CLINICAL STUDY PROTOCOL

Study Title	An Open-label Study to Evaluate the Efficacy and Safety of Avatrombopag for the Treatment of Thrombocytopenia in Japanese Adults with Chronic Immune Thrombocytopenia
Protocol Number:	AVA-ITP-307
NCT Number	05369208
Investigational Product:	Avatrombopag
Sponsor:	Sobi, Inc.
Analysis Plan Date:	10-JAN-2022
Analysis Plan Version:	Version 1.0

CLINICAL STUDY PROTOCOL

An Open-label Study to Evaluate the Efficacy and Safety of Avatrombopag for the Treatment of Thrombocytopenia in Japanese Adults with Chronic Immune Thrombocytopenia

Investigational Product: Avatrombopag tablets
Protocol Number: AVA-ITP-307

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

Version Number: 1.0
Date: 10 January 2022

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SIGNATURE PAGE

STUDY TITLE: An Open-label Study to Evaluate the Efficacy and Safety of Avatrombopag for the Treatment of Thrombocytopenia in Japanese Adults with Chronic Immune Thrombocytopenia

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

Signature

[redacted]

Vice President, Global Drug Development
Sobi, Inc.

Date

10 JAN 2022

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: An Open-label Study to Evaluate the Efficacy and Safety of Avatrombopag for the Treatment of Thrombocytopenia in Japanese Adults with Chronic Immune Thrombocytopenia

PROTOCOL NUMBER: AVA-ITP-307

PROTOCOL VERSION/DATE: V1.0 / 10 January 2022

PRODUCT: Avatrombopag 20 mg Tablet

PHASE: 3

RATIONALE AND BACKGROUND:

Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by low platelet counts from a combination of both impaired platelet production and increased peripheral platelet destruction. Current guidelines for the treatment of symptomatic ITP include agents that decrease platelet destruction (e.g., corticosteroids, intravenous gamma globulin [IVIg], and intravenous anti-Rho[D]) or suppress the production of antiplatelet antibodies (e.g., immunosuppressants). However, these drugs have variable and transient efficacy, significant toxicities, and relapse is common upon discontinuation. Second-line treatment options include rituximab, high-dose dexamethasone, the thrombopoietin receptor agonists (TPO-RAs) eltrombopag and romiplostim, and splenectomy.

Avatrombopag is an orally administered TPO-RA initially approved in the US in May 2018 for the treatment of thrombocytopenia in adults with chronic liver disease (CLD) who are scheduled for a procedure, and subsequently approved for this indication in the European Union (EU) (2019) and China (2020). In June 2019, avatrombopag was approved in the US for the treatment of thrombocytopenia in adult patients with chronic ITP who have had an insufficient response to a previous treatment, and subsequently approved for this indication in the EU (2021). Avatrombopag binds the human TPO receptor at a site that is distinct from TPO binding, but it is still capable of stimulating signal transduction and mimicking the biological effects of TPO. It has been shown in vitro to stimulate human megakaryocyte proliferation and differentiation, leading to thrombopoiesis in vivo, without affecting platelet function.

The avatrombopag clinical development program includes approximately 1260 patients and healthy volunteers who have received at least 1 dose of avatrombopag. In the Phase 2 and 3 studies conducted in adults with chronic ITP, avatrombopag was administered to 128 patients for a median duration of 7 months and a maximum duration of more than 2 years. The primary efficacy endpoint in the pivotal Phase 3 ITP study (Study 302), the cumulative number of weeks with platelet count $\geq 50 \times 10^9$/L during 26 weeks of treatment in the absence of rescue therapy, was a median of 12.4 weeks versus 0 weeks for placebo ($p<0.0001$). The most common (≥10%) adverse events in avatrombopag-treated subjects from the Phase 2 and 3 ITP studies (pooled data) were headache (31%), fatigue (28%), contusion (26%), epistaxis (19%), upper respiratory tract infection (15%), arthralgia (13%), gingival bleeding (13%), petechiae (11%), and nasopharyngitis (10%).

To evaluate the efficacy, safety, and pharmacokinetics (PK) of avatrombopag in Japanese adults with ITP, this confirmatory open-label study will be conducted. While a placebo control group was included in the pivotal avatrombopag overseas study, the mean number of cumulative weeks with a platelet response in this group was zero (0), a result which is consistent with placebo control groups in other ITP studies. Therefore, a placebo control is not included in this confirmatory study, as it would not be expected to be informative. Otherwise, the study design will replicate that in the overseas pivotal study, Study 302, to be able to compare this study's data to the data from the overseas study. Avatrombopag will be evaluated over a duration of 26 weeks and the primary efficacy endpoint will be the cumulative number of weeks of platelet response $\geq 50 \times 10^9$/L. All subjects who complete the Primary Investigation Phase (Core Phase) can continue to receive avatrombopag in the Extension Phase until market authorization in Japan. Safety and efficacy data will be collected monthly in the Extension Phase.

STUDY OBJECTIVES:

Primary Investigation Phase (Core Phase)

Primary Objective

- To evaluate the efficacy of avatrombopag in the treatment of Japanese adult subjects with ITP, as measured by cumulative number of weeks of platelet response over 26 weeks

Secondary Objectives

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

Exploratory Objectives

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

Extension Phase

Primary Objective

- To evaluate the safety and tolerability of long-term therapy with avatrombopag in Japanese subjects with chronic ITP

Secondary Objective

- To evaluate the effectiveness of long-term therapy with avatrombopag as measured by platelet response, bleeding, and the use of rescue medication

STUDY ENDPOINTS

Primary Investigation Phase (Core Phase):

Efficacy Assessments

Primary efficacy endpoint:

- The cumulative number of weeks in which the platelet count is $\geq 50\times10^9$/L during 26 weeks of treatment in the absence of rescue therapy.

Subjects using rescue therapy at any time during the 26-week treatment period will be considered not to have any platelet responses for all subsequent weeks after rescue therapy. A platelet response will be defined as a platelet count of $\geq 50\times10^9$/L and nonresponse will be defined as a platelet count $<50\times10^9$/L. All analyses of platelet counts will be based on local laboratory results.

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

Key secondary efficacy endpoint:

- Platelet response rate at Day 8 (as defined by the proportion of subjects with a platelet response $\geq 50\times10^9$/L at Day 8).

Subjects with missing platelet counts at Day 8 or use of a rescue therapy before or on Day 8 will be considered platelet nonresponders.

Other endpoints related to efficacy:

- Durable platelet response as defined by: proportion of subjects who have at least 6 of 8 (i.e., ≥75%) weekly platelet counts $\geq 50\times10^9$/L during the last 8 weeks of treatment over the 26-week treatment period in the absence of rescue therapy
- Incidence and severity of bleeding symptoms associated with ITP, including bleeding, bruising, and petechiae, measured using the WHO Bleeding Scale
- Maximum duration (in weeks) of continuous response for each subject
- Proportion of subjects receiving rescue therapy during the 26-week duration of the study
- Proportion of subjects with a discontinuation in use of concomitant ITP medications from baseline
- Complete responder by International Working Group (IWG) definition: platelet count $\geq 100\times10^9$/L and absence of bleeding
- Responder by IWG definition: platelet count $\geq 30\times10^9$/L and at least a 2-fold increase in baseline count and absence of bleeding

Extension Phase:

Effectiveness Assessments

Effectiveness will be assessed by measuring platelet counts, reduction in use of concomitant ITP medication, and bleeding events. Specifically,

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

Safety (Primary Investigation Phase (Core Phase) + Extension Phase):

Safety will be assessed by the monitoring and recording of all adverse events (AEs) and serious adverse events (SAEs), regular monitoring of hematology, blood chemistry, regular measurement of vital signs, and the performance of physical examinations. Thromboembolic events and bleeding events (WHO Grades 3 and 4) are considered as AEs of special interest (AESI) in this study. AEs of special interest (AESI) should be reported on SAE forms and in the timeframe for SAE reporting, regardless of whether they meet the seriousness criteria.

POPULATION:

Key Inclusion Criteria:

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

Primary Investigation Phase (Core Phase)

1. Men and women ≥18 years of age.
2. Subject must be able to provide informed consent.
3. Subject has a confirmed diagnosis of chronic ITP (≥12 months duration) and has had an insufficient response to a previous ITP treatment, in the opinion of the Investigator.
4. Subject has an average of 2 platelet counts $<30\times10^9$/L (no single count can be $>35\times10^9$/L). The 2 samples must be obtained ≥48 hours and ≤2 weeks apart.

Extension Phase

1. No significant safety or tolerability concerns with the subject's participation in the Primary Investigation Phase (Core Phase) as determined by the Investigator.

Key Exclusion Criteria:

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

Primary Investigation Phase (Core Phase)

1. Subjects with known secondary immune thrombocytopenia (e.g., with known *Helicobacter pylori*-induced ITP, subjects infected with known human immunodeficiency virus [HIV] or hepatitis C virus [HCV] or subjects with known systemic lupus erythematosus).

2. Subjects with known inherited thrombocytopenia (e.g., MYH-9 disorders) or hereditary thrombophilic disorders (e.g., Factor V Leiden, antithrombin III deficiency).
3. History of myelodysplastic syndrome (MDS).
4. History of arterial or venous thrombosis.
5. Subjects with a history of significant cardiovascular disease (e.g., congestive heart failure [CHF] New York Heart Association Grade III/IV, arrhythmia known to increase the risk of thromboembolic events [e.g., atrial fibrillation], angina, coronary artery stent placement, angioplasty, coronary artery bypass grafting).
6. Subjects with a history of cirrhosis, portal hypertension, or chronic active hepatitis.
7. Subjects with concurrent malignant disease or receiving cytotoxic chemotherapy for a reason other than ITP treatment.
8. Use of immunoglobulins (IVIg and anti-D) or corticosteroid rescue therapy within 1 week of Day 1/Baseline.
9. Splenectomy or use of rituximab within 12 weeks of Day 1/Baseline.
10. Use of romiplostim or eltrombopag within 1 week of Day 1/Baseline.
11. Use of chronic corticosteroid treatment or azathioprine within 4 weeks of Day 1/Baseline, unless receiving a stable dose for at least 4 weeks.
12. Use of mycophenolate mofetil, cyclosporin A, or danazol within 4 weeks of Day 1/Baseline, unless receiving a stable dose for at least 12 weeks.
13. Use of cyclophosphamide or vinca alkaloid regimens within 4 weeks of Baseline Visit.
14. Currently receiving moderate or strong dual inhibitors/inducers of CYP2C9 and CYP3A4.
15. Serum creatinine ≥1.5× the upper limit of normal (ULN).
16. Serum bilirubin ≥2×ULN
17. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3×ULN.
18. Females who are pregnant (positive beta-human chorionic gonadotropin positive [β-hCG] test) or breastfeeding.
19. Known allergy to avatrombopag or any of its excipients.
20. Received treatment with an investigational drug within 30 days or 5 half-lives (whichever is longer) before Day 1/Baseline.
21. Any clinically relevant abnormality which makes the subject unsuitable for participation in the study, in the opinion of the Investigator.
22. Considered unable or unwilling to comply with the study protocol requirements.

Extension Phase

1. Subjects for whom participation in the Extension Phase is considered inappropriate, based on the Investigator's judgment
2. Subjects considered unable or unwilling to comply with the study protocol requirements, as determined by the Investigator

STUDY DESIGN AND DURATION:

This study is an open-label study of avatrombopag in Japanese men and women ≥18 years who have ITP. Approximately 19 subjects who meet all the eligibility requirements will be enrolled into the study. The Screening Visit and Day 1 Baseline Visit platelet counts will be averaged to obtain the baseline platelet count value. The Primary Investigation Phase (Core Phase) will be 26 weeks in duration and the Extension Phase will continue until market authorization in Japan.

Subjects will receive a starting dose of 20 mg avatrombopag once daily and will be allowed to change their dose and dosing frequency (maximum dose 40 mg daily, minimum dose 20 mg once weekly) in accordance with their individual platelet responses. The overall goal of any dose modification will be to maintain the platelet count $\geq 50\times10^9$/L and $<200\times10^9$/L, and to decrease the need for concomitant ITP medications.

The study will consist of 3 phases: Pre-enrollment, Primary Investigation (Core), and Extension. The Pre-enrollment Phase will have 1 Screening Period (up to 4 weeks). The Primary Investigation Phase (Core Phase) will have 4 periods: Baseline (1 day), Titration (6 weeks), Concomitant ITP Medication Reduction (12 weeks), and Maintenance (8 weeks including the End-of-Treatment [EOT] Visit). Subjects will have weekly or bi-weekly visits during the 26-week Primary Investigation Phase (Core Phase) to collect the required data on platelet counts, bleeding events, and other AEs. All subjects who complete the Primary Investigation Phase (Core Phase) can continue to receive avatrombopag in the Extension Phase until market authorization in Japan. Safety and efficacy data will be collected monthly in the Extension Phase.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

Subjects will receive avatrombopag as a 20 mg film-coated oral tablet. The dose 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. Compliance with dosing will be reviewed with the subject at each visit. Subjects will be given a dosing diary to complete at home.

Study Drug Dose-Adjustment Guidelines

In accordance with approved overseas labeling, dose and dosage adjustments will target maintaining the platelet count $\geq 50\times10^9$/L and $<200\times10^9$/L and follow the dose-adjustment guidelines presented in Table 1 and Table 2. All subjects will initiate treatment at 20 mg once daily (Dose Level 4).

Investigators must consider dose and dosage titration in accordance with a subject's platelet count every 2 weeks. However, dose titration may be performed weekly for subjects with platelet counts $<50\times10^9$/L or $>400\times10^9$/L.

Table 1 Avatrombopag Dose Levels for Titration

Dose	Level
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	**4**
20 mg Three Times a Week	3
20 mg Twice a Week OR 40 mg Once Weekly	2
20 mg Once Weekly	1

Table 2 Avatrombopag Dose Adjustments

Platelet Count （× 10^9/L）	Dose Adjustment or Action
<50 after at least 2 weeks of Avatrombopag	• Increase One Dose Level per Table 1. • Wait 2 weeks to assess the effects of this regimen and any subsequent dose adjustments.
≥50 to <200	• Keep on the current dose and dosage
≥200 to ≤400	• Decrease One Dose Level per Table 1. • Wait 2 weeks to assess the effects of this regimen and any subsequent dose adjustments.
>400	• Stop Avatrombopag. • Increase platelet monitoring to twice weekly. • When platelet count is less than 150×10^9/L, decrease One Dose Level per Table 1 and reinitiate therapy.
<50 after 4 weeks of 40 mg Avatrombopag once daily	• Discontinue Avatrombopag.
>400 after 2 weeks of 20 mg Avatrombopag weekly	• Discontinue Avatrombopag.

Study Drug Discontinuation

In both the Primary Investigation Phase (Core Phase) and the Extension Phase, study drug may be permanently discontinued at the discretion of the Investigator due to safety reasons, at the request of the subject, or if any of the following occur:

- Platelet count remains <30×10^9/L after more than 3 weeks at the maximum dose level (Level 6) (subjects can be discontinued after 7 days of therapy at the maximum regimen level if they have dangerously low platelet counts in the opinion of the Investigator)
- Subjects who require rescue therapy more than 3 times or continuous rescue therapy for more than 3 weeks
- Excessive platelet count responses (>400×10^9/L) at the minimum dose level (Level 1)
- Treatment with certain ITP therapies/procedures, such as vinca alkaloids, cyclophosphamide, rituximab, splenectomy, or other TPO-RAs (eltrombopag, romiplostim).

Rescue therapy

Subjects will be allowed to receive rescue therapy at the discretion of the Investigator or Sub-Investigator based on their clinical assessment. Rescue therapy should be considered if there is an urgent need to increase platelet count for example:

- Life-threatening thrombocytopenia, such as a platelet count $<10\times10^9$/L
- Major bleed
- Clinical signs or symptoms suggesting potential bleed (i.e., wet purpura)

Rescue therapy will be defined as the addition of any new ITP medication or medication to treat thrombocytopenia (examples below). TPO-RAs are not allowed as rescue therapy.

- Corticosteroids
- Intravenous immunoglobulin (IVIg) therapy
- Anti-D therapy
- Mycophenolate mofetil
- Azathioprine
- Danazol
- Cyclosporin A
- Platelet transfusion
- Any increase in baseline dose of a concomitant ITP medication

Prohibited Concomitant Therapy

Platelet transfusion is prohibited within 7 days before the first dose of study drug. Antifibrinolytic agents (aprotinin, tranexamic acid, and aminocaproic acid) and recombinant activated factor VII are prohibited during the treatment phase of the study. Moderate or strong dual inhibitors/inducers of CYP2C9 and CYP3A4 are prohibited during the study due to PK interactions with avatrombopag. Heparin, warfarin, factor Xa inhibitors, direct thrombin inhibitors, fresh frozen plasma and cryoprecipitate, chronic antiplatelet therapy (>4 weeks) with aspirin, clopidogrel sulfate, prasugrel hydrochloride, ticlopidine, or glycoprotein IIb/IIIa antagonists are prohibited during the Primary Investigation Phase (Core Phase) of the study.

Some ITP therapies/procedures, such as vinca alkaloids, cyclophosphamide, rituximab, splenectomy, and other TPO-RAs (eltrombopag, romiplostim) are prohibited during the Primary Investigation Phase (Core Phase) due to their potential to confound efficacy results. Subjects requiring these therapies will be discontinued from the study.

Hematology Tests

When a hematology test is required, 2 blood samples will be collected: one for central laboratory analysis and one for local laboratory analysis. The local laboratory hematology test result will be used to qualify a subject's entry into the study, study drug and concomitant ITP medication dose titration, and clinical assessment.

Only platelet count data from local laboratories will be collected and entered into the electronic case report form (eCRF) for efficacy analysis. All other hematological parameters will be analyzed at and reported from the designated central laboratory.

Pharmacokinetic (PK) Tests

At Week 2 and at Week 10, three serial blood samples will be collected for bioanalysis of avatrombopag plasma concentrations at the following time points:

- Pre-dose (trough)
- Between 2 and 4 hours post-dose
- Between 6 and 8 hours post-dose

Additionally, sparse PK sampling (a single blood sample) will be obtained during clinic visits at Weeks 1, 4, 6, 16, and 26.

STATISTICAL/DATA ANALYSES:

Details of the statistical analyses will be described in the Statistical Analysis Plan (SAP).

Analysis Populations:

Full Analysis Set (FAS): The FAS will include all subjects who are enrolled into the study.

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

Safety Set: The safety set will include all subjects who receive at least 1 dose of study drug and have a post-dose safety assessment.

Disposition, Demographics, and Baseline Characteristics:

Subject disposition will be summarized for the Safety Population. 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 for the Safety Population. Medical history and concomitant medications will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and WHODrug dictionary and summarized for the Safety Population.

Primary Investigation Phase (Core Phase) Efficacy Analyses:

The primary efficacy variable, the cumulative number of weeks of platelet response, and key secondary efficacy variable, response rate at Day 8, will be determined in the FAS. Analyses in the PPS population will be used as supportive evidence. All analyses of platelet counts will be based on local laboratory results.

The pre-defined hurdle for the primary efficacy endpoint is set such that the lower limit of the 95% confidence interval (CI) of the mean number of cumulative weeks of platelet response $\geq 50 \times 10^9$/L will need to be ≥ 8.02 weeks.

Descriptive statistics will be generated to summarize effectiveness endpoints.

Effectiveness endpoints will be summarized as follows:

- Continuous variables will be summarized by number, mean, median, maximum, and minimum, as appropriate.
- Categorical variables will be summarized by number and percentage, as appropriate.

Additional analyses will be performed using appropriate statistical methodologies as deemed appropriate.

Extension Phase Analyses:

Evaluation of the safety and efficacy data will consist primarily of summary displays and data listings.

Safety:

Evaluation of safety will be performed on the Safety Set. Safety data that will be evaluated include AEs, clinical laboratory results, and vital signs. All AEs will be coded using MedDRA. Adverse events (AEs) will be coded to system organ class and preferred term using MedDRA. AEs will be presented with and without regard to causality based on the Investigator's judgment. The frequency of overall toxicity, categorized by Common Terminology Criteria for Adverse Events (CTCAE) criteria Grades 1 through 5, will be described. Treatment-emergent AEs (TEAEs) will be summarized by presenting the incidence of AEs. Descriptive summary statistics (mean plus standard deviation, median, and range) of the laboratory parameters, vital signs, and changes from baseline will be evaluated.

SAMPLE SIZE DETERMINATION:

Assuming a distribution of results similar to that observed in the overseas Study 302, a sample size of 19 subjects is required to meet the primary efficacy endpoint hurdle of a lower limit of 95% CI ≥8.02 weeks of cumulative platelet response.

SITES: The study will be conducted at approximately 18 sites in Japan.

SPONSOR:

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

TABLE OF CONTENTS

LIST OF TABLES

List of Abbreviations and Definition of Terms

Abbreviation	Definition
ADP	Adenosine Diphosphate
AE	Adverse Event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
β-hCG	Beta-human chorionic gonadotropin
CHF	Congestive Heart Failure
CI	Confidence interval
CIT	Chemotherapy-induced thrombocytopenia
CLD	Chronic liver disease
COVID-19	Coronavirus Disease 2019
CRA	Clinical research associate
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
eCRF	Electronic case report form
EDC	Electronic data capture
EOT	End-of-Treatment
EU	European Union
FAS	Full Analysis Set
GCP	Good Clinical Practice
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITP	Immune thrombocytopenia
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
IVIg	Intravenous gamma globulin
IWG	International Working Group
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
OLE	Open-label extension
PK	Pharmacokinetic(s)
PPS	Per-Protocol Set
SAE	Serious adverse event
SAP	Statistical Analysis Plan

Abbreviation	Definition
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TPO	Thrombopoietin
TPO-RA	Thrombopoietin receptor agonist
ULN	Upper limit of normal
WHO	World Health Organization

1 INTRODUCTION AND BACKGROUND INFORMATION

1.1 Immune Thrombocytopenia

Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by low platelet counts from a combination of both impaired platelet production and increased peripheral platelet destruction. Current guidelines for the treatment of symptomatic ITP include agents that decrease platelet destruction (e.g., corticosteroids, intravenous gamma globulin [IVIg], and intravenous anti-Rho[D]) or suppress the production of antiplatelet antibodies (e.g., immunosuppressants). However, these drugs have variable and transient efficacy, significant toxicities, and relapse is common upon discontinuation. Second-line treatment options include rituximab, high-dose dexamethasone, the thrombopoietin receptor agonists (TPO-RAs) eltrombopag and romiplostim, and splenectomy.

1.2 Avatrombopag

Avatrombopag is an orally administered TPO-RA initially approved in the US in May 2018 for the treatment of thrombocytopenia in adults with chronic liver disease (CLD) who are scheduled for a procedure, and subsequently approved for this indication in the EU (2019) and China (2020). In June 2019, avatrombopag was approved in the US for the treatment of thrombocytopenia in adult patients with chronic ITP who have had an insufficient response to a previous treatment, and subsequently approved for this indication in the EU (2021). Avatrombopag binds the human TPO receptor at a site that is distinct from TPO binding, but it is still capable of stimulating signal transduction and mimicking the biological effects of TPO. It has been shown in vitro to stimulate human megakaryocyte proliferation and differentiation, leading to thrombopoiesis in vivo, without affecting platelet function.

1.3 Nonclinical Studies

The toxicity of avatrombopag has been extensively evaluated in single- and repeated-dose oral toxicity studies in mice, rats, dogs, and cynomolgus monkeys (for up to 13 weeks in mice, 26 weeks in rats, 4 weeks in dogs, and 52 weeks in cynomolgus monkeys). The genotoxicity of avatrombopag was evaluated in vitro and in vivo. Two-year carcinogenicity studies have been conducted in mice and rats. Reproductive and developmental toxicity was evaluated by conducting male and female fertility studies in rats, embryo-fetal development toxicity studies in rats and rabbits, pre- and post-natal development studies in rats, and a juvenile toxicity study in rats. The potential for dermal and eye irritation in rabbits, dermal sensitization in guinea pigs, and phototoxicity in pigmented rats was also evaluated. Nonclinical studies have indicated that avatrombopag was well tolerated and data suggest that avatrombopag is a promising candidate for use in the treatment of thrombocytopenia of diverse etiologies.

Additional details are available in the avatrombopag Investigator's Brochure.

1.4 Clinical Studies

Avatrombopag has been studied in humans in both single- and multiple-dose Phase 1, dose-rising, safety and tolerability studies and in Phase 2 and Phase 3 efficacy and safety studies. Over 1500 subjects have been randomized across the avatrombopag clinical development program. The total safety population from completed studies includes 1260 subjects who received avatrombopag – 574 healthy subjects and 686 patients with either ITP, CLD, or chemotherapy-induced thrombocytopenia (CIT).

In the Phase 2 and 3 studies conducted in adults with chronic ITP, avatrombopag was administered to 128 patients for a median duration of 7 months and a maximum duration of more than 2 years. The primary efficacy endpoint in the pivotal Phase 3 ITP study (Study 302), the cumulative number of weeks with platelet count $\geq 50 \times 10^9$/L during 26 weeks of treatment in the absence of rescue therapy, was a median of 12.4 weeks versus 0 weeks for placebo ($p<0.0001$). The most common (≥10%) adverse events in avatrombopag-treated subjects from the Phase 2 and 3 ITP studies (pooled data) were headache (31%), fatigue (28%), contusion (26%), epistaxis (19%), upper respiratory tract infection (15%), arthralgia (13%), gingival bleeding (13%), petechiae (11%), and nasopharyngitis (10%).

1.4.1 Phase 1 Studies

The clinical pharmacology program was designed to establish the pharmacokinetic (PK) profile of avatrombopag, the determination of the elimination pathways, the investigation of potential clinically important drug-drug interactions, the effects of both intrinsic and extrinsic factors on PK, and the relationship between PK and pharmacodynamic effects related to clinical efficacy. In the completed Phase 1 studies involving 574 healthy subjects exposed to avatrombopag, the most common adverse event (AE) occurring in 5% or more of subjects treated with avatrombopag was headache.

Additional details are available in the avatrombopag Investigator's Brochure.

1.4.2 Phase 2 Studies

In 64 ITP patients who were randomized in a double-blind, placebo-controlled, Phase 2 efficacy and safety study (Study CL-003), avatrombopag demonstrated superior efficacy compared with placebo as measured by platelet response on Day 28. This response was dose-related. Avatrombopag continued to be effective after an additional 6 months of treatment as measured by durable and overall platelet response rates in 53 subjects who continued into a 6-month rollover study (Study CL-004). Durable platelet response was defined as subjects who had at least 75% of their measured platelet count values at response level during the last 14 weeks of the 24-week treatment period and did not receive rescue therapy during the study. All subjects needed to have at least 3 platelet count assessments in the last 14 weeks of Study CL-004. Overall response rate was defined as the proportion of subjects who achieved either a durable response or a transient response (transient response was defined as subjects whose platelet counts were at a response level at 2 or more consecutive analysis windows during the 24-week treatment period of Study CL-004, without having achieved a durable response).

In the combined CL-003 and CL-004 studies, the most common treatment-emergent adverse events (TEAEs), occurring in 5% or more of subjects treated with avatrombopag, were (by decreasing order of frequency) fatigue, headache, epistaxis, contusion, arthralgia, diarrhea, thrombocytopenia, gingival bleeding, back pain, edema peripheral, petechiae, platelet count

increased, vomiting, dyspnea, nausea, upper respiratory tract infection, pain in extremity, ecchymosis, cough, insomnia, dizziness, pharyngolaryngeal pain, hyperlipidemia, nasopharyngitis, and platelet count decreased. Most TEAEs were Grade 1 or Grade 2, transient, and completely resolved.

A total of 130 subjects with thrombocytopenia associated with CLD who were scheduled to undergo elective surgical or diagnostic procedures were enrolled in a Phase 2, randomized, placebo-controlled, double-blind, parallel-group study (Study 202). The subjects were split into 2 cohorts and received either avatrombopag (Cohort A: first generation formulation; Cohort B: second generation formulation) or placebo. The primary analysis of the responder rate in the overall combined avatrombopag group was statistically significant compared with the overall combined placebo group. A similar statistical significance was again noted when the data were adjusted for the etiology of liver disease by a Cochran-Mantel-Haenszel test. Within Cohort B, the response rate in platelet counts by Day 8 increased significantly in subjects receiving treatment with avatrombopag compared with placebo. In addition, a statistically significant reduction was achieved in the proportion of subjects receiving a platelet transfusion before elective invasive procedures in Cohort B compared with placebo. The most commonly reported TEAEs, occurring in 5% or more of subjects treated with avatrombopag, were (by decreasing order of frequency) nausea, fatigue, headache, portal hypertensive gastropathy, diarrhea, dizziness, muscle spasms, procedural pain, varices esophageal, vomiting, abdominal pain upper, and edema peripheral.

Study 203 was a Phase 2 multicenter, multinational, randomized, placebo-controlled, double-blind, parallel-group study to demonstrate the efficacy of once daily dosing with avatrombopag compared to placebo in subjects with chronic HCV-related thrombocytopenia who were potential candidates for antiviral treatment. Prior to the initiation of antiviral therapy, the most commonly reported TEAEs (≥5% of subjects) in the combined avatrombopag group were nausea and fatigue. The most commonly reported TEAEs (≥5% of subjects) during the Core Study and Extension Phase included anemia, neutropenia, nausea, fatigue, pruritus, leukopenia, chills, insomnia, headache, rash, diarrhea, influenza-like illness, cough, pyrexia, asthenia, vomiting, irritability, abdominal pain, ascites, injection site erythema, edema peripheral, epistaxis, abdominal pain upper, depression, lymphopenia, dyspepsia, hemorrhoids, nasopharyngitis, upper respiratory tract infection, hyperuricemia, dizziness, dyspnea, and dyspnea exertional. The majority of these commonly reported TEAEs occurred after the initiation of antiviral treatment and are consistent with what is expected in patients receiving antiviral therapy with interferon, ribavirin, and/or telaprevir.

In Study 204, a Phase 2, randomized, placebo-controlled, double-blind, parallel-group study, a total of 39 Japanese subjects with thrombocytopenia associated with CLD were randomly assigned to a study group and received placebo or avatrombopag. The primary analysis of the responder rate (responders were defined as subjects with a platelet count $\geq 50\times10^9$/L and who showed at least 20×10^9/L increase from baseline at Visit 4 [Days 10 to 13]) in the avatrombopag 40 mg and 60 mg groups was statistically significant compared with the placebo group. The most commonly reported TEAEs (≥5% of subjects) in the avatrombopag group were, by decreasing order of frequency, post-procedural complication, post-embolisation syndrome, diarrhea, blood glucose increased, hemorrhage subcutaneous, constipation, and nasopharyngitis.

1.4.3 Phase 3 Studies

Five Phase 3 efficacy and safety studies (Studies 302, 305, 310, 311, and 330) were conducted in patients with ITP, CIT, or CLD. A Phase 3 pediatric ITP study is ongoing (AVA-PED-301).

In Study 302, a multicenter, randomized, double-blind, placebo-controlled, parallel-group study with an open-label extension (OLE) phase treating thrombocytopenia in adults with chronic ITP, subjects received oral avatrombopag or matching placebo, with a starting dose of 20 mg once daily avatrombopag, followed with dose titration up to a maximum dose of 40 mg or down to a minimum dose of 5 mg. The OLE included once daily oral dosing with a starting dose of 20 mg avatrombopag, followed with dose titration (5, 10, 20, 30, or 40 mg doses). The primary efficacy endpoint was highly statistically significant, favoring avatrombopag ($p<0.0001$) compared with placebo. The median of the cumulative number of weeks with platelet count $\geq 50\times10^9$/L during the 6-month treatment was 12.4 weeks for avatrombopag and 0 weeks for placebo. The most commonly reported TEAEs (≥5% of subjects) in the avatrombopag group in the Core Study were headache, contusion, upper respiratory tract infection, arthralgia, epistaxis, fatigue, gingival bleeding, petechiae, back pain, insomnia, mouth hemorrhage, nasopharyngitis, nausea, anemia, blood gastrin increased, cough, hypertension, influenza, thrombocytopenia, and vomiting. In the combined Core Study and Extension Phase in the avatrombopag group (n=47), the most commonly reported TEAEs (≥5% of subjects) were contusion, headache, upper respiratory tract infection, thrombocytopenia, epistaxis, gingival bleeding, fatigue, petechiae, pharyngitis, arthralgia, hypertension, nasopharyngitis, back pain, influenza, mouth hemorrhage, cough, insomnia, nausea, pain in extremity, and urinary tract infection.

In Study 305, a multicenter, randomized, double-blind, active-controlled, parallel-group study with an OLE phase in adults with chronic ITP, subjects received oral avatrombopag at 5, 10, 20, 30, or 40 mg, with a starting dose of avatrombopag 20 mg, followed with dose titration down to 5 mg or up to 40 mg. A total of 23 subjects were randomized into the study prior to the premature termination of the study due to slow enrollment. The most commonly reported TEAEs in the avatrombopag group in the Core Study were dizziness, headache, insomnia, musculoskeletal pain, and nausea, (3 [25.0%] subjects each). During the combined Core Study and Extension Phase, the most commonly reported TEAEs were fatigue and headache (5 [29.4%] subjects each) and dizziness, insomnia, and nasopharyngitis (4 [23.5%] subjects each).

Two (16.7%) subjects in the avatrombopag group had serious adverse events (SAEs) during the Core Study. The event of ITP was not considered by the Investigator to be related to treatment. The events of portal vein thrombosis and thrombophlebitis septic were considered by the Investigator to be possibly related to investigational product.

Studies 310 and 311 enrolled adults with CLD and severe thrombocytopenia (mean baseline platelet count $<50\times10^9$/L), scheduled to undergo invasive procedures. Cohorts were defined based on baseline platelet count (Cohort 1, $<40\times10^9$/L or Cohort 2, 40 to $<50\times10^9$/L), and patients were randomized 2:1 to once daily oral avatrombopag (60 mg for Cohort 1, 40 mg for Cohort 2) or placebo for 5 days, with the procedure scheduled 5 to 8 days after their last dose.

The primary efficacy endpoint was the proportion of patients not requiring platelet transfusion or any bleeding rescue procedure up to 7 days post-procedure. Secondary endpoints assessed the proportion of patients achieving the target platelet count ($\geq 50\times10^9$/L), change in platelet count from baseline to Procedure Day, and safety.

Study 310 enrolled 231 patients to 1 of 2 possible cohorts based on baseline platelet count, then patients were randomized to avatrombopag or placebo within each cohort: Cohort 1 (90 avatrombopag patients/48 placebo patients) or Cohort 2 (59 avatrombopag patients/34 placebo patients). Patients had a median age of 57 years with 68% of patients being male and a baseline median platelet count of 38×10^9/L. The CLD etiology of patients was 14% alcohol, 62% viral hepatitis, and 23% other. Study 311 enrolled 204 patients to 1 of 2 possible cohorts based on baseline platelet count, then patients were randomized to avatrombopag or placebo within each cohort: Cohort 1 (70 avatrombopag patients/43 placebo patients) or Cohort 2 (58 avatrombopag patients/33 placebo patients). Patients had a median age of 59 years with 62% of patients being male and a baseline median platelet count of 39×10^9/L. The CLD etiology of patients was 15% alcohol, 53% viral hepatitis, and 33% other. Significantly greater proportions of avatrombopag-treated patients across all cohorts did not require platelet transfusion or bleeding rescue procedures compared with placebo: Study 310: Cohort 1, 66% versus 23%; Cohort 2, 88% versus 38%; each $p<0.0001$; Study 311: Cohort 1, 69% versus 35%, $p=0.0006$; Cohort 2, 89% versus 33%, $p<0.0001$. Avatrombopag was also superior to placebo for both secondary endpoints, increasing mean platelet counts on Procedure Day to 64×10^9/L in Cohort 1 and 85×10^9/L in Cohort 2. The most common TEAEs were pyrexia, abdominal pain, nausea, and headache, which were similar for placebo and avatrombopag arms in both studies. Most TEAEs were mild to moderate in severity; however, 1 thrombotic TEAE occurred in Cohort 2 (40 mg avatrombopag) in Study 311. The studies concluded avatrombopag given over 5 days significantly reduced the need for platelet transfusions or rescue procedures for bleeding, and it was well tolerated with a safety profile similar to placebo.

Study 330 randomized 122 subjects with CIT in a double-blind, placebo-controlled study with an OLE to evaluate the safety and efficacy of avatrombopag for the treatment of chemotherapy-induced thrombocytopenia in subjects with active non-hematological cancers. Subjects either received 60 mg daily avatrombopag (n=82) or placebo (n=40) for 5 days prior to and 5 days after the first day of a chemotherapy cycle in the Core Study.

The primary endpoint was a composite endpoint; responders could not have had a platelet transfusion or had a chemotherapy dose delay due to thrombocytopenia or had a chemotherapy dose reduction due to thrombocytopenia. While avatrombopag did increase platelet counts over placebo as expected, the percentage of responders in the avatrombopag arm was slightly lower than that of the placebo arm (69.5% vs. 72.5%; $p=0.72$). Based on the pre-specified threshold of two-sided alpha=0.05, the primary efficacy endpoint was not met. When performing the analysis on the Per-Protocol population, the percentage of responders was similar in the avatrombopag and placebo treatment groups (85.0% versus 84.4%; $p=0.96$).

In the Core Study, the incidence rate for TEAEs was similar between all subjects in the avatrombopag (86.6% [71/82] subjects) and placebo treatment groups (90.0% [36/40] subjects). The most commonly reported TEAEs, occurring in 5% or more of subjects treated with avatrombopag (by decreasing order of frequency) were: anaemia, leukopenia, neutropenia, thrombocytopenia, thrombocytosis, nausea, asthenia, and vomiting.

1.5 Rationale for Study Design

This confirmatory, open-label study will evaluate the efficacy, safety, and PK of avatrombopag in Japanese adults with ITP. While a placebo control group was included in the pivotal avatrombopag overseas study, the mean number of cumulative weeks with a platelet response in this group was zero (0), a result which is consistent with placebo control groups in other ITP studies. Therefore, inclusion of a placebo control group in this study would not be expected to be informative. To compare this study's data to the data from the pivotal Study 302, the study design (other than not including a placebo control) will replicate that of the overseas study. Avatrombopag will be evaluated over a duration of 26 weeks and the primary efficacy endpoint will be the cumulative number of weeks of platelet response $\geq 50 \times 10^9$/L. All subjects who complete the Primary Investigation Phase (Core Phase) can continue to receive avatrombopag in the Extension Phase until market authorization in Japan. Safety and efficacy data will be collected monthly in the Extension Phase.

2 STUDY OBJECTIVES

2.1 Primary Investigation Phase (Core Phase)

2.1.1 Primary Objective

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

2.1.2 Secondary Objectives

The secondary objectives are:

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

2.1.3 Exploratory Objectives

The exploratory objectives are:

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

2.2 Extension Phase

2.2.1 Primary Objective

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

2.2.2 Secondary Objective

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

3 STUDY ENDPOINTS

3.1 Primary Efficacy Endpoint

In the Primary Investigation Phase (Core Phase), the primary efficacy endpoint is the cumulative number of weeks in which the platelet count is $\geq 50\times10^9$/L during 26 weeks of treatment in the absence of rescue therapy.

Subjects using rescue therapy at any time during the 26-week treatment period will be considered not to have any platelet responses for all subsequent weeks after rescue therapy. A platelet response will be defined as a platelet count of $\geq 50\times10^9$/L and nonresponse will be defined as a platelet count $<50\times10^9$/L. All analyses of platelet counts will be based on local laboratory results.

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

3.2 Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is the platelet response rate at Day 8 (as defined by the proportion of subjects with a platelet response $\geq 50\times10^9$/L at Day 8). Subjects with missing platelet counts at Day 8 or use of a rescue therapy before or on Day 8 will be considered platelet nonresponders.

3.3 Other Efficacy Endpoints

Other efficacy endpoints include the following:

- Durable platelet response as defined by: proportion of subjects who have at least 6 of 8 (i.e., ≥75%) weekly platelet counts $\geq 50\times10^9$/L during the last 8 weeks of treatment over the 26-week treatment period in the absence of rescue therapy
- Incidence and severity of bleeding symptoms associated with ITP, including bleeding, bruising, and petechiae, measured using the WHO Bleeding Scale
- Maximum duration (in weeks) of continuous response for each subject
- Proportion of subjects receiving rescue therapy during the 26-week duration of the study
- Proportion of subjects with a discontinuation in use of concomitant ITP medications from baseline
- Complete responder by International Working Group (IWG) definition: platelet count $\geq 100\times10^9$/L and absence of bleeding (Rodeghiero, 2009)
- Responder by IWG definition: platelet count $\geq 30\times10^9$/L and at least a 2-fold increase in baseline count and absence of bleeding (Rodeghiero, 2009)

Additionally, in the Extension Phase, effectiveness will be assessed by measuring platelet counts, reduction in use of concomitant ITP medication, and bleeding events. Specifically,

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

4 STUDY DESCRIPTION

4.1 Summary of Study Design

This study is an open-label study of avatrombopag in Japanese men and women ≥18 years who have chronic ITP. Approximately 19 subjects who meet all the eligibility requirements will be enrolled. The Screening Visit and Day 1 Baseline Visit platelet counts will be averaged to obtain the baseline platelet count value. The 2 samples must be obtained ≥48 hours and ≤2 weeks apart and the results must be available prior to enrollment. No single platelet count can be $>35\times10^9$/L. An additional screening platelet count is required if the second platelet count is outside of the 2-week window.

Subjects will receive a starting dose of 20 mg avatrombopag once daily and will be allowed to change their dose and dosing frequency (maximum dose 40 mg daily, minimum dose 20 mg once weekly) in accordance with their individual platelet responses. The overall goal of any dose modification will be to maintain the platelet count $\geq50\times10^9$/L and $<200\times10^9$/L, and to decrease the need for concomitant ITP medications.

The study will consist of 3 phases: Pre-enrollment, Primary Investigation (Core Phase), and Extension. The Pre-enrollment Phase will have 1 Screening Period (up to 4 weeks). The Primary Investigation Phase (Core Phase) will have 4 periods: Baseline (1 day), Titration (6 weeks), Concomitant ITP Medication Reduction (12 weeks), and Maintenance (8 weeks including the End-of-Treatment [EOT] Visit). Subjects will have weekly or bi-weekly visits during the 26-week Primary Investigation Phase (Core Phase) to collect the required platelet count data, bleeding events, and other AEs. All subjects who complete the Primary Investigation Phase (Core Phase) can continue to receive avatrombopag in the Extension Phase until market authorization in Japan. Safety and efficacy data will be collected monthly in the Extension Phase. Dose-tapering and Follow-up at the end of the Core Phase are required only for those subjects not continuing into the Extension Phase.

The total study duration of the Pre-enrollment and Primary Investigation Phase will be up to 7 months. Subjects may continue in the Extension Phase until market authorization in Japan.

4.2 Pre-enrollment Phase

4.2.1 Screening Period (Visit 1)

During this period, subjects will be assessed for eligibility and have a platelet count performed.

The Screening Visit and Day 1 Baseline Visit platelet counts will be averaged to obtain the baseline platelet count value. The 2 samples must be obtained ≥48 hours and ≤2 weeks apart and the results must be available prior to enrollment. Therefore, an additional screening platelet count may be required due to issues with scheduling. If an additional platelet count is taken, an average of the last 2 platelet counts of ≥48 hours apart must be $<30\times10^9$/L for eligibility. No single platelet count can be $>35\times10^9$/L.

Reasons for screen failure will be collected in the electronic case report form (eCRF).

4.3 Core Phase

4.3.1 Baseline Visit (Visit 2)

During this visit, baseline assessments, including platelet count, will be performed and avatrombopag administration will be started.

4.3.2 Dose and Dosage Titration Period (Visits 3 to 7)

During this period, dose, and dosage titration of avatrombopag from the initial starting dose will be performed in accordance with protocol-specified dose and dosage titration guidelines in order to find the minimum dose required to maintain platelet counts of $\geq 50\times10^9$/L and $<200\times10^9$/L. No downward titration of concomitant ITP medication will be permitted during this period unless there is a safety concern. Subjects will return on Days 5, 8, 14, 21 and 28 during this period.

4.3.3 Concomitant ITP Medication Reduction Period (Visits 8 to 13)

During this period, downward titration of concomitant ITP medication will be permitted in accordance with the guidelines described in Section 6.5.3. This may require additional study drug dose and dosage adjustments before and after the concomitant ITP medication downward titration. Subjects will return every 2 weeks during this period.

4.3.4 Maintenance Period (Visits 14 to 22)

Subjects will continue treatment in order to maintain platelet counts of $\geq 50\times10^9$/L and $<200\times10^9$/L. Study drug dose and dosage adjustments will be made in accordance with the dose and dosage titration guidelines. No downward titration of concomitant ITP medication will be permitted during this period unless there is a safety concern. Subjects will return weekly for visits.

At the EOT Visit (Visit 22), subjects will have the option to enter the Extension Phase and continue to receive avatrombopag. Subjects who are unable or unwilling to continue in the Extension Phase of the study will enter the Dose/dosage tapering and Follow-up Periods.

Subjects who require study drug dose adjustments, who undergo concomitant ITP medication reduction or who receive rescue therapy during the periods of Concomitant Medication Reduction and Maintenance Periods are required to return for weekly visits for 3 consecutive weeks.

4.3.5 Dose-tapering Period (Visits 23 to 26)

During this period, subjects who do not continue into the Extension Phase will be required to attend weekly visits at which the study drug will be down titrated 1 dose level per week until the study drug is discontinued. This can take up to 4 weeks (see Table 1). During the Dose-tapering Period, subsequent upward titration or addition of concomitant ITP medication should be considered, at the Investigator's discretion, to prevent the recurrence of thrombocytopenia. Once the dose tapering is complete, subjects will go directly to the Follow-up Visit (Visit 27).

4.3.6 Follow-up Period (Visits 27 to 30)

During this period, subjects will be followed for 4 weeks after the last dose taken in the Dose-tapering Period. Subjects will return approximately every week for visits during this period and will have their final evaluations on the last day of the Follow-up Period. Platelet counts will be carefully monitored during this period for the recurrence of thrombocytopenia.

Subsequent upward titration or addition of concomitant ITP medication should be considered, at the Investigator's discretion, to prevent the recurrence of thrombocytopenia.

4.4 Extension Phase

Those subjects who meet all the eligibility requirements for the Extension Phase and who are willing and able will enter the Extension Phase and can continue to receive avatrombopag in the Extension Phase until market authorization in Japan. Subjects entering directly into the Extension Phase will not enter the Dose-tapering and Follow-up Periods of the Core Study.

Safety and efficacy data will be collected monthly in the Extension Phase. Subjects who require study drug dose adjustments, who undergo concomitant ITP medication reduction, or who receive rescue therapy during the Extension Phase are required to return for weekly visits for 3 consecutive weeks.

4.5 Study Indication

The indication for this study is the treatment of chronic primary ITP in adults.

5 SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Inclusion Criteria

5.1.1 Primary Investigation Phase (Core Phase)

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

1. Men and women ≥18 years of age.
2. Subject must be able to provide informed consent.
3. Subject has a confirmed diagnosis of chronic ITP (≥12 months duration) and has had an insufficient response to a previous ITP treatment, in the opinion of the Investigator.
4. Subject has an average of 2 platelet counts $<30\times10^9$/L (no single count can be $>35\times10^9$/L). The 2 samples must be obtained ≥48 hours and ≤2 weeks apart.

5.1.2 Extension Phase

1. No significant safety or tolerability concerns with the subject's participation in the Primary Investigation Phase (Core Phase) as determined by the Investigator.

5.2 Exclusion Criteria

5.2.1 Primary Investigation Phase (Core Phase)

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

1. Subjects with known secondary immune thrombocytopenia (e.g., with known *Helicobacter pylori*-induced ITP, subjects infected with known human immunodeficiency virus [HIV] or HCV or subjects with known systemic lupus erythematosus).
2. Subjects with known inherited thrombocytopenia (e.g., MYH-9 disorders) or hereditary thrombophilic disorders (e.g., Factor V Leiden, antithrombin III deficiency).
3. History of myelodysplastic syndrome (MDS).
4. History of arterial or venous thrombosis.
5. Subjects with a history of significant cardiovascular disease (e.g., congestive heart failure [CHF] New York Heart Association Grade III/IV, arrhythmia known to increase the risk of thromboembolic events [e.g., atrial fibrillation], angina, coronary artery stent placement, angioplasty, coronary artery bypass grafting).
6. Subjects with a history of cirrhosis, portal hypertension, or chronic active hepatitis.
7. Subjects with concurrent malignant disease or receiving cytotoxic chemotherapy for a reason other than ITP treatment.
8. Use of immunoglobulins (IVIg and anti-D) or corticosteroid rescue therapy within 1 week of Day 1/Baseline.
9. Splenectomy or use of rituximab within 12 weeks of Day 1/Baseline.
10. Use of romiplostim or eltrombopag within 1 week of Day 1/Baseline.

11. Use of chronic corticosteroid treatment or azathioprine within 4 weeks of Day1/Baseline, unless receiving a stable dose for at least 4 weeks.
12. Use of mycophenolate mofetil, cyclosporin A, or danazol within 4 weeks of Day1/Baseline, unless receiving a stable dose for at least 12 weeks.
13. Use of cyclophosphamide or vinca alkaloid regimens within 4 weeks of Baseline Visit.
14. Currently receiving moderate or strong dual inhibitors/inducers of CYP2C9 and CYP3A4 (see Appendix D for examples).
15. Serum creatinine ≥1.5× the upper limit of normal (ULN).
16. Serum bilirubin ≥2×ULN.
17. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3×ULN.
18. Females who are pregnant (positive beta-human chorionic gonadotropin positive [β-hCG] test) or breastfeeding.
19. Known allergy to avatrombopag or any of its excipients.
20. Received treatment with an investigational drug within 30 days or 5 half-lives (whichever is longer) before Day 1/Baseline.
21. Any clinically relevant abnormality which makes the subject unsuitable for participation in the study, in the opinion of the Investigator.
22. Considered unable or unwilling to comply with the study protocol requirements.

5.2.2 Extension Phase

1. Subjects for whom participation in the Extension Phase is considered inappropriate, based on the Investigator's judgment.
2. Subjects considered unable or unwilling to comply with the study protocol requirements, as determined by the Investigator.

5.3 Withdrawal Criteria

Participation of a subject in this clinical study may be discontinued for any of the following reasons:

- The subject withdraws consent or requests discontinuation from the study for any reason
- Occurrence of any medical condition or circumstance that exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements of the protocol
- Subject non-compliance or unwillingness to comply with the procedures required by the protocol
- Subject failed to meet inclusion/exclusion criterion

- Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition which indicates to the Investigator that continued participation is not in the best interest of the subject
- Pregnancy
- Investigator discretion
- Sponsor request
- Subject requires prohibited concomitant medication
- Termination of the study by the Sponsor or the regulatory authority

If a subject withdraws prematurely from the study due to the above criteria or any other reason, study staff should make every effort to complete the EOT assessments for the applicable phase. The reason for subject withdrawal must be documented in the eCRF.

In the case of subjects lost to follow-up, attempts to contact the subject must be made and documented.

If a subject is early terminated from the study, the EOT procedures should be performed. Subjects early terminated from the study will not be replaced, regardless of the reason for early termination.

5.3.1 Subjects with Study Drug Discontinuation

In both the Primary Investigation Phase (Core Phase) and the Extension Phase, study drug may be permanently discontinued at the discretion of the Investigator due to safety reasons, at the request of the subject, or if any of the following occur:

- Platelet count remains $<30\times10^9$/L after more than 3 weeks at the maximum dose level (Level 6) (subjects can be discontinued after 7 days of therapy at the maximum dose level if they have dangerously low platelet counts in the opinion of the Investigator)
- Subjects who require rescue therapy more than 3 times or continuous rescue therapy for more than 3 weeks
- Excessive platelet count responses ($>400\times10^9$/L) at the minimum dose level (Level 1)
- Treatment with certain ITP therapies/procedures, such as vinca alkaloids, cyclophosphamide, rituximab, splenectomy, or other TPO-RAs (eltrombopag, romiplostim).

If a subject discontinues study drug due to an AE, the Investigator will attempt to follow the event until it has resolved or stabilized.

If possible, a subject who discontinues treatment will complete the EOT assessments for the applicable phase and protocol-specified information will be collected. The primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from study drug(s) as well as the date of last dose should be collected in the CRF.

6 STUDY TREATMENTS

6.1 Treatment Groups

All subjects enrolled in this study will receive open-label avatrombopag.

6.2 Rationale for Dosing

Avatrombopag dosing instructions in this protocol are in accordance with approved overseas labeling, dose and dosage adjustments and will target maintaining the platelet count $\geq 50\times10^9$/L and $<200\times10^9$/L and follow the dose-adjustment guidelines presented in Table 1 and Table 2. All subjects will initiate treatment at 20 mg once daily (Dose Level 4).

6.3 Blinding

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

6.4 Drug Supplies

6.4.1 Formulation and Packaging

Avatrombopag will be provided as film-coated tablets, with each tablet containing avatrombopag maleate (equivalent to 20 mg of avatrombopag) and the following excipients: lactose monohydrate, colloidal silicon dioxide, crospovidone, magnesium stearate, microcrystalline cellulose, and Opadry II 85F42244.

6.4.2 Study Drug Dispensing

A sufficient supply of tablets will be provided to the clinical site in blister cards. The clinical site will dispense the number of tablets required for dosing each subject during the study.

6.4.3 Study Drug Administration

Subjects will receive avatrombopag as a 20 mg film-coated oral tablet. The dose 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. Compliance with dosing will be reviewed with the subject at each visit. Subjects will be given a dosing diary to complete at home.

6.4.4 Study Drug Dose-Adjustment Guidelines

In accordance with approved overseas labeling, dose and dosage adjustments will target maintaining the platelet count $\geq 50\times10^9$/L and $<200\times10^9$/L and follow the dose-adjustment guidelines presented in Table 1 and Table 2. All subjects will initiate treatment at 20 mg once daily (Dose Level 4).

Investigators must consider dose and dosage titration in accordance with a subject's platelet count every 2 weeks. However, dose titration may be performed weekly for subjects with platelet counts $<50\times10^9$/L or $>400\times10^9$/L.

Table 1 Avatrombopag Dose Levels for Titration

Dose*	Level
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	**4**
20 mg Three Times a Week	3
20 mg Twice a Week OR 40 mg Once Weekly	2
20 mg Once Weekly	1

* Subjects taking avatrombopag less frequently than once daily should take the medication in a consistent manner from week to week.
Dose Level 3: Three non-consecutive days a week, e.g., Monday, Wednesday and Friday
Dose Level 2: Two non-consecutive days a week, e.g., Monday and Friday
Dose Level 1: The same day each week, e.g., Monday

Table 2 Avatrombopag Dose Adjustments

Platelet Count (× 10^9/L)	Dose Adjustment or Action
<50 after at least 2 weeks of Avatrombopag	• Increase One Dose Level per Table 1. • Wait 2 weeks to assess the effects of this regimen and any subsequent dose adjustments.
≥50 to <200	• Keep on the current dose and dosage
≥200 to ≤400	• Decrease One Dose Level per Table 1. • Wait 2 weeks to assess the effects of this regimen and any subsequent dose adjustments.
>400	• Stop Avatrombopag. • Increase platelet monitoring to twice weekly. • When platelet count is less than 150×10^9/L, decrease One Dose Level per Table 1 and reinitiate therapy.
<50 after 4 weeks of 40 mg Avatrombopag once daily	• Discontinue Avatrombopag.
>400 after 2 weeks of 20 mg Avatrombopag weekly	• Discontinue Avatrombopag.

6.4.5 Treatment Compliance

Subjects will be given a dosing diary to complete at home. Compliance with study drug administration will be reviewed with the subject at each visit and assessed by counting returned study drug packages and any unused study drug in addition to reviewing the dosing diary entries. Any discrepancies between the returned study drug (number of packages and number of tablets) and dosing in the dosing diary will be discussed with the subject and recorded in the source documents. Number of tablets dispensed, and number of tablets returned will be recorded on the appropriate drug accountability eCRF.

6.4.6 Storage and Accountability

Avatrombopag should be stored in a secure location at a controlled room temperature (20˚C to 25˚C/68˚F to 77˚F) with excursions permitted to 15˚C to 30˚C (59˚F to 86˚F).

Records will be maintained indicating the receipt and dispensation of all study drug. At the conclusion of the study, any unused study drug will be returned to the Sponsor or the Sponsor's designee or may be destroyed at the site if appropriate procedures are in place. If no supply remains, this will be indicated in the Drug Accountability Log.

6.5 Concomitant Medications and/or Procedures

For subjects who receive study drug, any medication (including over-the-counter medications), therapy administered, or have procedures performed during the course of the study will be recorded on the eCRF. The Investigator will record any AE for which the concomitant medication/therapy was administered.

6.5.1 Excluded Medications and/or Procedures

The following medications and/or procedures are excluded:

- Platelet transfusion within 7 days before the first dose of study drug.
- Antifibrinolytic agents (aprotinin, tranexamic acid, and aminocaproic acid) and recombinant activated factor VII are prohibited during the treatment phase of the study.
- Moderate or strong dual inhibitors/inducers of CYP2C9 and CYP3A4 are prohibited during the study due to PK interactions with avatrombopag (see Appendix D for examples).
- Heparin, warfarin, factor Xa inhibitors, direct thrombin inhibitors, fresh frozen plasma and cryoprecipitate, chronic antiplatelet therapy (>4 weeks) with aspirin, clopidogrel sulfate, prasugrel hydrochloride, ticlopidine, or glycoprotein IIb/IIIa antagonists are prohibited during the Primary Investigation Phase (Core Phase) of the study.
- Some ITP therapies/procedures, such as vinca alkaloids, cyclophosphamide, rituximab, splenectomy, and other TPO-RAs (eltrombopag, romiplostim) are prohibited during the Primary Investigation Phase (Core Phase) due to their potential to confound efficacy results. Subjects requiring these therapies will be discontinued from the study.
- 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 is permitted.

6.5.2 Allowed Medications and/or Procedures

Coronavirus Disease 2019 (COVID-19) vaccinations (and any other vaccinations) are allowed with no restrictions on the specific type. There will be no impact due to a vaccination on the study drug administration or the ability to enroll in the study. Any administered vaccine should be recorded as a concomitant medication.

Subjects should be instructed to contact site personnel before starting any new treatments. Treatments not specified as prohibited are permitted during the study.

Permitted ITP concomitant background therapies are as follows:

- Corticosteroids and/or azathioprine must be taken at a stable dose for 4 weeks before enrollment
- mycophenolate mofetil, cyclosporin A, or danazol must be taken at a stable dose for at least 12 weeks before enrollment

At the discretion of the Investigator, subjects will be allowed to use aspirin, other salicylates, or approved adenosine diphosphate (ADP) receptor antagonists, (e.g., clopidogrel, prasugrel) during the study once their platelet count has risen.

6.5.3 Concomitant ITP Medication Downward Titration Guidelines

Those subjects receiving concomitant ITP medication when entering the study may have this medication down titrated and ultimately eliminated. This can only occur during the Concomitant ITP Medication Reduction Period (Visits 8 to 13) of the Core Phase.

Downward titration of concomitant ITP medication can be implemented at the discretion of the Investigator but should only be considered if the subject's platelet count remains $>200\times10^9$/L. The downward titration of concomitant ITP medication will be preferred over downward titration of study drug (i.e., instead of titrating down avatrombopag, the concomitant ITP medication will be down titrated). Any downward titration of ITP medication should occur in a controlled manner in order to prevent an excessive and unsafe drop in the subject's platelet count. Concomitant ITP medication downward titration guidelines are detailed below.

- Concomitant ITP medication downward titration should not take place at a rate faster than once (1 time) every 14 days.
- If a subject has 2 or more concomitant ITP medications, only 1 medication can be down titrated at a time.
- It is preferable that a concomitant ITP medication is eliminated before the downward titration of a second concomitant ITP medication, unless the Investigator considers it beneficial for the subject to continue to receive low-dose steroids.

If a subject has a platelet count of $>400\times10^9$/L and the subject is undergoing concomitant ITP medication downward titration, avatrombopag should not be stopped; this is to prevent a dangerous drop in platelet count.

6.5.4 Rescue Therapy

Subjects will be allowed to receive rescue therapy at the discretion of the Investigator or Sub-Investigator based on their clinical assessment. Rescue therapy should be considered if there is an urgent need to increase platelet count for example:

- Life-threatening thrombocytopenia, such as a platelet count $<10\times10^9$/L
- Major bleed
- Clinical signs or symptoms suggesting potential bleed (i.e., wet purpura)

Rescue therapy will be defined as the addition of any new ITP medication or medication to treat thrombocytopenia (examples below). TPO receptor agonists are not allowed as rescue therapy.

- Corticosteroids
- Intravenous immunoglobulin (IVIg) therapy
- Anti-D therapy
- Mycophenolate mofetil
- Azathioprine
- Danazol
- Cyclosporin A
- Platelet transfusion
- Any increase in baseline dose of a concomitant ITP medication

6.5.5 Contraception Requirements

For this study, a woman is considered of childbearing potential, i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Females of childbearing potential and males who are sexually active must agree to use one of the following effective methods of birth control while participating in the study and for 30 days after the last dose of study drug

- oral hormonal contraception
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomized partner
- male or female condom
- cap, diaphragm, or sponge with spermicide

Sexual abstinence, defined as refraining from heterosexual intercourse, 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.

6.5.6 Documentation of Concomitant Medication Use

All concomitant medications (including concurrent therapies and concurrent procedures) will be documented from the time of informed consent to the subject's last visit. Dose, indication for administration, and dates of medication administration will also be captured in source documents and on the appropriate eCRF.

6.6 Screen Failures

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

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

- ICF signature date
- Demographic information
- Reason for screen failure (e.g., inclusion criteria not met/exclusion criteria met)

Subjects who screen fail may be re-screened one time.

7 STUDY PROCEDURES

A schedule of procedures in tabular format for the Core Phase is provided in Appendix A. If any subject visits or assessments are impacted by COVID they will be documented in the corresponding eCRF page.

7.1 Pre-enrollment Phase

7.1.1 Visit 1/Day -28 to Day -1: Screening

The following assessments must be completed at the Screening Visit:

- Collect signed and dated informed consent prior to any study procedures.
- Review of inclusion/exclusion criteria (Section 5).
- Record demographic information.
- Perform physical exam
- Complete medical/medication/surgical history to include all past significant illnesses and/or surgeries (in the opinion of the Investigator) and all medications currently being taken (including non-prescription medications, vitamins, dietary supplements, and herbal products).
- Collect ITP history
    - Date of diagnosis.
    - Number of platelet transfusions in the previous 1 year, including date of last platelet transfusion.
    - Number of previous hospitalizations for ITP.
    - Number of previous significant bleeding events (e.g., blood loss ≥100 mL).
    - Other previous treatments for ITP, including duration.
- Collect height and weight to determine body mass index (calculated by eCRF).
- Collect vital signs (blood pressure and pulse). Vital signs should be taken after sitting for 5 minutes whenever possible. Vital signs should be taken prior to any blood draws.
- Collect blood for central laboratory tests (see Section 9.7).
- Collect platelet counts via local lab.
- Perform pregnancy test for female subjects of childbearing potential.
- Review and record AEs that may have occurred after signing informed consent.
- Record concomitant medications and procedures.

7.2 Core Phase

7.2.1 Visit 2/Day 1: Baseline Visit

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

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

- Review of inclusion/exclusion criteria (Section 5) to confirm continued study eligibility.
- Collect vital signs (blood pressure and pulse). Vital signs should be taken after sitting for 5 minutes whenever possible. Vital signs should be taken prior to any blood draws.
- Collect blood for central laboratory tests (see Section 9.7).
- Collect platelet counts via local lab.
- Perform pregnancy test for female subjects of childbearing potential. Urine or serum pregnancy test should be performed prior to enrollment.
- Perform WHO Bleeding Scale Assessment (Appendix C). The Investigator should ask the subject the following question: "Have you had any bleeding or bruising within the last 7 days?"
- Dispense study drug and review administration instructions.
- Dispense diary.
- Perform physical exam.
- Review and record AEs that may have occurred after signing informed consent.
- Record concomitant medications and procedures.

7.2.2 Visits 3-7/Days 5-28 and Weeks 1-4: Dose-Titration Period (Weekly Visits)

The following procedures should be performed:

- Collect vital signs (blood pressure and pulse). Vital signs should be taken after sitting for 5 minutes whenever possible. Vital signs should be taken prior to any blood draws.
- Collect blood for central laboratory tests at Visit 4/Week 1 (see Section 9.7).
- Collect platelet counts via local lab at each visit.
- Perform PK sampling:
    - Sparse PK samples are collected at Visit 4/Week 1 and Visit 7/ Week 4
    - Three (3) serial PK samples are collected at Visit 5/Week 2, one pre-dose, one between 2 and 4 hours post-dose, and one between 6 and 8 hours post-dose. Visit 5 should occur on a regular dosing day, and subjects should be instructed to take study drug at the clinic during this visit.
      Note: serial PK sampling may need to occur at a visit later than Visit 5 if study drug was held or if the dose changed; see Section 8.3.

- Perform WHO Bleeding Scale Assessment (Appendix C) at all visits. The Investigator should ask the subject the following question: "Have you experienced any bruising or bleeding since the last visit?"
- Dispense study drug, if applicable, and review administration instructions at each visit.
- Retrieve unused medication, as needed, and review subject dosing diary to record compliance at every visit.
- Dispense new diary monthly.
- Perform physical exam at Visit 4/Week 1 and Visit 7/Week 4.
- Review and record AEs that may have occurred since the previous visit.
- Record any use of rescue medication since the previous visit.
- Record concomitant medications and procedures.

7.2.3 Visits 8-13/ Weeks 6-16: Concomitant ITP Medication Reduction Period (Bi-Weekly Visits)

Study visits occur every two weeks. If additional visits are needed, refer to Section 7.2.8 for Unscheduled Visits.

The following procedures should be performed:

- Collect vital signs (blood pressure and pulse). Vital signs should be taken after sitting for 5 minutes whenever possible. Vital signs should be taken prior to any blood draws.
- Collect blood for central laboratory tests at Visit 10/Week 10 and Visit 13/Week16 (see Section 9.7).
- Collect platelet counts via local lab.
- Perform PK sampling:
  - Sparse PK samples are collected at Visit 8/Week 6 and Visit 13/ Week 16.
  - Three (3) serial PK samples are collected at Visit 10/Week 10; one pre-dose, one between 2 and 4 hours post-dose, and one between 6 and 8 hours post-dose. Visit 10 should occur on a regular dosing day, and subjects should be instructed to take study drug at the clinic during this visit.
    Note: serial PK sampling may need to occur at a visit later than Visit 10 if study drug was held or if the dose changed; see Section 8.3.
- Perform pregnancy test for female subjects of childbearing potential at Visit 10/Week 10. Urine or serum pregnancy test should be performed.
- Perform WHO Bleeding Scale Assessment (Appendix C) at all visits. The Investigator should ask the subject the following question: "Have you experienced any bruising or bleeding since the last visit?"
- Dispense study drug, if applicable, and review administration instructions at each visit.
- Retrieve unused medication, as needed, and review subject dosing diary to record compliance at every visit.

- Dispense new diary monthly.
- Down titrate concomitant ITP medication per Section 4.3.3.
- Perform physical exam at Visit 10/Week 10 and Visit 13/Week 16.
- Review and record AEs that may have occurred since the previous visit.
- Record any use of rescue medication since the previous visit.
- Record concomitant medications and procedures at each visit.

7.2.4 Visits 14-21/Weeks 18-25: Maintenance Period (Weekly Visits)

The following procedures should be performed:

- Collect vital signs (blood pressure and pulse). Vital signs should be taken after sitting for 5 minutes whenever possible. Vital signs should be taken prior to any blood draws.
- Collect platelet counts via local lab at each visit.
- Perform pregnancy test for female subjects of childbearing potential at Visit 16/Week 20. Urine or serum pregnancy test should be performed.
- Perform WHO Bleeding Scale Assessment (Appendix C) at all visits. The Investigator should ask the subject the following question: “Have you experienced any bruising or bleeding since the last visit?”
- Dispense study drug, if applicable, and review administration instructions at each visit.
- Retrieve unused medication, as needed, and review subject dosing diary to record compliance at every visit.
- Dispense new diary monthly.
- Perform physical exam at Visit 16/Week 20.
- Review and record AEs that may have occurred since the previous visit.
- Record any use of rescue medication since the previous visit.
- Record concomitant medications and procedures at each visit.

7.2.5 Visit 22/Week 26: End of Treatment

The following procedures should be performed:

- Collect vital signs (blood pressure and pulse). Vital signs should be taken after sitting for 5 minutes whenever possible. Vital signs should be taken prior to any blood draws.
- Collect platelet counts via local lab.
- Collect blood for central laboratory tests (see Section 9.7).
- Perform Sparse PK sampling.
- Perform pregnancy test for female subjects of childbearing potential - Urine or serum pregnancy test should be performed.

- Perform WHO Bleeding Scale Assessment (Appendix C). The Investigator should ask the subject the following question: "Have you experienced any bruising or bleeding since the last visit?"
- Dispense study drug, if applicable, and review administration instructions.
- Retrieve unused medication, as needed, and review subject dosing diary to record compliance.
- Dispense new diary.
- Perform physical exam.
- Review and record AEs that may have occurred since the previous visit.
- Record any use of rescue medication since the previous visit.
- Record concomitant medications and procedures.
- For subjects who are willing and able to enter the Extension Phase, review all inclusion and exclusion criteria to confirm subject eligibility. Subjects entering directly into the Extension Phase will not enter the Dose-tapering and Follow-up Periods of the Core Study.

7.2.6 Visits 23-26/Weeks 27-30: Dose Taper (Weekly Visits)

The following procedures should be performed for those subjects not entering the Extension Phase.

- Collect vital signs (blood pressure and pulse) at each visit. Vital signs should be taken after sitting for 5 minutes whenever possible. Vital signs should be taken prior to any blood draws.
- Collect platelet counts via local lab at each visit.
- Perform WHO Bleeding Scale Assessment (Appendix C) at all visits. The Investigator should ask the subject the following question: "Have you experienced any bruising or bleeding since the last visit?"
- Dispense study drug, if applicable, and review administration instructions at each visit.
- Retrieve unused medication, as needed, and review subject dosing diary to record compliance at every visit.
- Dispense new diary, if needed.
- Review and record AEs that may have occurred since the previous visit.
- Record any use of rescue medication since the previous visit.
- Record concomitant medications and procedures at each visit.

7.2.7 Visits 27-30/Weeks 31-34: Follow-Up (Weekly Visits)

The following procedures should be performed for those subjects not entering the Extension Phase.

- Collect vital signs (blood pressure and pulse) at each visit. Vital signs should be taken after sitting for 5 minutes whenever possible. Vital signs should be taken prior to any blood draws.
- Collect platelet counts via local lab at each visit.
- Collect blood for central laboratory tests at Visit 30/Week 34 (see Section 9.7).
- Perform pregnancy test for female subjects of childbearing potential at Visit 30/Week 34. Urine or serum pregnancy test should be performed.
- Perform WHO Bleeding Scale Assessment (Appendix C) at all visits. The Investigator should ask the subject the following question: “Have you experienced any bruising or bleeding since the last visit?”
- Perform physical exam at Visit 30/Week 34.
- Review and record AEs that may have occurred since the previous visit.
- Record any use of rescue medication since the previous visit.
- Record concomitant medications and procedures at each visit.

7.2.8 Unscheduled Visit

The Unscheduled Visit details the minimum assessments required for those subjects who need an Unscheduled Visit for dose titration or additional platelet count blood draws, however, additional assessments may be performed as needed based on other reasons for an Unscheduled Visit.

The following procedures should be performed:

- Collect vital signs (blood pressure and pulse) at each visit. Vital signs should be taken after sitting for 5 minutes whenever possible. Vital signs should be taken prior to any blood draws.
- Collect platelet counts via local lab.
- Perform WHO Bleeding Scale Assessment (Appendix C) at each visit. The Investigator should ask the subject the following question: “Have you experienced any bruising or bleeding since the last visit?”
- Review and record AEs that may have occurred since the last visit.
- Record concomitant medications and procedures since the last visit.

7.3 Extension Phase

7.3.1 Visits E1-E23/Months 1-23: Extension Phase (Monthly Visits)

Subjects should return to the clinic for monthly visits during the extension phase. Additional visits may be needed beyond 23 months if marketing authorization has not occurred. Subjects who require study drug dose adjustments, who undergo concomitant ITP medication reduction, or who receive rescue therapy during the Extension Phase are required to return for weekly visits for 3 consecutive weeks.

The following procedures should be performed at every visit:

- Collect vital signs (blood pressure and pulse) at each visit. Vital signs should be taken after sitting for 5 minutes whenever possible. Vital signs should be taken prior to any blood draws.
- Collect platelet counts via local lab.
- Perform WHO Bleeding Scale Assessment (Appendix C). The Investigator should ask the subject the following question: “Have you experienced any bruising or bleeding since the last visit?”
- Dispense study drug, if applicable, and review administration instructions at each visit.
- Retrieve unused medication, as needed, and review subject dosing diary to record compliance at every visit.
- Dispense new diary, if needed.
- Review and record AEs that may have occurred since the last visit.
- Record any use of rescue medication since the previous visit.
- Record concomitant medications and procedures.

The following procedures should be performed every three months starting at Visit E1/Month 1 in addition to the assessments performed at every visit:

- Collect blood for central laboratory tests (see Section 9.7).
- Perform pregnancy test for female subjects of childbearing potential.
- Perform physical exam.

7.3.2 Visit E24/Month24: End of Treatment

The following procedures should be performed:

- Collect vital signs (blood pressure and pulse). Vital signs should be taken after sitting for 5 minutes whenever possible. Vital signs should be taken prior to any blood draws.
- Collect platelet counts via local lab.
- Collect blood for central laboratory tests (see Section 9.7).
- Perform pregnancy test for female subjects of childbearing potential- Urine or serum pregnancy test should be performed.

- Perform WHO Bleeding Scale Assessment (Appendix C). The Investigator should ask the subject the following question: “Have you experienced any bruising or bleeding since the last visit?”
- Perform physical exam.
- Retrieve unused medication and review subject dosing diary to record.
- Review and record AEs that may have occurred since the previous visit.
- Record any use of rescue medication since the previous visit.
- Record concomitant medications and procedures.

7.3.3 Unscheduled Visit

The Unscheduled Visit details the minimum assessments required for those subjects who need an Unscheduled Visit for dose titration or additional platelet count blood draws, however, additional assessments may be performed as needed based on other reasons for an Unscheduled Visit.

The following procedures should be performed:

- Collect vital signs (blood pressure and pulse) at each visit. Vital signs should be taken after sitting for 5 minutes whenever possible. Vital signs should be taken prior to any blood draws.
- Collect platelet counts via local lab.
- Perform WHO Bleeding Scale Assessment (Appendix C) at each visit. The Investigator should ask the subject the following question: “Have you experienced any bruising or bleeding since the last visit?”
- Review and record AEs that may have occurred since the last visit.
- Record concomitant medications and procedures since the last visit.

8 EFFICACY ASSESSMENTS

8.1 Platelet Count (Local Lab)

Platelet count will be assessed in all subjects at all visits and recorded in the eCRF. In order to be eligible for the study, the subject must have an average of 2 platelet counts $<30\times10^9$/L (no single count may be $>35\times10^9$/L). The 2 samples must be obtained ≥48 hours and ≤2 weeks apart.

8.2 WHO Bleeding Scale

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

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 the last visit?"

8.3 Pharmacokinetic Sampling

Plasma concentrations of avatrombopag will be measured using a validated bioanalytical assay. Blood samples for the sparse or serial measurement of avatrombopag plasma concentrations will be collected as shown in Table 3.

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

During the serial PK sampling visits, subjects will have three blood samples (2 mL each) drawn: pre-dose; between 2 and 4 hours post-dose; and between 6 and 8 hours post-dose. Blood samples for sparse PK assessments (2 mL each) will be collected while the subject is at the clinic during Weeks 1, 4, 6, 16 and 26/EOT (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 3 Pharmacokinetic Sampling Schedule

Study Day	Sparse/Serial	Sampling Times
Visit 4/Week 1	Sparse	During clinic visit
Visit 5/Week 2	**Serial**	• **Pre-dose** • **Between 2 and 4 hours post-dose** • **Between 6 and 8 hours post-dose**
Visit 7/Week 4	Sparse	During clinic visit
Visit 8/Week 6	Sparse	During clinic visit
Visit 10/Week 10	**Serial**	• **Pre-dose** • **Between 2 and 4 hours post-dose** • **Between 6 and 8 hours post-dose**
Visit 13/Week 16	Sparse	During clinic visit
Visit 22 (EOT)/Week 26	Sparse	During clinic visit

9 SAFETY ASSESSMENTS

9.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

Adverse Events, which include clinical laboratory test variables, will be monitored, and documented from the time of informed consent until the time the subject is discharged from the study. Subjects should be instructed to report any AE that they experience to the Investigator. Beginning with the Informed Consent signature, Investigators should make an assessment for AEs at each visit and record the event on the appropriate AE eCRF. Events associated with disease progression should not be reported as AEs/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 the Screening Visit should not be reported as an AE unless the medical condition or signs or symptoms present at baseline changes 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 the Screening Visit 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. Laboratory abnormalities are not considered AEs unless they are associated with clinical signs or symptoms or require medical intervention. Any abnormal test that is determined to be an error does not require reporting as an AE.

Clinically significant abnormal findings in physical examinations will be reported as AEs.

9.1.1 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each AE and will also categorize each AE as to its potential relationship to study drug using the categories of yes or no.

9.1.1.1 Assessment of Severity

The severity of all AEs should be graded according to the Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE). For those AEs not listed in the CTCAE, the following grading system should be used:

- Mild (CTCAE Grade 1): Transient symptoms, awareness of sign/symptom, but easily tolerated and no interference with subject's daily activities.
- Moderate (CTCAE Grade 2): Marked signs/symptoms that interfere with subject's usual activities, but still acceptable.
- Severe (CTCAE Grade 3): Incapacitating signs/symptoms which cause considerable interference with the subject's daily activities, unacceptable.
- Life-threatening (CTCAE Grade 4): Life-threatening or disabling AE.
- Death (CTCAE Grade 5): Death-related AE.

9.1.1.2 Causality Assessment

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

- No (unrelated, not related, no relation) – The time course between the administration of study drug and the occurrence or worsening of the AE rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.
- Yes (related) – The time course between the administration of study drug and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

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
    - 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.

9.1.2 Adverse Events of Special Interest

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

The AESI defined in this protocol include:

- Thromboembolic events (any thrombotic or embolic event, whether arterial or venous); and
- Bleeding events (WHO Grades 3 and 4).

These events will be recorded in the AE eCRF page. The Investigator will assess and record any additional information on the AESI in detail on a SAE form (whether or not the event meets seriousness criteria in Section 9.3), to be submitted within 24 hours of awareness of the event. During the course of the study, additional AESI may be identified by the Sponsor.

Efficacy endpoints, as described in Section 3, should not be reported as AEs unless in the opinion of the Investigator the event is causally associated with the study drug. For example, thrombocytopenia or platelet transfusions for thrombocytopenia should not be reported as AEs; however, clinically significant bleeding events should always be reported as AESIs.

9.2 Method of Detecting Adverse Events and Serious Adverse Events

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

9.3 Serious Adverse Events

An adverse event 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 adverse event
    - NOTE: An adverse event 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 hospitalization
    - NOTE: Any hospital admission even if admitted and discharged the same day will be considered an inpatient hospitalization. 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. Hospitalization due to expected recovery time for the planned procedure will not be counted as an SAE. 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.
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- An important medical event
    - 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 or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

9.4 Serious Adverse Event Reporting − Procedures for Investigators

9.4.1 Initial Reports

All SAEs occurring from the time of informed consent until completion or discontinuation of the subject from the study must be reported within 24 hours of the knowledge of the occurrence (this refers to any AE that meets any of the aforementioned serious criteria), regardless of the causal relationship of the event to study drug. All SAEs that the Investigator becomes aware of and considers related to study drug occurring after subject completion or discontinuation must be reported to the Sponsor.

To report the SAE, complete the appropriate form for the study. 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. Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital discharge summaries, biopsy/autopsy reports, and other documents requested by the Sponsor or designee. The Investigator must notify his/her Institutional Review Board (IRB) or Independent Ethics Committee (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 or designee to be filed in the Trial Master File.

9.4.2 Follow-Up Reports

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

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

9.5 Pregnancy Reporting

If the subject becomes pregnant during the study or within 30 days of discontinuing study drug, the Investigator shall report the pregnancy to the Sponsor 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 complete and submit 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, ectopic pregnancy, 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.

9.6 Regulatory Reporting Requirements for Serious Adverse Events

Regulatory reporting requirements for SAEs include the following:

- 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, IRBs/IEC, and Investigators.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing a SUSAR or other specific safety information (e.g., summary or listing of SUSARs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.7 Clinical Laboratory Evaluations

Clinical safety laboratory assessments will include serum chemistry and hematology, as specified below, and will be obtained as indicated in Section 7, Appendix A and Appendix B.

Safety Chemistry Panel

Alanine aminotransferase	Aspartate aminotransferase
Alkaline phosphatase	Direct bilirubin
Total carbon dioxide (Bicarbonate)	Urea (Blood urea nitrogen)
Sodium	Chloride
Total bilirubin	Creatinine
Potassium	Glucose
Calcium	Phosphorus

Hematology

Hematocrit	Hemoglobin
Platelets	Red blood cell count (w/o RBC indices)
White blood cell count (w/ differential)	

Coagulation

Prothrombin time	Activated partial thromboplastin time
International normalized ratio	

When a central laboratory hematology test is required, two blood samples will be collected: one for central laboratory analysis and one for local laboratory analysis. The local laboratory hematology test result will be used to qualify a subject's entry into the study, study drug and concomitant ITP medication dose titration, and clinical assessment.

Only platelet count data from local laboratories will be collected and entered into the eCRF for efficacy analyses. All other hematological parameters will be analyzed at and reported from the designated central laboratory.

9.8 Vital Signs

Vital sign measurements will include height and weight (at the Screening Visit only), blood pressure, and pulse rate as indicated in Appendix A and Appendix B.

9.9 Physical Examinations

Brief physical examinations will be symptom-directed and focused on common symptoms of ITP (e.g., skin, mucosa). Clinically significant abnormal physical exam findings should be reported as AEs. Brief physical examinations should be performed at the visits indicated in Appendix A and Appendix B.

10 STATISTICS

10.1 Analysis Populations

Full Analysis Set (FAS): The FAS will include all subjects who are enrolled into the study.

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

Safety Set: The safety set will include all subjects who receive at least 1 dose of study drug and have a post-dose safety assessment.

10.2 Statistical Methods

The database will be locked when the last subject completes the Core Phase of the study. When the last subject completes the Extension Phase, additional data will be summarized, and the final database lock will occur.

Statistical analysis will be performed using SAS software. Details of the statistical analysis will be included in a separate statistical analysis plan (SAP).

10.2.1 Disposition, Demographics, and Baseline Characteristics

Subject disposition will be summarized for the Safety Population. 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 for the Safety Population. Medical history and concomitant medications will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and WHODrug dictionaries and summarized for the Safety Population.

10.2.2 Analysis of Efficacy

10.2.2.1 Primary Investigation Phase (Core Phase) Efficacy Analyses

The primary efficacy variable, the cumulative number of weeks of platelet response, and key secondary efficacy variable, response rate at Day 8, will be determined in the FAS. Analyses in the PPS will be used as supportive evidence. All analyses of platelet counts will be based on local laboratory results.

The pre-defined hurdle for the primary efficacy endpoint is set such that the lower limit of the 95% confidence interval (CI) of the mean number of cumulative weeks of platelet response $\geq 50 \times 10^9$/L will need to be ≥8.02 weeks.

Descriptive statistics will be generated to summarize effectiveness endpoints.

Effectiveness endpoints will be summarized as follows:

- Continuous variables will be summarized by number, mean, median, maximum, and minimum, as appropriate.
- Categorical variables will be summarized by number and percentage, as appropriate.

Additional analyses will be performed using appropriate statistical methodologies as deemed appropriate.

10.2.2.2 Extension Phase Analyses

Evaluation of the efficacy data will consist primarily of summary displays and data listings.

10.2.3 Analysis of Safety

Evaluation of safety will be performed on the Safety Set. Safety data that will be evaluated include AEs, clinical laboratory results, and vital signs. All AEs will be coded using MedDRA. Adverse events will be coded to system organ class and preferred term using MedDRA. AEs will be presented with and without regard to causality based on the Investigator's judgment. The frequency of overall toxicity, categorized CTCAE criteria Grades 1 through 5, will be described. Treatment-emergent AEs (TEAEs) will be summarized by presenting the incidence of AEs. Descriptive summary statistics (mean plus standard deviation, median, and range) of the laboratory parameters, vital signs, and changes from baseline will be evaluated.

10.2.4 Interim Analysis

No formal interim analysis is planned for this study.

10.2.5 Hurdle and Sample Size Determination

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

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

11 DATA MANAGEMENT AND RECORD KEEPING

11.1 Data Management

11.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the clinical research associate (CRA) on an ongoing basis and during monitoring visits. The CRAs 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.

11.1.2 Computer Systems

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

11.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure username and password in order to enter, review, or correct study data. These procedures must comply with relevant national and international regulations. All passwords will be strictly confidential.

11.1.4 Medical Information Coding

For medical information, the thesauri listed below will be used:

- Medical Dictionary for Regulatory Activities (MedDRA) for medical history and adverse events
- World Health Organization Drug Dictionary (WHODrug) for concomitant medications.

11.1.5 Data Validation

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

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

11.2 Record Keeping

Records of subjects, source documents, monitoring visit logs, eCRFs, inventory of study drug, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data are 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 trial agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

12 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

12.1 Ethical Conduct of the Study

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

12.2 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, Investigator's Brochure, ICF, advertisements (if applicable), written information given to the subjects, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Head of Medical Institution.

The Investigator is obligated to keep the IRB/IEC informed of any unanticipated problems. This may include notification to the IRB/IEC of SUSARs.

Federal regulations and ICH 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, advertisements to be used for subject recruitment, and any other written information regarding this study to be provided to a subject or subject's legal guardian must be approved by the IRB/IEC.

No 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 ethics committees according to the national regulations.

The study will only start in the respective sites once the respective committee's written approval has been given.

12.3 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigators by the Sponsor or designee. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB/IEC and submitted to/approved by regulatory authorities as required unless immediate implementation is necessary for subject safety. Urgent implementation of an amendment due to safety concerns must be documented and reported to the IRB/IEC within 5 working days.

12.4 Informed Consent

The ICF and any changes to the ICF 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 is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the subject has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each subject before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB/IEC, and/or regulatory agencies. A copy of the signed ICF will be given to the subject.

12.5 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, ICH GCP, 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, Investigator's Brochure, eCRFs and procedures for their completion, informed consent 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.

12.6 Disclosure of Data

Data generated by this study must be available for inspection by the Pharmaceutical and Medical Devices Agency, other applicable health authorities, the Sponsor or their designee, 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.

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

12.7 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating subjects (sufficient information to link records, e.g., eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, 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.

12.8 Publication Policy

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

12.9 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.

13 REFERENCES

Fogarty PF, Tarantino MD, Brainsky A, Signorovitch J, Grotzinger KM. Selective Validation of the WHO Bleeding Scale in Patients with Chronic Immune Thrombocytopenia. *Current Medical Research and Opinion*. 2012; 28(1): 79-87.

Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting Results of Cancer Treatment. *Cancer*. 1981; 47: 207-214.

Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Arnold DM, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood*. 2009 Mar 12;113(11):2386-93.

APPENDIX A: CORE PHASE SCHEDULE OF EVENTS

Phase	**PE**	**Core Phase**																		
Period	**Screen**	**BL**	**Titration**				**Concomitant ITP Medication Reduction[a]**						**Maintenance**					**Dose-Taper[b]**	**Follow-up[b]**	**Unsch Visit[c]**
Visits[d]	**1**	**2**	**3**	**4**	**5, 6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14, 15**	**16, 17**	**18, 19**	**20, 21**	**EOT 22**	**23-26**	**27-30**	**—**
Days	**-28 to -1**	**1**	**5±1**	**8+2**	**14-21**	**28**														
Weeks	**-4**			**1**	**2-3**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18, 19**	**20, 21**	**22, 23**	**24, 25**	**26**	**27-30**	**31-34**	**—**
Informed consent	X																			
Demographics	X																			
Medical/surgical history, including ITP history	X																			
Height/Weight	X																			
Concomitant medications/procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion	X	X															X[e]			
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X		X		X			X			X		X[f]			X		X[f]	
Dispense study drug and diary, as needed		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Retrieve unused study medication and record compliance			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant ITP drug dose titration							X	X	X	X	X	X								
Platelet counts	X[g]	X[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry, Hematology and Coag	X	X		X					X			X					X		X[h]	
PK blood sampling				X[i]	X[j]	X[i]	X[i]		X[j]			X[i]					X[i]			
Pregnancy testing	X	X							X					X[k]			X		X[k]	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
WHO Bleeding score		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

BL = Baseline, EOT = End-of-Treatment, ITP = Immune Thrombocytopenia, PK = pharmacokinetic, PE = Pre-enrollment, Unsch = unscheduled, WHO = World Health Organization.

a: Subjects requiring study drug dose adjustments, undergoing concomitant ITP medication reduction or those who receive rescue therapy during the Core Phase are required to return for weekly visits for 3 consecutive weeks.

b: Dose-tapering and Follow-up Visits are for subjects who will not be entering the Extension Phase.

c: This column details the minimum assessments required for those subjects who need an unscheduled visit for dose titration or additional platelet count blood draws, however additional assessments may be performed as required based on other reasons for the unscheduled visit.

d: Visits scheduled on a weekly basis should occur within a +/- 2-day timeframe, except Day 5 this visit should occur within +/- 1 day and Day 8 this visit should occur within a +2-day window. Visits scheduled on an every 2-week basis should be within a +/- 3-day timeframe.

e: At Visit 22 the inclusion/exclusion criteria for the Extension Phase should be reviewed to confirm subject eligibility for those subjects who are willing to enter the Extension Phase.

f: The physical exam will be performed at Week 20 and Week 34.

g: The Screening Visit and Day 1 Baseline Visit platelet count will be averaged to obtain the baseline platelet count value. The 2 samples must be obtained ≥48 hours and ≤2 weeks apart and the results must be available prior to enrollment. Therefore, an additional screening platelet count maybe required due to issues with scheduling.

h: To be performed at Visit 30 during Follow-up only:

i: The sparse PK sample will be obtained at Visits 4, 7, 8, 13, and 22 (EOT).

j: At Visits 5 and 10, one blood sample will be obtained pre-dose (trough), one sample between 2 and 4 hours post-dose, and another sample between 6 and 8 hours post-dose. Therefore, subjects should be instructed to take the study drug at the clinic during this visit, after collection of the pre-dose PK sample. These visits should be scheduled on a subject's regular dosing day. Serial sampling may need to occur at a visit later than Visit 5 or Visit 10 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.

k: The pregnancy test will be performed at Week 20 and Week 34.

APPENDIX B: EXTENSION PHASE SCHEDULE OF EVENTS

Visits[a]	**E1 - 2**	**E3**	**E4-5**	**E6**	**E7-8**	**E9**	**E10-11**	**E12**	**E13-14**	**E15**	**E16-17**	**E18**	**E19-20**	**E21**	**E22-23**	**E24 or EOT**	**Unsch Visit**[b]
Months[c]	**1-2**	**3**	**4-5**	**6**	**7-8**	**9**	**10-11**	**12**	**13-14**	**15**	**16-17**	**18**	**19-20**	**21**	**22-23**	**24 or EOT**	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X		X[d]		X[d]		X[d]		X[d]		X[d]		X[d]		X[d]	X	
Dispense study drug and diary, as needed	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Retrieve unused study medication and record compliance	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Platelet counts	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry/ Hematology/ Coagulation	X		X[d]		X[d]		X[d]		X[d]		X[d]		X[d]		X[d]	X	
Pregnancy Test	X		X[d]		X[d]		X[d]		X[d]		X[d]		X[d]		X[d]	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
WHO Bleeding	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

EOT = end-of-treatment, Unsch = unscheduled, WHO = World Health Organization.

a: Subjects requiring study drug dose adjustments, undergoing concomitant ITP medication reduction or those who receive rescue therapy during the Extension Phase are required to return for weekly visits for 3 consecutive weeks.

b: This column details the minimum assessments required for those subjects who need an unscheduled visit for dose titration or additional platelet count blood draws, however additional assessment may be performed as required based on other reasons for the unscheduled visit.

c: Visits should occur within a +/- 7-day timeframe.

d: Physical exams, central labs and pregnancy tests will be performed every 3 months starting at Month 1 (Months 1, 4, 7, 10, 13, 16, 19, 22) and EOT.

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 BOTH CYP2C9 AND CYP3A4/5

Note: This list is not all-inclusive; it presents examples of common medications which are excluded during the study.

Dual Inducer examples

- Carbamazepine
- Enzalutamide
- Rifampin/Rifampicin
- Phenytoin
- Phenobarbital

Dual Inhibitor examples

- Fluconazole
- Ritonavir
- Grapefruit juice