central Lab)	X	X[o]				X				X				X	X
Platelet Count (Local Lab)	X[p]	X[o]	X	X[o]	X	X	X	X	X	X	X	X[o]	X	X	X
Assess need for Dose Titration				X	X	X	X	X	X	X	X	X	X	X[q,r]	
Pregnancy Test[s]	X	X[o,t]				X				X				X	X
Plasma PK Sample(s)[u]			X	X[v,w]	X	X	X	X	X	X	X	X[v,w]			
Record Date/Time of Last Dose of Study Drug in eCRF			X	X	X	X	X	X	X	X	X	X			
Randomize Subject to Study Drug Arm		X[o]													
Randomize Subjects in Cohort 3 to PK Timepoint		X[o]													

[m] Vital signs (blood pressure, heart rate, and temperature) should be taken after sitting for 5 minutes, whenever possible. Vital signs should also be taken prior to any blood draws.
[n] Collect vital signs prior to study drug administration and 30 minutes (±15 minutes) after study drug administration.
[o] Prior to dosing with study drug in clinic.
[p] The platelet count obtained at the Screening Visit/Visit 1 and 1 other platelet count taken within 28 days on either side of the Screening Visit (may use a historical value collected per standard of care if within 28 days of Screening) will be averaged to obtain the study eligibility platelet count value, which must be $<30\times10^9$/L. The 2 samples must be obtained ≥24 hours and ≤28 days apart and the results must be available prior to randomization.
[q] Only if subject is continuing into the open-label Extension Phase.
[r] If subject is continuing into the Extension Phase, determine appropriate starting dose based on protocol defined criteria.
[s] Serum or urine pregnancy test should be performed for females of childbearing potential only.
[t] Serum or urine pregnancy test should be performed prior to dosing with study drug.
[u] Sparse blood sampling for the pharmacokinetic (PK) assessment will be performed, with the exception of Visit 4 (Week 2) and Visit 12 (Week 10) where serial PK samples will be taken.
[v] Serial PK samples will be taken pre-dose and within each of the following post-dose windows: 2-4 hours, 6-8 hours, and 10-12 hours. Serial sampling may need to occur at a visit later than Visit 4 or Visit 12 if study drug has been held or the dosing regimen has changed in the previous week. This is to ensure that the subject has been on a stable dose for at least 1 week when serial samples are collected.
[w] Subjects between the ages of ≥1 to <6 (Cohort 3) will be randomized in a 1:1 ratio, stratified by treatment group, to either the 6-8 hour post-dose timepoint or the 10-12 hour post-dose PK timepoint at Week 2. The timepoint not collected at Week 2 will be collected at Week 10.

Period	Screening[a]	Treatment													End of Study/ Early Termination[b]
Visit	**1**	**2 Baseline**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14[c]**	**Visit 15**
Day	**-28 to -1**	**1**	**8±1**	**15±1**	**22±1**	**29±1**	**36±1**	**43±1**	**50±1**	**57±1**	**64±1**	**71±1**	**78±1**	**85±1**	**30 Days (±7 days) after the last dose of study drug**
Week (# is the End of Week)	**-4**	**/**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**/**
Administer Study Drug in Clinic[x]		X		X[y]								X[x]			
Administer Palatability/ Acceptability Questionnaire[z]		X													
Dispense 1-Month Supply of Study Drug[aa]		X				X				X				X	
Dispense New Dosing Diary		X				X				X				X	
Review Study Drug Administration Instructions and Provide to Subject/Review Dosing Diary		X	X	X	X	X	X	X	X	X	X	X	X	X	
Retrieve Unused Medication and Record Compliance						X				X				X	X[bb]
Adverse Events[cc]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[x] Study drug should be administered with food. Record dose, date and time of dose, and vehicle used, if applicable on the electronic case report form.
[y] Regardless of the subject's current study drug regimen (once daily, three times a week, etc.) this visit must fall on a day that study drug will be administered in order to collect planned pre- and post-dose serial PK samples.
[z] The Palatability Questionnaire should be administered to subjects in Cohort 3 and the Acceptability Questionnaire should be administered to the subject's parent/caregiver within 2 minutes of subjects receiving the powder for oral suspension.
[aa] Additional study drug may need to be dispensed to the subject during other study visits than noted in the schedule of events in the case of upward dose titrations.
[bb] For subjects who are early terminating from the study, only. Final study drug collection will occur at Visit 14 for subjects who have completed the Core Phase.
[cc] Adverse events (AEs) should be recorded from the time the subject/subject's legally authorized representative (LAR) signs the informed consent/assent.

Table 8 AVA-PED-301 – Extension Phase Schedule of Events

Visit	E-1[a]	E-2	E-3	E-4	E-5	E-6	E-7 – E-24	E-25
Day	**1**	**30 (±7 Days)**	**60 (±7 Days)**	**90 (±7 Days)**	**120 (±7 Days)**	**150 (±7 Days)**	**Every 30 Days (±7 Days)**	**720 (±7 Days)**
Informed Consent/Assent[b]	X							
Inclusion/Exclusion Criteria Review	X							
WHO Bleeding Scale[c]	X	X	X	X	X	X	X	X
Vital Signs[d]	X							X
Height, Weight, BMI	X	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	
Abbreviated Physical Exam[f]	X			X			X[g]	X
Serum Chemistry/Hematology (Central Lab)	X							
Platelet Count (Local Lab)[h]	X	X	X	X	X	X	X	X
Pregnancy Test[i]	X		X			X	X	X
Determine Appropriate Starting Dose/Assess need for Dose Titration	X	X	X	X	X	X	X	
Administer Avatrombopag in Clinic[j]	X					X	X	
Dispense 1-month Supply of Open-label Avatrombopag	X	X	X	X	X	X	X	

BMI = Body Mass Index

[a] Visit E-1 will be the first visit of the Extension Phase and the last Visit of the Core Phase (Visit 14).

[b] Informed consent/assent may be performed at any time during the Core Phase for the Extension Phase.

[c] WHO = World Health Organization. The following question should be asked of the subject during each visit: "Have you experienced any bruising or bleeding since I saw you last?".

[d] Vital signs (blood pressure, heart rate, respiratory rate, and temperature) should be taken after sitting for 5 minutes, whenever possible. Vital signs should also be taken prior to any blood draws.

[e] Weight only.

[f] The abbreviated physical exam (PE) will consist of the following: general appearance, head, neck, eyes, ears, nose, throat, chest, lungs, heart, abdomen, extremities, joints, lymph nodes, and neurology.

[g] The abbreviated PE should be performed every 3 months while the subject is enrolled in the extension phase (e.g., Day 90, Day 180, Day 270, Day 360, Day 450, Day 540, Day 630, and Day 720).

[h] Platelet counts are to be assessed **weekly** until the subject is determined to be on a stable dose of avatrombopag. Record weekly visits, dose changes, and platelet counts on the electronic case report form (eCRF).

[i] For females of childbearing potential. A pregnancy test should be performed every 3 months during Visit E-3, Visit E-6, Visit E-9, Visit E-12, Visit E-15, Visit E-18, Visit E-21, Visit E-24, and Visit E-25.

[j] Study drug should be administered with food. Administer study drug in clinic during Visit E-1, E-6, Visit E-12, and Visit E-18 in order to confirm proper administration technique.

Visit	E-1[a]	E-2	E-3	E-4	E-5	E-6	E-7 – E-24	E-25
Day	**1**	**30 (±7 Days)**	**60 (±7 Days)**	**90 (±7 Days)**	**120 (±7 Days)**	**150 (±7 Days)**	**Every 30 Days (±7 Days)**	**720 (±7 Days)**
Review Administration Instructions and Provide to Subject	X	X	X	X	X	X	X	
Dispense Dosing Diary	X	X	X	X	X	X	X	
Retrieve Unused Medication and Record Compliance	X	X	X	X	X	X	X	X
Adverse Events[k]	X	X	X	X	X	X	X	X
Prior/Concomitant Medications	X	X	X	X	X	X	X	X

[k] Adverse events (AEs) should be recorded from the time the subject/subject's legally authorized representative (LAR) signs the informed consent/assent.

APPENDIX B: PALATABILITY QUESTIONNAIRES

Palatability Questionnaire for Subjects <6 Years of Age

Subject ID: _____

1. **What did you think of the taste of the medicine you just took?**

5. Very good	4. Good	3. Neither good nor bad	2. Bad	1. Very bad

2. **What did you think of the smell of the medicine you just took?**

5. Very good	4. Good	3. Neither good nor bad	2. Bad	1. Very bad

3. **How did the medicine feel in your mouth?**

5. Very good	4. Good	3. Neither good nor bad	2. Bad	1. Very bad

Acceptability Questionnaire for Parents/Caregivers of Subjects <6 Years of Age

Subject ID: _____

1. How did your child accept taking the suspension?

____5 = very well

____4 = well

____3 = neither well nor badly

____2 = badly

____1 = very badly

2. On the basis of reaction/facial expression of your child, do you think that the medication is:

____3 = Pleasant

____2 = Not sure

____1 = Unpleasant

APPENDIX C: 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 D: MODERATE OR STRONG INDUCERS AND INHIBITORS OF CYTOCHROME P450 (CYP)2C9 AND CYP3A4

- Carbamazepine (US Brand Names: Carbatrol; Epitol; Equetro; Tegretol; Tegretol-XR)
- Enzalutamide (US Brand Name: Xtandi)
- Fluconazole (US Brand Name: Diflucan)
- Rifampin/Rifampicin (US Brand Name: Rifadin)
- Phenytoin (US Brand Names: Dilantin; Dilantin Infatabs; Phenytek; Phenytoin Infatabs)
- Phenobarbital
- Ritonavir (US Brand Name: Norvir)

Note: This list may not be all-inclusive.

APPENDIX E: PROTOCOL AMENDMENTS

Amendment #2 – 02 November 2021

Rationale for Amendment

Amendment 2 has been introduced to update the sponsor name, and to clarify corticosteroid use prior to Baseline, the minimum subject age at Baseline, and the timing of serial PK sampling.

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 now be the sponsor going forward.

Two inclusion criteria have been made more specific to clarify the washout period prior to Baseline for chronic use (30 days) versus rescue, or short-term, use (14 days) of corticosteroids for the treatment of ITP. The inclusion criterion for age has been updated to clarify that subjects must be less than 18 years old at Baseline as well as Screening. Caveats for the timing of serial PK sampling at Visits 4 and 12 have been added to specify that subjects need to be on a stable dose of study drug for one week prior to the serial sampling visit.

Typographical corrections and corrections to minor errors in procedural descriptions have also been made.

Summary of Significant Changes in Amendment 2

- Dova Pharmaceuticals, Inc. has been changed to Sobi, Inc. throughout the protocol.
- Updated inclusion criterion #1 to clarify that subjects must be less than 18 years old at both the Baseline and Screening visits.
- Updated inclusion criteria #5 and #7 to clarify the washout period prior to Baseline of chronic use versus rescue use of corticosteroids.
- Added clarification that the serial PK collection at Visits 4 and 12 should occur after a subject has been on a stable dose for 1 week.

The following presents changes made by this amendment. ***New/revised text is presented in bold italics***; deleted text is identified by ~~strikethrough~~. Administrative updates based on the change in Sponsor name and address, as well as typographic corrections, including grammatical and punctuation errors, are not shown.

SYNOPSIS

Inclusion Criteria

1. Male or female subjects ≥1 and <18 years of age at Screening ***and Baseline***.

5. Subjects being treated ***chronically*** with corticosteroids or azathioprine/6-mercaptopurine must be receiving a stable dose for at least 30 days prior to Day 1/Visit 2 or must have completed these therapies more than 30 days prior to Day 1/Visit 2.

7. Previous therapy for ITP with immunoglobulins (IVIg and anti-D) ***or corticosteroid rescue therapy*** must have been completed at least 14 days prior to Day 1/Visit 2.

Section 1.4.2 Pharmacokinetic Sampling Schedule

In order to minimize the number of blood draws subjects are subjected to, blood samples for *serial* PK assessments will be collected only during Visit 4 (Week 2) and Visit 12 (Week 10) of the 12 week Core Phase. Regardless of the subject's current treatment regimen (~~e.g.,~~ once daily, three times a week, etc.) Visit 4 and Visit 12 must fall on a day the subject is scheduled to take their dose of study drug. ***Serial PK sampling may need to occur at a visit later than Visit 4 or Visit 12 if study drug was held or if the dose changed; see Section 9.6.***

Section 6.1.1, Inclusion Criteria

1. Male or female subjects ≥1 and <18 years of age at Screening ***and Baseline***.
5. Subjects being treated ***chronically*** with corticosteroids or azathioprine/6-mercaptopurine must be receiving a stable dose for at least 30 days prior to Day 1/Visit 2 or must have completed these therapies more than 30 days prior to Day 1/Visit 2.
7. Previous therapy for ITP with immunoglobulins (IVIg and anti-D) ***or corticosteroid rescue therapy*** must have been completed at least 14 days prior to Day 1/Visit 2.

Section 9.1.5 Visit 4 (Week 2; Day 15 ±1 Day)

Regardless of the subject's current treatment regimen (~~e.g.,~~ once daily, three times weekly, etc.) Visit 4 must fall on a day the subject is scheduled to take their dose of study drug. ***Note: serial PK sampling may need to occur at a visit later than Visit 4 if study drug was held or if the dose changed; see Section 9.6.***

Section 9.1.13 Visit 12 (Week 10; Day 71 ± 1 Day)

Regardless of the subject's current treatment regimen (once daily, three times weekly, etc.) Visit 12 must fall on a day the subject is scheduled to take their dose of study drug. Note: serial PK sampling may need to occur at a visit later than Visit 12 if study drug was held or if the dose changed; see Section 9.6. Study drug will be administered in the clinic during Visit 12. Subjects in Cohort 1 and Cohort 2 should plan to remain in the clinic for 10 to 12 hours after study drug administration to allow for collection of the serial PK blood samples. Subjects in Cohort 3 should plan to remain in the clinic for 6 to 8 hours or 10 to 12 hours, depending on the timepoint they were randomized to during Day 1/Visit 2.

9.6 Pharmacokinetic Sampling

Plasma concentrations of avatrombopag during the Core Phase will be measured using a validated bioanalytical assay. Blood samples for the measurement of avatrombopag plasma concentrations will be collected as shown in Table 6.

Regardless of the subject's current treatment regimen (~~e.g.,~~ once daily, three times a week, etc.) ***the serial PK sampling at*** Visit 4 and Visit 12 must ***occur*** ~~fall~~ on a day the subject is scheduled to take their dose of study drug. ***If study drug has been held or the dosing regimen has changed within the past week, the serial PK samples should be collected at a visit later than Visit 4 or Visit 12. This is to ensure that serial PK samples will be obtained when the subject has been on a stable dose for at least 1 week.***

Appendix A: Schedule of Events Footnote "V"

Serial PK samples will be taken pre-dose and within each of the following post-dose windows: 2-4 hours, 6-8 hours, and 10-12 hours. ***Serial sampling may need to occur at a visit later than Visit 4 or Visit 12 if study drug has been held or the dosing regimen has changed in the previous week. This is to ensure that the subject has been on a stable dose for at least 1 week when serial samples are collected.***

Amendment #1 – 17 December 2020

Rationale for Amendment

Amendment 1 has been introduced to refine several inclusion and exclusion criteria, clarify the allowable contraception methods, align the definition of a lack of treatment effect in the Extension Phase with the Core Phase definition, and confirm that a protocol amendment will be implemented if two subjects in Cohort 3 require medical monitor approved dose escalations above 20 mg daily.

Updates to the inclusion and exclusion criteria have been made to exclude 1) females who are breastfeeding, as avatrombopag may be excreted in breast milk; 2) subjects >95% BMI for age, as a cutoff of >30 kg/m^2 is not appropriate for all age groups; 3) a previous history of myeloid hematological malignancies, as TPO-RAs may aggravate this condition; and 4) subjects with known hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption because avatrombopag tablets contain lactose.

The allowed contraceptive methods have been aligned with the 'highly effective' methods as defined in the EU "Clinical Trial Facilitation Group's Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials" of September 2015, and a definition of females of childbearing potential has been added. The definition of a lack of treatment effect in the Extension Phase has been made consistent with the Core Phase definition, defined as a platelet count $<30\times10^9$/L after more than 3 weeks at the cohort defined maximum dose.

A protocol amendment to modify the dosing will be implemented if two subjects in Cohort 3 require medical monitor approved dose escalations above Dose Level 6 (20 mg daily). Based on pediatric experience with similar ITP medications, it is possible that a dose of avatrombopag higher than two times the starting dose may be required in some children aged 1 to 5 years. This will allow for an individual subject in Cohort 3 to dose escalate if needed; however, if two subjects require doses above Dose Level 6, an amendment will be implemented before any additional subjects can have this escalation.

Typographical corrections and corrections to minor errors in procedural descriptions have also been made.

Summary of Significant Changes in Amendment 1

- Updated inclusion criteria to clarify that females must not be breastfeeding.
- Added exclusion criteria of >95% BMI for age, a previous history of myeloid hematological malignancies, and known hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption.
- In the Extension Phase a lack of treatment effect is now defined as a platelet count $<30\times10^9$/L after more than 3 weeks at the protocol defined maximum dose of study drug.
- Revised approved methods of contraception.
- Confirmed that a protocol amendment will be implemented prior to permitting more than two subjects in Cohort 3 to have medical monitor approved dose escalations above Dose Level 6.

The following presents changes made by this amendment. ***New/revised text is presented in bold italics***; deleted text is identified by ~~strikethrough~~. Typographic corrections, including grammatical and punctuation errors, are not shown.

SYNOPSIS

Inclusion Criteria

14. Females of childbearing potential must have a negative urine or serum pregnancy test at Screening and Day 1/Visit 2 ***and must not be breastfeeding***.

Exclusion Criteria

2. Body Mass Index (BMI) >30 kg/m^2 ***or >95% for age***.
10. Concurrent malignant disease ***or previous history of myeloid hematologic malignancies***.
12. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m2 ~~(calculated by electronic case report form [eCRF] using the Modification of Diet in Renal Disease Study [MDRD] equation)~~.
15. Subject is unable to take oral medication, ~~or~~ has a malabsorption syndrome, ***or has known hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption*** or any other uncontrolled gastrointestinal condition.

AVA-PED-301 Study Design, Last Sentence

Subjects may be early terminated from the Extension Phase if they have a platelet count >250×10^9/L after 2 weeks of once weekly dosing for any age cohort or ~~if~~***<30×10^9/L after 3 weeks of once daily dosing at the cohort defined maximum dose***~~they have a platelet count <50×10^9/L after 4 weeks of once daily dosing at the cohort defined maximum dose~~.

Section 1.4, Study Design, 6th Paragraph, Last Sentence

Subjects may be early terminated from the Extension Phase if they have a platelet count >250×10^9/L after 2 weeks of once weekly dosing for any age cohort or ~~if~~ ***<30×10^9/L after 3 weeks of once daily dosing at the cohort defined maximum dose***~~they have a platelet count <50×10^9/L after 4 weeks of once daily dosing at the cohort defined maximum dose~~.

Section 1.5.3, Core Phase Dosing Regimen, 4th Paragraph, Last Sentence

If two subjects in Cohort 3 require escalation above Dose Level 6, a protocol amendment must be implemented before any additional subjects will be permitted to escalate above Dose Level 6.

Section 1.5.3, Core Phase Dosing Regimen, Table 3

<***3***~~5~~0×10^9/L after 4***3*** weeks of once daily dosing at the cohort defined maximum dose per Table 4. *Also see protocol stopping criteria in Section 5.3 and early termination criteria in Section 6.1.6.*	Discontinue study drug.

Section 1.5.4, Extension Phase Dosing Regimen, 4th Paragraph, Last Sentence

If two subjects in Cohort 3 require escalation above Dose Level 6, a protocol amendment must be implemented before any additional subjects will be permitted to escalate above Dose Level 6.

Section 6.1.1, Inclusion Criteria

14. Females of childbearing potential must have a negative urine or serum pregnancy test at Screening and Day 1/Visit 2 ***and must not be breastfeeding***.

Section 6.1.2, Exclusion Criteria

2. Body Mass Index (BMI) >30 kg/m^2 ***or >95% for age***.
10. Concurrent malignant disease ***or previous history of myeloid hematologic malignancies***.
12. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m2 ~~(calculated by electronic case report form [eCRF] using the Modification of Diet in Renal Disease Study [MDRD] equation)~~.
15. Subject is unable to take oral medication, ~~or~~ has a malabsorption syndrome, ***or has known hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption*** or any other uncontrolled gastrointestinal condition.

Section 6.3.2, Early Termination, 2nd Paragraph

In addition, a subject may be early terminated from the Extension Phase if ***they have a platelet count <30×10^9/L after 3 weeks of once daily dosing at the cohort defined maximum dose*** ~~they have a platelet count <50×109/L after 4 weeks of once daily dosing at the cohort defined maximum dose per Table 4~~**.**

Section 8.1, Documentation of Prior and Concomitant Medications, Last Paragraph

Dose, frequency, indication for administration, and dates of medication administration will be captured for all medications taken within ~~30~~***90*** days of Screening.

Section 8.2, Contraception Requirements

For this study, a woman is considered of childbearing potential, i.e. fertile, following menarche unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

- Females of childbearing potential who are sexually active must agree to use highly effective methods of birth control (i.e., ~~diaphragm plus spermicide or male condom plus spermicide,~~oral or injectable contraceptive in combination with a second method, contraceptive implant, indwelling intrauterine device (IUD), ~~sexual abstinence,~~ or a vasectomized partner) while participating in the study and for 30 days after the last dose of study drug.
- Males who are sexually active must agree ***that their female partner has had a bilateral tubular occlusion or agree*** to use a ~~double barrier methods of contraception~~male ~~(~~condom plus spermicide ~~or~~***combined with female*** diaphragm plus spermicide while participating in the study and for 30 days after the last dose of study drug.
- ***Sexual abstinence is acceptable as an effective method of birth control only as true abstinence: when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.***

Section 9.5, Table 5 Clinical Laboratory Tests

Category	Parameters
Hematology	
Complete Blood Count	
Chemistry	
Electrolytes	Bicarbonate Chloride Potassium Sodium
Liver Function Tests	ALT AST Alkaline Phosphatase Total Bilirubin
Renal Function Tests	Blood Urea Nitrogen (BUN) ~~eGFR *(calculated in the eCRF by MDRD Equation[a])*~~
Other	Glucose
Females of Child-bearing Potential Only	
	Urine or Serum Pregnancy Test

~~a: Abbreviated MDRD equation: $186 \times (\text{Creatinine}/88.4)^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black})$~~