CLINICAL STUDY PROTOCOL

An Open-Label Study to Evaluate the Efficacy and Safety of Avatrombopag for the Treatment of Subjects with Thrombocytopenia Scheduled for a Surgical Procedure

Investigational Product: Avatrombopag tablets

Protocol Number: AVA-PST-320

Sponsor:

Dova Pharmaceuticals

240 Leigh Farm Road, Suite 245

Durham, NC 27707

United States

Telephone: 919-748-5975

Fax: 919-748-5976

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SIGNATURE PAGE

STUDY TITLE: An Open-Label Study to Evaluate the Efficacy and Safety of Avatrombopag for the Treatment of Subjects with Thrombocytopenia Scheduled for a Surgical Procedure

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

Signature | Date

[redacted] 17 Sep 2018

[redacted]
Dova Pharmaceuticals

[redacted] September 17, 2018

[redacted]
Dova Pharmaceuticals

[redacted] 17 SEP 2018

[redacted]
Dova Pharmaceuticals

[redacted] 17 Sep 2018

[redacted]
Dova Pharmaceuticals

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 Dova Pharmaceuticals 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 Dova Pharmaceuticals 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 Dova Pharmaceuticals 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 Food and Drug Administration Regulations, Institutional Review Board Regulations, and 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 Subjects with Thrombocytopenia Scheduled for a Surgical Procedure

PROTOCOL NUMBER: AVA-PST-320

INVESTIGATIONAL PRODUCT: Oral avatrombopag

PHASE: 3b

INDICATION: Treatment of thrombocytopenia in subjects scheduled for operations to critical sites (eg, eye surgery, neurosurgery) or operations with a high risk of bleeding (eg, major abdominal surgery)

OBJECTIVES:

The primary objective of this study is to evaluate the efficacy of avatrombopag in increasing platelet counts in subjects with thrombocytopenia scheduled for operations to critical sites or operations with a high risk of bleeding.

The secondary objectives of this study are the following:

- To evaluate the safety of avatrombopag in subjects with thrombocytopenia scheduled for operations to critical sites or operations with a high risk of bleeding,
- To evaluate the effect of avatrombopag on the need for transfusions in subjects with thrombocytopenia scheduled for operations to critical sites or operations with a high risk of bleeding, and
- To evaluate the effect of avatrombopag on bleeding in subjects with thrombocytopenia scheduled for operations to critical sites or operations with a high risk of bleeding.

POPULATION:

The population for this study is subjects ≥18 years of age at the time of informed consent who are scheduled to undergo operations to critical sites (eg, eye surgery, neurosurgery) or operations with a high risk of bleeding (eg, major abdominal surgery), OR, in the opinion of the Investigator, would otherwise require a pre-operative platelet transfusion to prevent bleeding. Subjects without chronic liver disease must have a mean baseline platelet count between 50×10^9/L and $<100 \times 10^9$/L, measured on 2 separate occasions, with neither platelet count $\geq 100 \times 10^9$/L. Subjects with chronic liver disease (CLD) must have a mean baseline platelet count between 50×10^9/L and $<75 \times 10^9$/L, measured on 2 separate occasions, with neither platelet count $\geq 75 \times 10^9$/L.

STUDY DESIGN AND DURATION:

This is a Phase 3b open-label, multicenter study of the efficacy and safety of oral avatrombopag for the treatment of subjects with thrombocytopenia scheduled for a surgical procedure. Eligible subjects scheduled to undergo operations to critical sites (eg, eye surgery, neurosurgery) or operations with a high risk of bleeding (eg, major abdominal surgery) will be enrolled into the study and receive avatrombopag.

Mean baseline platelet count in subjects without CLD must be between 50×10^9/L and $<100 \times 10^9$/L and between 50×10^9/L and $<75 \times 10^9$/L in subjects with CLD. Platelet counts must be measured on 2 separate occasions, and must be performed at least 1 day apart with neither platelet count $\geq 100 \times 10^9$/L in subjects without CLD and $\geq 75 \times 10^9$/L in subjects with CLD. One standard of care platelet count measurement may be used if collected within 14 days of Baseline and the mean of these 2 platelet counts (mean baseline platelet count) will be used for entry criteria.

Subjects will receive 60 mg oral avatrombopag once daily for 5 days beginning on Day 1, followed by a wait period prior to the procedure, which will occur on Day 10 (+3 days). The platelet response data will be reviewed after approximately 25% and 50% of subjects have been enrolled in the study. If required, the dose may be adjusted for subsequent subjects based on insufficient increase in platelet counts on Procedure Day. If a higher dose is considered necessary, subjects will receive 80 mg oral avatrombopag once daily for 5 days beginning on Day 1, followed by a wait period prior to the procedure, which will occur on Day 10 (+3 days).

The Follow-up Period will include 2 visits, which will occur at approximately 7 days (+3 days) post-procedure and 30 days (±3 days) after the last dose of study drug.

The total study duration will be approximately 5 to 7 weeks.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

Subjects will receive 60 mg oral avatrombopag once daily for 5 days. If required, the dose may be adjusted for subsequent subjects based on insufficient increase in platelet counts on Procedure Day. If a higher dose is considered necessary, subjects will receive 80 mg oral avatrombopag once daily for 5 days.

EFFICACY VARIABLES:

The primary efficacy endpoint is the proportion of subjects achieving a platelet count of $\geq 100 \times 10^9$/L on Procedure Day, when measured prior to a platelet transfusion (if any).

The secondary efficacy endpoints include the following:

- Change in platelet count from baseline to Procedure Day,
- Proportion of subjects without platelet transfusion and any other treatment for bleeding after the Baseline Visit and up to 7 days following Procedure Day,
- Proportion of subjects without platelet transfusion after the Baseline Visit and up to 7 days following Procedure Day, and
- Proportion of subjects without bleeding after the Baseline Visit and up to 7 days following Procedure Day.

SAFETY VARIABLES:

Safety variables will include adverse events, physical examination findings, clinical laboratory parameters, and vital signs.

STATISTICAL ANALYSES:

Efficacy Analysis

All primary and secondary efficacy endpoints will be analyzed using the Full Analysis Set (FAS). The Per-Protocol Analysis Set (PPS) will be used only for sensitivity analysis of the primary and secondary efficacy endpoints.

Primary Efficacy Analysis: The primary efficacy endpoint is the proportion of subjects achieving a platelet count of $\geq 100 \times 10^9$/L on Procedure Day, when measured prior to a platelet transfusion (if any). Subjects with missing information due to early withdrawal or other reasons are considered as having a platelet count $<100 \times 10^9$/L in the analysis; that is, missing values are considered as non-responders. The primary endpoint will be estimated from a binomial distribution, with 95% confidence interval (CI) of the proportion calculated. The study will be claimed successful if the lower boundary of the 2-sided 95% CI is above the 0.65. The primary analysis will be performed on the FAS and repeated on the PPS.

Secondary Efficacy Analysis

The following secondary efficacy endpoints will be summarized and analyzed in the same manner as the primary efficacy endpoint:

- Proportion of subjects without platelet transfusion and any other treatment for bleeding after the Baseline Visit and up to 7 days following Procedure Day,
- Proportion of subjects without platelet transfusion after the Baseline Visit and up to 7 days following Procedure Day, and
- Proportion of subjects without bleeding after the Baseline Visit and up to 7 days following Procedure Day.

Change in platelet count from baseline to Procedure Day for avatrombopag will be calculated for each subject and summarized descriptively. The mean (95% CI) and median (range) will be provided.

Additional efficacy analyses will be performed if deemed necessary. The details of the analyses will be described in the Statistical Analysis Plan that will be finalized prior to database lock.

Safety and tolerability will be assessed by examining the incidence of adverse events, physical examination findings, clinical laboratory parameters, and vital signs over time using the Safety Analysis Set.

SAMPLE SIZE DETERMINATION:

It is estimated from pharmacokinetic/pharmacodynamic modeling that the proportion of subjects treated with avatrombopag expected to achieve a platelet count of $\geq 100 \times 10^9$/L on Procedure Day, when measured prior to platelet transfusion (if any), is approximately 85%. Assuming the true response rate is 0.8 and the desired lower boundary of the 2-sided 95% CI is at least 0.65, 60 enrolled subjects will provide greater than 90% power. If the decision is made to increase the dose of study drug at one of the interim reviews of the data based on the pre-defined boundaries, up to an additional 30 subjects may be enrolled in the study for a maximum sample size of 90 subjects.

SITES: Approximately 30 sites in the United States

SPONSOR:

Dova Pharmaceuticals
240 Leigh Farm Road, Suite 245
Durham, NC 27707
United States
Telephone: 919-748-5975
Fax: 919-748-5976

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
21 CFR	Title 21 of the Code of Federal Regulations
β-hCG	Beta-human chorionic gonadotropin
BCLC	Barcelona Clinic Liver Cancer
CI	Confidence interval
CLD	Chronic Liver Disease
CRA	Clinical Research Associate
CYP	Cytochrome P450
eCRF	Electronic case report form
EDC	Electronic data capture
FAS	Full Analysis Set
GCP	Good Clinical Practice
HCC	Hepatocellular Carcinoma
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IRB	Institutional Review Board
IRT	Interactive response technology
ISTH	International Society on Thrombosis and Haemostasis
ITP	Idiopathic thrombocytopenic purpura
OLE	Open-label extension
PD	Pharmacodynamic
PK	Pharmacokinetic
PPS	Per-Protocol Analysis Set
SAE	Serious adverse event
TEAE	Treatment-emergent adverse event
TPO	Thrombopoietin

1 INTRODUCTION AND BACKGROUND INFORMATION

1.1 Thrombocytopenia

Platelets are an important component of blood that function to maintain normal hemostasis. In the case of vessel injuries, platelets immediately control bleeding by adhesion, activation, and aggregation, thereby forming a stable clot in conjunction with blood coagulation factors. Thrombopoietin (TPO), the principal physiologic regulator of platelet production, is produced constitutively in the liver, circulates in the bloodstream, and is delivered to the bone marrow, where it stimulates the early development of multiple hematopoietic lineages and megakaryocytopoiesis. Bone marrow production of platelets is directly affected by TPO levels.

The circulating platelet count in blood is determined by the rates of platelet production and platelet destruction. In healthy individuals, the average lifespan of platelets is 7 to 10 days, after which they are destroyed and replaced with newly-generated platelets. A normal blood platelet count ranges from 150×10^9/L to 450×10^9/L, and patients who have less than 150×10^9/L have the condition known as thrombocytopenia. Thrombocytopenia is a potentially serious condition that is characterized by a deficiency of platelets in the circulatory system that is associated with an increased risk of bleeding. Thrombocytopenia can result from decreased platelet production in the bone marrow, increased platelet destruction in the blood (such as from auto-antibodies) or sequestration of platelets in the spleen.

There are no approved pharmaceutical options to treat thrombocytopenia in patients prior to undergoing surgery. Treatment decisions are guided by platelet count measurements, clinical guidelines, and healthcare providers' clinical judgment regarding the risk of bleeding for each category of procedure. Patients with thrombocytopenia are commonly administered platelet transfusions immediately prior to surgery in order to proactively mitigate the risk of bleeding. The extent of the bleeding risk relates to the degree of thrombocytopenia and other coexisting coagulopathies as well as the type of scheduled procedure.

Platelet transfusions are effective, but associated with substantial risks. Approximately 30% of platelet transfusions are associated with serious complications including febrile and allergic reactions, circulatory overload, acute pulmonary injury, and bacterial or viral infections.[1] In the 15% to 25% of patients who require repeated platelet transfusions, the platelet response may become inadequate due to human leukocyte antigen alloimmunization.[2]

Additionally, like all blood products, platelets are a limited clinical commodity, and even more so because of their very limited shelf life (approximately 5 days). Approximately 9 million units of platelets are transfused each year in the United States,[2] of which 40% are transfused in the surgical settings.[3]

1.2 Avatrombopag

Avatrombopag maleate (previously known as AKR-501 monomaleate, YM477 monomaleate, and YM-301477 monomaleate) is an orally administered TPO receptor agonist that mimics the biologic effects of TPO in vitro and in vivo. Thrombopoietin exerts its effect on megakaryocytopoiesis and thrombocytopoiesis through binding and activation of the TPO receptor, which is expressed on hematopoietic stem cells, cells of the megakaryocytic lineage, and platelets. Avatrombopag activates the human TPO receptor by binding to a different site on the

TPO receptor, but it is still capable of stimulating signal transduction and mimicking the biologic effects of TPO, resulting in a measured increase in platelet counts.

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 postnatal development studies in rats, and a juvenile dose range-finding 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, including the treatment of thrombocytopenia in subjects scheduled for operations to critical sites or operations with a high risk of bleeding.

Additional details are available in the avatrombopag Investigator's Brochure.[4]

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. A total of 1365 subjects have been randomized across the 24 completed studies in the avatrombopag clinical development plan. The total safety database for avatrombopag includes 1143 subjects in the completed clinical studies. This includes 559 healthy volunteers, 394 subjects with thrombocytopenia associated with chronic liver disease prior to scheduled surgical or diagnostic procedures, 62 subjects with chronic hepatitis C virus related thrombocytopenia to enable initiation and maintenance of antiviral treatment, and 128 subjects with chronic idiopathic thrombocytopenic purpura (ITP).

Based on these data, avatrombopag (DOPTELET®) was approved by FDA in May 2018 for the treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure.

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 (PD) effects related to clinical efficacy. In 15 completed Phase 1 studies involving 559 healthy volunteers exposed to avatrombopag, the most common adverse event 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 (501-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 (501-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 501-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 501-CL-004, without having achieved a durable response).

In the combined 501-CL-003 and 501-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 2, transient, and completely resolved.

A total of 130 subjects with thrombocytopenia associated with chronic liver disease who were scheduled to undergo elective surgical or diagnostic procedures were enrolled in a Phase 2, randomized, placebo-controlled, double-blind, parallel-group study (E5501-G000-202). 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 Cochran-Mantel-Haenszel test. Within Cohort B, the response rate in platelet counts by Day 08 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 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 E5501-G000-203 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 with placebo in subjects with chronic hepatitis C virus related thrombocytopenia who are 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 E5501-J081-204, a Phase 2, randomized, placebo-controlled, double-blind, parallel-group study, a total of 39 Japanese subjects with thrombocytopenia associated with chronic liver disease were randomly assigned to a study group and received the placebo or avatrombopag. The primary analysis of the responder rate (a responder was defined as subjects with a platelet count $\geq 50 \times 10^9$/L and 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

Four Phase 3 efficacy and safety studies (E5501-G000-302, E5501- G000-305, E5501-G000-310, and E5501-G000-311) were completed.

In Study E5501-G000-302, 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 once daily, 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 $\geq 50 \times 10^9$/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) presented 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 E5501-G000-305, 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 study drug.

Studies E5501-G000-310 and E5501-G000-311 enrolled adults with chronic liver disease and severe thrombocytopenia (mean baseline platelet count $<50 \times 10^9$/L), scheduled to undergo invasive procedures. Cohorts were defined based on baseline platelet count (Cohort 1, $<40 \times 10^9$/L or Cohort 2, 40 to $<50 \times 10^9$/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 ($\geq 50 \times 10^9$/L), change in platelet count from baseline to Procedure Day, and safety.

Study 310 randomized 231 patients to 1 of 2 possible cohorts: Cohort 1 (90 avatrombopag/48 placebo) or Cohort 2 (59 avatrombopag/34 placebo). 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 chronic liver disease etiology of patients was 14% alcohol, 62% viral hepatitis, and 23% other. Study 311 randomized 204 patients to 1 of 2 possible cohorts: Cohort 1 (70 avatrombopag/43 placebo) or Cohort 2 (58 avatrombopag/33 placebo). Patients had a median age of 59 years with 62% of patients being male and a baseline median platelet of 39×10^9/L. The chronic liver disease 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.

1.5 Rationale

Avatrombopag is being developed to potentially address the unmet medical need of thrombocytopenia in subjects scheduled for operations to critical sites or operations with a high risk of bleeding complications. The study aims to evaluate the efficacy of avatrombopag in increasing platelet counts. The safety of avatrombopag will also be assessed through monitoring of adverse events, physical examination findings, clinical laboratory parameters, and vital signs.

Data to date suggest that avatrombopag is a promising candidate for use in the treatment of thrombocytopenia of diverse etiologies.

1.6 Risk/Benefit

The current treatment for thrombocytopenia in subjects scheduled for operations at critical sites or that have a high risk of bleeding is a platelet transfusion immediately prior to the therapeutic procedure in order to proactively mitigate the risk of bleeding. While the risks of single platelet transfusions are generally considered acceptable, they are only transiently effective at increasing platelet counts, and are associated with important patient risks that can have significant health and economic consequences. In addition to the potential risks of transfusion reactions and infections, which in rare cases can be fatal, the development of anti-platelet antibodies and the resultant refractoriness to subsequent platelet transfusions are of particular importance. Given that avatrombopag stimulates the body's own megakaryocytes to produce platelets, there is no risk for infection, and no immune response and thus no risk of refractoriness. This has important implications in preserving the utilization of platelets for emergent or future needs of the patient, which may not be available if they become refractory.

Given these considerations, a safe thrombopoietic agent that can lessen or eliminate the need for platelet transfusions and provide options for the treatment of moderate thrombocytopenia would provide an important public health benefit.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to evaluate the efficacy of avatrombopag in increasing platelet counts in subjects with thrombocytopenia scheduled for operations to critical sites or operations with a high risk of bleeding.

2.2 Secondary Objectives

The secondary objectives of this study are the following:

- To evaluate the safety of avatrombopag in subjects with thrombocytopenia scheduled for operations to critical sites or operations with a high risk of bleeding,
- To evaluate the effect of avatrombopag on the need for transfusions in subjects with thrombocytopenia scheduled for operations to critical sites or operations with a high risk of bleeding, and
- To evaluate the effect of avatrombopag on bleeding in subjects with thrombocytopenia scheduled for operations to critical sites or operations with a high risk of bleeding.

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is a Phase 3b open-label, multicenter study of the efficacy and safety of oral avatrombopag for the treatment of subjects with thrombocytopenia scheduled for a surgical procedure. Eligible subjects scheduled to undergo operations to critical sites (eg, eye surgery, neurosurgery) or operations with a high risk of bleeding (eg, major abdominal surgery) will be enrolled into the study and receive avatrombopag.

Mean baseline platelet count in subjects without CLD must be between 50×10^9/L and $<100 \times 10^9$/L and between 50×10^9/L and $<75 \times 10^9$/L in subjects with CLD. Platelet counts must be measured on 2 separate occasions, and must be performed at least 1 day apart with neither platelet count $\geq 100 \times 10^9$/L in subjects without CLD and $\geq 75 \times 10^9$/L in subjects with CLD. One standard of care platelet count measurement may be used if collected within 14 days of Baseline and the mean of these 2 platelet counts (mean baseline platelet count) will be used for entry criteria.

Subjects will receive 60 mg oral avatrombopag once daily for 5 days beginning on Day 1, followed by a wait period prior to the procedure, which will occur on Day 10 (+3 days). The platelet response data will be reviewed after approximately 25% and 50% of subjects have been enrolled in the study. If required, the dose may be adjusted for subsequent subjects based on insufficient increase in platelet counts on Procedure Day. If a higher dose is considered necessary, subjects will receive 80 mg oral avatrombopag once daily for 5 days beginning on Day 1, followed by a wait period prior to the procedure, which will occur on Day 10 (+3 days).

The Follow-up Period will include 2 visits, which will occur at approximately 7 days (+3 days) post-procedure and 30 days (±3 days) after the last dose of study drug.

The total study duration will be approximately 5 to 7 weeks.

3.2 Study Indication

The indication for this study is the treatment of thrombocytopenia in subjects scheduled for operations to critical sites (eg, eye surgery, neurosurgery) or operations with a high risk of bleeding (eg, major abdominal surgery).

4 SELECTION AND WITHDRAWAL OF SUBJECTS

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

4.1 Inclusion Criteria

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

1. Subject is ≥18 years of age at the time of informed consent;
2. Subject has a mean baseline platelet count between:
    a. 50×10^9/L and $<100 \times 10^9$/L in subjects without a diagnosis of chronic liver disease. or
    b. 50×10^9/L and $<75 \times 10^9$/L in subjects with diagnosed chronic liver disease.

    Platelet counts must be measured on 2 separate occasions, and must be performed at least 1 day apart with neither platelet count $\geq 100 \times 10^9$/L in subjects without CLD and $\geq 75 \times 10^9$/L in subjects with CLD. One standard of care platelet count measurement may be used if collected within 14 days of Baseline and the mean of these 2 platelet counts (mean baseline platelet count) will be used for entry criteria;
3. Subject is scheduled to undergo operations to critical sites (eg, eye surgery, neurosurgery) or operations with a high risk of bleeding (eg, major abdominal surgery), OR, in the opinion of the Investigator, would otherwise require a pre-operative platelet transfusion to prevent bleeding;
4. Female subjects of childbearing potential must agree to use a highly effective method of contraception (eg, total abstinence; an intrauterine device; a double-barrier method [such as condom plus diaphragm with spermicide]; hormonal contraceptive given orally, by injection, or by implant; or has a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 30 days after study drug discontinuation. If currently abstinent, the subject must agree to use a double-barrier method as described above if she becomes sexually active during the study period or for 30 days after study drug discontinuation;

    Note: All female subjects are considered to be of childbearing potential unless they are postmenopausal (at least 12 months consecutive amenorrhea in the appropriate age group and without another known or suspected cause) or has been sterilized surgically (ie, bilateral tubal ligation, hysterectomy, or bilateral oophorectomy) at least 1 month before dosing.
5. Subject is willing and able to comply with all aspects of the protocol; and
6. Subject (or legally authorized representative) must provide written informed consent.

4.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participation in the study:

1. Subject has a history of arterial or venous thrombosis within the previous 6 months of Baseline;
2. Known portal vein blood flow velocity rate <10 cm/second or previous occurrence of a portal vein thrombosis within 6 months of Baseline;

3. Subject plans to have a platelet transfusion or plans to receive blood products containing platelets within 7 days of the Baseline Visit; however, packed red blood cells are permitted;
4. Subject is unable to temporarily withhold anticoagulant or antiplatelet therapy per local standard of care prior to the operation (low dose aspirin may be continued);
5. Use of erythropoietin-stimulating agents within 7 days of the Baseline Visit;
6. Use of moderate or strong inducers of cytochrome P450 (CYP) 2C9 or CYP3A4/5 from 7 days prior to Baseline through the end of the dosing regimen (see Appendix C);
7. Current use of a thrombopoietin receptor agonist (eg, eltrombopag or romiplostim);
8. Subject has an active infection requiring systemic antibiotic therapy within 7 days of the Baseline Visit; however, prophylactic use of antibiotics is permitted;
9. Subject with alcohol abuse, alcohol dependence syndrome, drug abuse, or drug dependence within 6 months of the Baseline Visit (unless participating in a controlled rehabilitation program) or alcoholic hepatitis within 6 months of the Screening Visit;
10. Subject has a surgery between the Baseline Visit and Visit 4 (Procedure Day);
11. Subject is known to be human immunodeficiency virus positive;
12. Subject has any clinically significant bleeding at the Baseline Visit;
13. Subject has a known medical history of genetic prothrombotic syndromes (eg, Factor V Leiden, prothrombin G20210A, ATIII deficiency, etc.);
14. Subject has a recent history (within the previous 6 months) of significant cardiovascular disease (eg, exacerbation of congestive heart failure, arrhythmia known to increase the risk of thromboembolic events [eg, atrial fibrillation], coronary or peripheral artery stent placement or angioplasty, and coronary or peripheral artery bypass graft);
15. Female subjects who are lactating or pregnant at the Baseline Visit (as documented by a positive serum beta-human chorionic gonadotropin [β-hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG) or are planning to become pregnant during the study;
16. Subject has a hypersensitivity to avatrombopag or any of its excipients;
17. Subject has hemoglobin levels ≤8.0 g/dL or ≥18.0 g/dL for males and >15 g/dL for females at the Baseline Visit, with hematocrit ≥54% for males and ≥45% for females;
18. Subject has prothrombin time/international normalized ratio and activated partial thromboplastin time outside 80% to 120% of the normal range;
19. Subject with a current malignancy including solid tumors and hematologic malignancies whose thrombocytopenia may be attributed to chemotherapy;
20. Hepatic encephalopathy that cannot be effectively treated;
21. Subjects with hepatocellular carcinoma (HCC) and Barcelona Clinic Liver Cancer (BCLC) staging classification C or D;
22. Subject has any history of a concomitant medical condition that, in the opinion of the Investigator, would compromise the subject's ability to safely complete the study; or

23. Subject is currently enrolled in another clinical study with any investigational drug or device within 30 days of the Baseline Visit; however, participation in observational studies is permitted.

4.3 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;
- Any SAE, clinically significant adverse event, 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;
- Requirement of prohibited concomitant medication;
- Subject failure to comply with protocol requirements or study-related procedures; or
- 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 full panel of assessments scheduled for the Visit 6 (Day 35 [±3 days]). The reason for subject withdrawal must be documented in the electronic case report form (eCRF).

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

Subjects withdrawn prior to receiving a dose of study drug may be replaced as needed to meet the enrollment objectives of the study.

4.3.1 Subjects with Study Drug Interruption or Discontinuation

The Investigator should contact the Medical Monitor with any questions regarding how to handle a study drug discontinuation.

Subjects who discontinue study drug will be followed for the entire study duration through the Follow-up Period, and all procedures should be followed according to the protocol.

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

If a subject misses a dose of study drug, temporarily interrupts treatments (whether due to an adverse event or other reason), the Investigator should contact the Medical Monitor regarding how to handle treatment re-initiation or if permanent study drug discontinuation is required.

5 STUDY TREATMENTS

5.1 Treatment Groups

This is a Phase 3b open-label, single-arm, multicenter study of the efficacy and safety of oral avatrombopag for the treatment of subjects with thrombocytopenia scheduled for a surgical procedure. Eligible subjects scheduled to undergo operations to critical sites (eye surgery, neurosurgery) or operations with a high risk of bleeding (eg, major abdominal surgery) will be enrolled into the study and receive avatrombopag.

Subjects will receive 60 mg oral avatrombopag once daily for 5 days beginning on Day 1, followed by a wait period prior to the procedure, which will occur on Day 10 (+3 days).

At the Screening or Baseline Visit, site personnel will contact the interactive response technology (IRT) to register the subject. A subject identification number will be used to identify the subject throughout the study and will be entered on all documentation. A subject identification number will not be assigned to more than 1 subject. If a subject is not eligible to receive treatment, or if a subject discontinues from the study, the subject identification number cannot be assigned to another subject. The IRT will be used throughout the study.

5.2 Rationale for Dosing

A PK/PD model was developed to simulate platelet response to avatrombopag administration in order to select a dose regimen for this study. Using data from healthy volunteers and patients with chronic liver disease, the PK/PD model evaluated the relationship of avatrombopag concentrations to increases in platelet counts. Simulations were performed assuming the baseline platelet count ranged between 50 and $<100 \times 10^9$/L with a requirement to increase the platelet count to levels $\geq 100 \times 10^9$/L prior to the procedure. Simulations suggested that 60 mg avatrombopag administered once daily for 5 days with the procedure scheduled 5 to 8 days after the last dose of study drug would result in approximately 85% of subjects having platelet counts that exceed 100×10^9/L. Simulations were also performed for subjects with CLD. In order to limit the number of subjects with a platelet count $>200 \times 10^9$/L after treatment yet still have the majority of subjects with a platelet count $\geq 100 \times 10^9$/L on the day of surgery, subjects with CLD must have a platelet count between 50 and $<75 \times 10^9$/L at Baseline.

To ensure the accuracy of the predictions, platelet response data will be reviewed by the Sponsor and Medical Monitor, and if necessary, the Investigators participating in the study, after the enrollment of 25% and 50% of subjects to determine if the dose for subsequent subjects enrolled in the study should be increased to 80 mg once daily for 5 days.

5.3 Randomization and Blinding

This is an open-label, single-arm study; therefore, no randomization or blinding will occur.

5.4 Breaking the Blind

Not applicable.

5.5 Drug Supplies

5.5.1 Formulation and Packaging

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

Study drug will be packaged in blister packages.

5.5.2 Study Drug Preparation and Dispensing

Study drug will be provided to subjects in blister packages. The Investigator or designee will provide subjects with sufficient study drug to complete the 5-day regimen.

5.5.3 Study Drug Administration

Subjects will receive 60 mg oral avatrombopag once daily for 5 days beginning on Day 1, followed by a wait period prior to the procedure, which will occur on Day 10 (+3 days).

For study site visits during the Treatment Period, study drug may be administered at the site or the subject may self-dose. Subjects will self-dose at all other times and be instructed to take study drug with food.

The number of tablets to be taken will be as follows:

- 60 mg: three 20 mg tablets, or
- 80 mg: four 20 mg tablets (if needed).

5.5.4 Treatment Compliance

Compliance with study drug administration will be assessed by counting returned study drug packages and any unused study drug. Study drug compliance will be recorded on the drug accountability log.

5.5.5 Storage and Accountability

Avatrombopag tablets should be stored at controlled room temperature (20 to 25°C/68 to 77°F) and in the containers provided.

Records will be maintained indicating the receipt and dispensation of all study drug supplies. At the conclusion of the study, any unused study drug will be returned to the Sponsor or the Sponsor's designee. If no supply remains, this will be indicated in the Drug Accountability Log.

5.6 Prior and Concomitant Medications and/or Procedures

5.6.1 Excluded Medications and/or Procedures

The following medications and/or procedures are excluded:

- Platelet transfusion or receipt of blood products containing platelets within 7 days of the Baseline Visit; however, packed red blood cells are permitted;

- Use of anticoagulant or antiplatelet therapy (other than low dose aspirin) onVisit 4 (Procedure Day)
- Use of erythropoietin-stimulating agents within 7 days of the Baseline Visit;
- Use of moderate or strong inducers of CYP2C9 or CYP3A4/5 from 7 days prior to Baseline through the end of the dosing regimen (see Appendix C);
- Use of thrombopoietin receptor agonists (eg, eltrombopag or romiplostim);
- Use of systemic antibiotic therapy within 7 days of the Baseline Visit; however, prophylactic use of antibiotics is permitted;
- A surgery between the Baseline Visit and Visit 4 (Procedure Day); and
- Currently enrolled in another clinical study with any investigational drug or device within 30 days of the Baseline Visit; however, participation in observational studies is permitted.

5.6.2 Documentation of Concomitant Medication Use

All concomitant medications (including concurrent therapies and concurrent procedures) will be documented as indicated in Appendix A. Dose, indication for administration, and dates of medication administration will also be captured in source documents and on the appropriate eCRF.

6 STUDY PROCEDURES

A schedule of procedures in tabular format is provided in Table 1 in Appendix A.

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

Two platelet counts collected on different days must be used to calculate the mean baseline platelet count to determine eligibility as described in Inclusion Criterion #2. If a platelet count obtained per standard of care within 14 days of Baseline (Visit 2) is not available, a platelet count must be obtained at Screening (Visit 1) and then repeated at Baseline (Visit 2) to confirm eligibility. If an eligible platelet count obtained per standard of care is available from this time period, Visit 1 is not required and all Screening and Baseline procedures can be performed at Visit 2.

6.1 Informed Consent

Prior to conducting any study-related activities, written informed consent must be signed and dated by the subject (or legally authorized representative). See Section 11.3 for additional information on informed consent.

6.2 Screening

6.2.1 Visit 1 – Screening Visit (optional)

If an eligible platelet count obtained per standard of care within 14 days of the Baseline visit is available, this visit is not required and study procedures may commence as described for Visit 2. The following procedures will be performed at the Screening Visit at Visit 1 (Day -14 to Day -1):

- Obtain informed consent prior to screening procedures;
- Obtain demographics and medical history (including etiology of thrombocytopenia);
- Collect blood samples for the following assessments:
  - Platelet count (local and central laboratories),
- Contact IRT to register the subject in the study.

6.2.2 Visit 2 - Baseline Visit

The following procedures will be performed prior to study drug administration at the Baseline Visit at Visit 2 (Day 1):

- Obtain informed consent prior to screening procedures, if Visit 1 not performed;
- Conduct eligibility assessment based on inclusion/exclusion criteria;
- Obtain demographics and medical history (including etiology of thrombocytopenia), if Visit 1 not performed;
- Collect procedure-related information;
- Record concomitant medications;
- Assess adverse events;

- Perform physical examination;
- Record vital signs (includes weight, body temperature, blood pressure, and pulse rate);
- Record an eligible platelet count collected within the previous 14 days, if available; Collect blood samples for the following assessments (-1 Day permitted):
  - Hematology (local and central laboratories),
  - Platelet count (local and central laboratories);
  - Coagulation (local and central laboratories);
  - Serum chemistry (central laboratory only); and
  - Pregnancy test for female subjects of childbearing potential only (serum or urine);
- Contact IRT;
- Dispense study drug; and
- Administer or self-dose study drug.

6.3 Treatment Period

Subjects will receive 60 mg oral avatrombopag once daily for 5 days. For study site visits during the Treatment Period, study drug may be administered at the site or the subject may self-dose. Subjects will self-dose at all other times and be instructed to take study drug with food. The Investigator or designee will provide subjects with sufficient study drug to complete the 5-day regimen.

6.3.1 Visit 3

The following procedures will be performed at Visit 3 (Day 5 [-2 days]):

- Record concomitant medications,
- Assess adverse events,
- Collect blood samples for the following assessments:
  - Hematology (central laboratory only),
  - Platelet count (local and central laboratories), and
  - Coagulation (central laboratory only),
- Assess whether subject required any rescue procedure for bleeding,
- If any bleeding, perform ISTH non-surgical bleeding assessment (see Appendix D),
- Contact IRT, and
- Administer or self-dose study drug.

6.4 Visit 4 - Procedure Day

The following procedures will be performed pre-operatively on Procedure Day at Visit 4 (Day 10 [+3 days]):

- Record vital signs (includes weight, body temperature, blood pressure, and pulse rate);
- Collect blood samples for the following assessments:
  - Hematology (central laboratory only),
  - Platelet count (local and central laboratories),
  - Coagulation (central laboratory only), and
  - Serum chemistry (central laboratory only);
- Record whether subject required a platelet transfusion;
- If any bleeding, perform ISTH non-surgical bleeding assessment (see Appendix D);
- Contact IRT; and
- Collect study drug package and any unused study drug.

The following procedures will be performed post-operatively on Procedure Day at Visit 4 (Day 10 [+3 days]):

- Record concomitant medications,
- Record adverse events,
- Record whether subject required any rescue procedure for bleeding, and
- If any bleeding, perform ISTH surgical bleeding assessment (see Appendix D).

6.5 Follow-Up Period

6.5.1 Visit 5

The following procedures will be performed at Visit 5 (7 days post-procedure [+3 days]):

- Record concomitant medications;
- Assess adverse events;
- Perform physical examination;
- Record vital signs (includes weight, body temperature, blood pressure, and pulse rate);
- Collect blood samples for the following assessments:
  - Hematology (central laboratory only),
  - Platelet count (local and central laboratories),
  - Coagulation (central laboratory only), and
  - Serum chemistry (central laboratory only);
- Assess whether subject required a platelet transfusion;

- Assess whether subject required any rescue procedure for bleeding;
- If any bleeding, perform ISTH surgical and non-surgical bleeding assessment (see Appendix D); and
- Contact IRT.

6.5.2 Visit 6

The following procedures will be performed at Visit 6 (Day 35 [±3 days]):

- Record concomitant medications;
- Assess adverse events;
- Perform physical examination;
- Record vital signs (includes weight, body temperature, blood pressure, and pulse rate);
- Collect blood samples for the following assessments:
  - Hematology (central laboratory only),
  - Platelet count (local and central laboratories),
  - Coagulation (central laboratory only), and
  - Serum chemistry (central laboratory only);
- Perform pregnancy test for female subjects of childbearing potential only (serum or urine);
- Assess whether subject required a platelet transfusion;
- Assess whether subject required any rescue procedure for bleeding;
- If any bleeding, perform ISTH surgical and non-surgical bleeding assessment (see Appendix D); and
- Contact IRT.

6.6 Early Termination Visit and Withdrawal Procedures

For subjects who are withdrawn from the study prior to completion, all Visit 6 procedures will be performed at an Early Termination Visit. These procedures include the following:

- Record concomitant medications;
- Assess adverse events;
- Perform physical examination;
- Record vital signs (includes weight, body temperature, blood pressure, and pulse rate);
- Collect blood samples for the following assessments:
  - Hematology (central laboratory only),
  - Platelet count (local and central laboratories),

  - Coagulation (central laboratory only), and
  - Serum chemistry (central laboratory only);
- Perform pregnancy test for female subjects of childbearing potential only (serum or urine);
- Assess whether subject required a platelet transfusion;
- Assess whether subject required any rescue procedure for bleeding;
- If any bleeding, perform ISTH surgical and/or non-surgical bleeding assessment (see Appendix D); and

  Note: For an Early Termination Visit where a subject withdraws from the study prior to surgery on Procedure Day, the non-surgical ISTH bleeding definitions will be used. If a subject withdraws after surgery on Procedure Day, both the non-surgical and surgical ISTH bleeding definitions will be used.
- Contact IRT.

7 EFFICACY ASSESSMENTS

The primary efficacy endpoint is the proportion of subjects achieving a platelet count of $\geq 100 \times 10^9$/L on Procedure Day, when measured prior to a platelet transfusion (if any).

The secondary efficacy endpoints include the following:

- Change in platelet count from baseline to Procedure Day,
- Proportion of subjects without platelet transfusion and any other treatment for bleeding after the Baseline Visit and up to 7 days following Procedure Day,
- Proportion of subjects without platelet transfusion after the Baseline Visit and up to 7 days following Procedure Day, and
- Proportion of subjects without bleeding after the Baseline Visit and up to 7 days following Procedure Day.

Blood samples to assess platelet count will be collected as indicated in Appendix A. Local laboratories will be used to determine eligibility; however, for study analysis and reporting purposes, only values determined at a central laboratory will be used with the exception of platelet count. Local laboratories may be used if immediate results are clinically needed.

Whether a subject requires a platelet transfusion will be determined by the Investigator or treating physician. Transfusion may be deemed necessary if the platelet count is below the target value of $\geq 100 \times 10^9$/L or at the discretion of the Investigator or treating physician.

Bleeding will be evaluated by the Investigator using the non-surgical and surgical ISTH bleeding definitions described in Appendix D. The non-surgical ISTH bleeding definitions (Table 3) will be used when evaluating subjects prior to surgery on Procedure Day, and the surgical ISTH bleeding definitions (Table 4) will be used when evaluating subjects after surgery on Procedure Day. Both the non-surgical and surgical ISTH bleeding definitions will be used to evaluate subjects during the Follow-up Period. For an Early Termination Visit where a subject withdraws from the study prior to surgery on Procedure Day, the non-surgical ISTH bleeding definitions will be used. If a subject withdraws after surgery on Procedure Day, both the non-surgical and surgical ISTH bleeding definitions will be used.

8 SAFETY ASSESSMENTS

8.1 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 adverse event 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 adverse events, 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 study participation is complete. Subjects should be instructed to report any adverse event that they experience to the Investigator. Investigators should make an assessment for adverse events at each visit and record the event on the appropriate adverse event eCRF.

Wherever possible, a specific disease or syndrome 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 adverse event on the eCRF. Additionally, the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an adverse event, not the procedure.

Any medical condition already present at the Baseline Visit should not be reported as an adverse event unless the medical condition or signs or symptoms present at baseline change in severity or seriousness at any time during the study. In this case, it should be reported as an adverse event.

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

8.1.1 Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. “Responses” to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

8.1.2 Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information.

8.1.3 Assessment of Adverse Events by the Investigator

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

Assessment of Severity:

Mild – An event that is easily tolerated and generally not interfering with normal daily activities.

Moderate – An event that is sufficiently discomforting to interfere with normal daily activities.

Severe – An event that is incapacitating with inability to work or perform normal daily activities.

Causality Assessment:

The relationship of an adverse event 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 adverse event 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 adverse event 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.

8.2 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 hospitalizations,
    - NOTE: Any hospital admission with at least 1 overnight stay 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. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness. Admission to the hospital for social or situational reasons (ie, no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations. Hospitalization due to expected recovery time for the planned procedure will not be counted as an SAE.
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions,
- A congenital anomaly/birth defect, or
- An important medical event.
    - NOTE: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

8.3 Serious Adverse Event Reporting − Procedures for Investigators

Initial Reports

All SAEs occurring from the time of informed consent until 30 days following the last administration of study drug must be reported within 24 hours of the knowledge of the occurrence (this refers to any adverse event that meets any of the aforementioned serious criteria). All SAEs that the Investigator considers related to study drug occurring after the 30-day Follow-up Period 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. Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the Investigator's assessment of causality, this should also be noted on the appropriate SAE follow-up form. Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor. The Investigator must notify his/her Institutional Review Board (IRB) of the occurrence of the SAE, in writing, if required by their institution. A copy of this communication must be forwarded to the Sponsor to be filed in the Sponsor's Trial Master File.

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

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), or the subject dies.

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

8.4 Pregnancy Reporting

If the subject becomes pregnant during the study or within 30 days of discontinuing study drug, the Investigator should report the pregnancy within 24 hours of being notified. Safety will then forward the appropriate form to the Investigator for completion.

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

The subject should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify Safety. 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 (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

8.5 Expedited Reporting

The Sponsor will report all relevant information about suspected unexpected serious adverse reactions that are fatal or life-threatening as soon as possible to the FDA, and in any case no later than 7 days after knowledge by the Sponsor of such a case, and that relevant follow-up information will subsequently be communicated within an additional 8 days.

All other suspected unexpected serious adverse reactions will be reported to the FDA as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor.

The Sponsor will also inform all Investigators as required.

8.6 Clinical Laboratory Evaluations

Clinical safety laboratory assessments will include serum chemistry, hematology, and coagulation and will be obtained as indicated in Appendix A. See Appendix B for a complete list of analytes.

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

8.7 Vital Signs

Vital sign measurements will include height (at the Baseline Visit only), weight, body temperature, blood pressure, and pulse rate and will be measured after resting for 5 minutes as indicated in Appendix A.

8.8 Physical Examinations

Physical examinations will consist of the following at a minimum: chest, lungs, heart, and abdomen.. Physical examinations will be performed as indicated in Appendix A.

8.9 Demographic and Medical History

Demographic information (date of birth, gender, race, and ethnic group) and relevant medical history will be recorded at the Screening or Baseline Visit.

9 STATISTICS

9.1 Analysis Populations

Full Analysis Set (FAS): The FAS will include all enrolled subjects who receive at least 1 dose of avatrombopag.

Per-Protocol Analysis Set (PPS): The PPS will include the subset of subjects from the FAS who are treated according to the protocol without any major deviations. A full list of major protocol deviations will be finalized prior to database lock.

Safety Analysis Set: The Safety Analysis Set will include all subjects who receive at least 1 dose of avatrombopag.

9.2 Statistical Methods

9.2.1 Analysis of Efficacy

All primary and secondary efficacy endpoints will be analyzed using the FAS. The PPS will be used only for sensitivity analysis of the primary and secondary efficacy endpoints.

9.2.1.1 Primary efficacy analysis

The primary efficacy endpoint is the proportion of subjects achieving a platelet count of $\geq 100 \times 10^9$/L on Procedure Day, when measured prior to a platelet transfusion (if any). Subjects with missing information due to early withdrawal or other reasons are considered as having a platelet count $<100 \times 10^9$/L in the analysis; that is, missing values are considered as non-responders. The primary endpoint will be estimated from a binomial distribution, with 95% confidence interval (CI) of the proportion calculated. The study will be claimed successful if the lower boundary of the 2-sided 95% CI is above the 0.65. The primary analysis will be performed on the FAS and repeated on the PPS.

9.2.1.2 Secondary efficacy analysis

The following secondary efficacy endpoints will be summarized and analyzed in the same manner as the primary efficacy endpoint:

- Proportion of subjects without platelet transfusion and any other treatment for bleeding after the Baseline Visit and up to 7 days following Procedure Day,
- Proportion of subjects without platelet transfusion after the Baseline Visit and up to 7 days following Procedure Day, and
- Proportion of subjects without bleeding after the Baseline Visit and up to 7 days following Procedure Day.

Change in platelet count from baseline to Procedure Day for avatrombopag will be calculated for each subject and summarized descriptively. The mean (95% CI) and median (range) will be provided.

9.2.1.3 Other efficacy analysis

Additional efficacy analyses will be performed if deemed necessary. The details of the analyses will be described in the Statistical Analysis Plan that will be finalized prior to database lock.

9.2.2 Analysis of Safety

Safety and tolerability will be assessed by examining the incidence of adverse events, physical examination findings, clinical laboratory parameters, and vital signs over time using the Safety Analysis Set.

9.2.3 Interim Analysis

Two interim data reviews are planned to assess study design assumptions and adjust study drug dose regimen if necessary.

The first interim data review will be conducted when approximately 25% of subjects (approximately 15 subjects) have been enrolled. For the primary efficacy endpoint, if fewer than 10 responders out of 15 enrolled subjects are observed (the probability of observing <10 responders out of 15 enrolled subjects is 0.0611 if the true response rate is 0.8), the avatrombopag dose increase (to 80 mg) will be considered for the subsequent enrolled subjects. Otherwise, the study will continue as planned until the second interim data review.

In the event that the avatrombopag dose was not adjusted after the first interim data review, the second interim data review will be conducted when approximately 50% of subjects (approximately 30 subjects) have been enrolled. If fewer than 21 responders out of 30 enrolled subjects are observed (the probability of observing <21 responders out of 30 enrolled subjects is 0.0611 if the true response rate is 0.8), the avatrombopag dose increase (to 80 mg) will be considered for the subsequent enrolled subjects. Otherwise, the study will continue as planned until the completion of the study.

Details of the planned interim analyses will be provided in the Interim Analysis Plan.

9.2.4 Sample Size Determination

It is estimated from PK/PD modeling that the proportion of subjects treated with avatrombopag expected to achieve a platelet count of $\geq 100 \times 10^9$/L on Procedure Day, when measured prior to platelet transfusion (if any), is approximately 85%. Assuming the true response rate is 0.8 and the desired lower boundary of the 2-sided 95% CI is at least 0.65, 60 enrolled subjects will provide greater than 90% power. If the decision is made to increase the dose of study drug at one of the interim reviews of the data based on the pre-defined boundaries, up to an additional 30 subjects may be enrolled in the study for a maximum sample size of 90 subjects.

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 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 (eg, safety, IRT) is complete.

10.1.2 Computer Systems

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

10.1.3 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 user name and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR) Part 11 and other appropriate international regulations. All passwords will be strictly confidential.

10.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

- Medical Dictionary for Regulatory Activities for medical history and adverse events, and
- World Health Organization Drug Dictionary for prior and concomitant medications.

10.1.5 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.

10.2 Record Keeping

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

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human subjects. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

11.2 Institutional Review Board

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

Federal regulations and International Council on Harmonisation (ICH) require that approval be obtained from an IRB prior to participation of subjects in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, 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.

No drug will be released to the site until written IRB authorization has been received by the Sponsor.

11.3 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 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 (or legally authorized representative) 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 (or legally authorized representative) before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB and/or regulatory agencies. A copy of the signed ICF will be given to the subject (or legally authorized representative).

11.4 Study Monitoring Requirements

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

To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized and easily retrievable data. Before the enrollment of any subject in this study, the Sponsor or their designee will review with the

Investigator and site personnel the following documents: protocol, 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 monitor 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.

11.5 Disclosure of Data

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

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

11.6 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, eg, eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, forms for SAEs, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

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

11.7 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.

11.8 Financial Disclosure

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

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigators by [redacted] or the Sponsor. 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, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IRB within 5 working days.

12.2 Address List

12.2.1 Sponsor

Dova Pharmaceuticals
240 Leigh Farm Road, Suite 245
Durham, NC 27707
Telephone: 919-748-5975
Fax: 919-748-5976

12.2.2 Contract Research Organization

[redacted]

12.2.3 Drug Safety

[redacted]

12.2.4 Biological Specimens

[redacted]

13 REFERENCES

1. McCullough J. Current issues with platelet transfusion in patients with cancer. Semin Hematol. 2000;37(2 Suppl 4):3-10.
2. Schiffer CA, Anderson KC, Bennett CL, et al. Platelet transfusion for patients with cancer: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol. 2001;19(5):1519-1538.
3. Kuter DJ. Thrombopoietin: biology and potential clinical applications. In: McCrae KR, eds. *Thrombocytopenia*. New York, New York: Taylor & Francis Group; 2006.
4. Avatrombopag maleate Global Investigator's Brochure, v12, April 2016.

APPENDIX A: SCHEDULE OF PROCEDURES

Table 1 Schedule of Procedures

Period	**Screening**		**Treatment**	**Procedure Day**	**Follow-Up**	
Visit	**1 (optional)**	**2 (Baseline Visit)**	**3**	**4**	**5**	**6 (ET Visit)**
Day	**Day -14 to -1**	**Day 1 [1]**	**Day 5**	**Day 10 [2]**	**7 Days Post-Procedure**	**Day 35**
Window			**(-2 days)**	**(+3 days)**	**(+3 days)**	**(±3 days)**
Procedures						
Subject informed consent	X	X [11]				
Inclusion/exclusion criteria		X				
Demographics	X	X [11]				
Medical history [10]		X				
Concomitant medications		X	X	X	X	X
Adverse events	X	X	X	X	X	X
Physical examination [3]		X		X	X	X
Vital signs [4]		X		X	X	X
Hematology		X [5]	X	X	X	X
Platelet count [5]	X	X	X	X	X	X
Coagulation		X [5]	X	X	X	X
Serum chemistry		X		X	X	X
Pregnancy testing [6]		X [7]				X [7]
Assessment of platelet transfusion				X	X	X
Assessment of any rescue procedure for bleeding			X	X	X	X
Procedure-related information (type, risk, etc.)		X				
Contact IRT	X	X	X	X	X	X
Dispense study drug [8]		X				
Study drug dosing [8]		X	X			
Bleeding assessment (ISTH) [9]			X	X	X	X
Collect study drug				X		

Note: Prior to conducting any study-related activities, written informed consent must be signed and dated by the subject. Local laboratories will be used to determine eligibility; however, for study analysis and reporting purposes, only values determined at a central laboratory will be used with the exception of platelet count. Local laboratories may be used if immediate results are clinically needed.

1. All assessments will be performed prior to study drug dosing.

2. The following procedures will be performed pre-operatively on Procedure Day: vital signs, hematology, platelet count, coagulation, serum chemistry, record whether subject required a platelet transfusion, ISTH non-surgical bleeding assessment (if any bleeding), contact IRT, and collect study drug. The following procedures will be performed post-operatively on Procedure Day: concomitant medications, adverse events, record any rescue procedure for bleeding, and ISTH surgical bleeding assessment (if any bleeding).
3. Physical examinations will consist of the following at a minimum: chest, lungs, heart, and abdomen.
4. Vital sign measurements will include height (at the Baseline Visit only), weight, body temperature, blood pressure, and pulse rate and will be measured after resting for 5 minutes.
5. Local and central laboratories. Baseline hematology, platelet count and coagulation laboratories may be collected up to one day prior to the Baseline visit (Visit 2).
6. For female subjects of childbearing potential only. A serum or urine pregnancy test will be performed at the Baseline Visit prior to study drug administration.
7. Either a serum or urine pregnancy test may be used.
8. Subjects will receive 60 mg oral avatrombopag once daily for 5 days beginning on Day 1. For study site visits during the Treatment Period, study drug may be administered at the site or the subject may self-dose. Subjects will self-dose at all other times and be instructed to take study drug with food. The Investigator or designee will provide subjects with sufficient study drug to complete the 5-day regimen.
9. Bleeding will be evaluated, if present, by the Investigator using the non-surgical and surgical ISTH bleeding definitions described in Appendix D. The non-surgical ISTH bleeding definitions (Table 3) will be used when evaluating subjects prior to surgery on Procedure Day, and the surgical ISTH bleeding definitions (Table 4) will be used when evaluating subjects after surgery on Procedure Day. Both the non-surgical and surgical ISTH bleeding definitions will be used to evaluate subjects during the Follow-up Period. For an Early Termination Visit where a subject withdraws from the study prior to surgery on Procedure Day, the non-surgical ISTH bleeding definitions will be used. If a subject withdraws after surgery on Procedure Day, both the non-surgical and surgical ISTH bleeding definitions will be used.
10. Document etiology of thrombocytopenia.
11. If Visit 1 not performed

ET = Early Termination; IRT = Interactive Response Technology; ISTH = International Society on Thrombosis and Haemostasis.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Standard Safety Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Aspartate aminotransferase
Bicarbonate	Blood urea nitrogen
Calcium	Chloride
Creatine kinase	Creatinine
Gamma-glutamyl transferase	Glucose
Inorganic phosphorus	Lactate dehydrogenase
Potassium	Sodium
Total bilirubin	Total protein

Hematology

Hematocrit	Hemoglobin
Platelets	Red blood cell count

White blood cell count and differential [1]

1. Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

Coagulation

Prothrombin time	Activated partial thromboplastin time
International normalized ratio	

Pregnancy Test

Beta-human chorionic gonadotropin

APPENDIX C: CYTOCHROME P450 INDUCERS AND INHIBITORS

Table 2 CYP450 Inducers

	Strong	Moderate
CYP2C9 inducers	NA	Aprepitant, carbamazepine, enzalutamide, rifampin, ritonavir
CYP3A4 inducers	Carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort	Bosentan, efavirenz, etravirine, modafinil

CYP = cytochrome P450; NA = not applicable.
Source:
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#inVivo

APPENDIX D: INTERNATIONAL SOCIETY ON THROMBOSIS AND HAEMOSTASIS BLEEDING DEFINITIONS

Table 3 Non-Surgical International Society on Thrombosis and Haemostasis Bleeding Definition

Major bleeding	Defined as overt bleeding with 1 or more of the following: • Associated with a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more; • Leads to a transfusion of 2 or more units of packed red blood cells or whole blood; • Occurs in a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal; and/or • Contributes to death.
Non-major clinically relevant bleeding	Defined as overt bleeding not meeting the criteria for major bleeding, but associated with medical intervention, unscheduled contact with a physician (visit or telephone call), (temporary) cessation of study treatment, or associated with any other discomfort, such as pain or impairment of daily activities. Examples of such bleeding include: • Any bleeding compromising hemodynamics; • Any bleeding leading to hospitalization; • Epistaxis if it lasts for >5 minutes, if it is repetitive (ie, ≥2 episodes of true bleeding, [ie, not spots on a handkerchief] within 24 hours), or if it leads to an intervention (packing, electrocoagulation, etc); • Gingival bleeding if it occurs spontaneously (ie, unrelated to tooth brushing or eating) or lasts >5 minutes; • Hematuria if it is macroscopic and either spontaneous or lasts >24 hours after instrumentation (eg, catheter placement or surgery) of the urogenital tract; • Macroscopic gastrointestinal hemorrhage (at least 1 episode of melena/hematemesis, if clinically apparent, and hemoccult positive rectal blood loss, if more than a few spots on toilet paper); • Hemoptysis, if more than a few speckles in the sputum and not occurring within the context of a pulmonary embolism; • Intramuscular hematoma; • Subcutaneous (skin) hematoma if the size is >25 cm^2 or >100 cm^2 if provoked; and/or • Any other bleeding type that is considered to have clinical consequences for a subject.
Minor bleeding	Defined as all other overt bleeding episodes not meeting the criteria for major or clinically relevant non-major bleeding.
Sources: Schulman S, Angeras D, Bergqvist B, et al. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. J Thromb Haemost. 2010;8:202-204 and Tangelder M, Nwachuku C, Jaff M, et al. A review of antithrombotic therapy and the rationale and design of the randomized edoxaban in patients with peripheral artery disease (ePAD) trial adding edoxaban or clopidogrel to aspirin after femoropopliteal endovascular intervention. J Endovasc Ther. 2015; 22(2)261-268.	

Table 4 Surgical International Society on Thrombosis and Haemostasis Bleeding Definition

Major bleeding	• Fatal bleeding; • Bleeding that is symptomatic and occurs in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, pericardial, in a non-operated joint, or intramuscular with compartment syndrome, assessed in consultation with the surgeon; • Extrasurgical site bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of 2 or more units of whole blood or red cells, with temporal association within 24 to 48 hours to the bleeding; • Surgical site bleeding that requires a second intervention – open, arthroscopic, endovascular – or a hemarthrosis of sufficient size as to interfere with rehabilitation by delaying mobilization or delayed wound healing, resulting in prolonged hospitalization or a deep wound infection; and • Surgical site bleeding that is unexpected and prolonged and/or sufficiently large to cause hemodynamic instability, as assessed by the surgeon. There should be an associate fall in hemoglobin level of at least 20 g/L (1.24 mmol/L), or transfusion, indicated by the bleeding, of at least 2 units of whole blood or red cells, with temporal association within 24 hours to the bleeding.
Minor bleeding	Defined as all other overt bleeding episodes not meeting the criteria for major bleeding.

Sources: Schulman S, Angeras D, Bergqvist B, et al. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. J Thromb Haemost. 2010;8:202-204 and Tangelder M, Nwachuku C, Jaff M, et al. A review of antithrombotic therapy and the rationale and design of the randomized edoxaban in patients with peripheral artery disease (ePAD) trial adding edoxaban or clopidogrel to aspirin after femoropopliteal endovascular intervention. J Endovasc Ther. 2015; 22(2)261-268.

APPENDIX E: Protocol Amendments

Amendment #2 – 17 September 2018

Rationale for Amendment

Amendment 2 has been introduced to clarify certain inclusion and exclusion criteria and to allow for a single Baseline visit (Visit 2) prior to study drug administration. The Screening visit (Visit 1) has been modified to an optional visit, required only if a subject does not have an eligible platelet count collected per standard of care within 14 days of Baseline which can be used to determine eligibility. If an eligible platelet count is available from this time period, this may serve as one of the 2 required platelet counts to determine the mean baseline platelet count for inclusion criterion #2.

Due to varying local platelet count thresholds, the specification of a 100×10^9/L target after platelet transfusion has been removed. Inclusion criterion #3 has been clarified to include subjects scheduled to undergo operations to critical sites or with a high risk of bleeding, OR if, in the opinion of the Investigator, a pre-operative platelet transfusion would otherwise be required. Exclusion criteria #1 and #14 have been clarified to exclude only a recent history, defined as the previous 6 months, of thrombotic events or significant cardiovascular events. Exclusion #4 has been clarified to require subjects to be able to temporarily withhold antiplatelet or anticoagulant medications pre-operatively per local standard of care, with low dose aspirin excepted.

Certain study procedures have also been removed or clarified. The ISTH bleeding assessments are to be performed only if bleeding occurs; the requirement to perform a physical exam on Procedure Day has been removed; the scope of physical exams will now only require chest, lungs, heart, and abdomen at a minimum.

Summary of Significant Changes in Amendment 2

- Inclusion criterion #2 has be modified to allow for an eligible platelet count obtained per standard of care within 14 days of Baseline to be used as 1 of the 2 required in order to calculate the mean baseline platelet count to determine eligibility
- Inclusion criterion #3 has been clarified to include subjects scheduled to undergo operations to critical sites or with a high risk of bleeding, OR if, in the opinion of the Investigator, a pre-operative platelet transfusion would otherwise be required
- Exclusion criteria #1 and #14 have been clarified to exclude only a recent history of thrombotic or significant cardiovascular events
- Visit 1 is now optional, required only for subjects without an eligible pre-existing platelet count; all screening and baseline procedures can be performed at Visit 2

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

SYNOPSIS

POPULATION:

The population for this study is subjects ≥18 years of age at the time of informed consent who are scheduled to undergo operations to critical sites (eg, eye surgery, neurosurgery) or operations with a high risk of bleeding (eg, major abdominal surgery) ~~who~~ ***OR***, in the opinion of the Investigator, would otherwise require a ***pre-operative*** platelet transfusion ~~aiming for a platelet count of at least 100×10^9/L~~ to prevent bleeding. Subjects without chronic liver disease must have a mean baseline platelet count between 50×10^9/L and $<100 \times 10^9$/L, measured on 2 separate occasions ~~(the Screening Visit and the Baseline Visit)~~, with neither platelet count $\geq 100 \times 10^9$/L. Subjects with chronic liver disease (CLD) must have a mean baseline platelet count between 50×10^9/L and $<75 \times 10^9$/L, measured on 2 separate occasions ~~(the Screening Visit and the Baseline Visit)~~, with neither platelet count $\geq 75 \times 10^9$/L.

STUDY DESIGN AND DURATION:

~~Subjects must be screened prior to the Baseline Visit.~~ Mean baseline platelet count in subjects without CLD must be between 50×10^9/L and $<100 \times 10^9$/L ***and*** between 50×10^9/L and $<75 \times 10^9$/L in subjects with CLD. Platelet counts must be measured on 2 separate occasions ~~(the Screening Visit and the Baseline Visit)~~, and must be performed at least 1 day apart with neither platelet count $\geq 100 \times 10^9$/L in subjects without CLD and $\geq 75 \times 10^9$/L in subjects with CLD. ***One standard of care platelet count measurement may be used if collected within 14 days of Baseline and*** the mean of these 2 platelet counts (mean baseline platelet count) will be used for entry criteria.

1.4 Clinical Studies

Based on these data, avatrombopag (DOPTELET®) was approved by FDA in May 2018 for the treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure.

3.1 Summary of Study Design

~~Subjects must be screened prior to the Baseline Visit.~~ Mean baseline platelet count in subjects without CLD must be between 50×10^9/L and $<100 \times 10^9$/L ***and*** between 50×10^9/L and $<75 \times 10^9$/L in subjects with CLD. Platelet counts must be measured on 2 separate occasions ~~(the Screening Visit and the Baseline Visit)~~, and must be performed at least 1 day apart with neither platelet count $\geq 100 \times 10^9$/L in subjects without CLD and $\geq 75 \times 10^9$/L in subjects with CLD. ***One standard of care platelet count measurement may be used if collected within 14 days of Baseline and*** the mean of these 2 platelet counts (mean baseline platelet count) will be used for entry criteria.

4.1 Inclusion Criteria

2. Subject has a mean baseline platelet count between:

   a. 50×10^9/L and $<100 \times 10^9$/L in subjects without a diagnosis of chronic liver disease. or

   b. 50×10^9/L and $<75 \times 10^9$/L in subjects with diagnosed chronic liver disease.

Platelet counts must be measured on 2 separate occasions ~~(the Screening Visit and the Baseline Visit)~~, and must be performed at least 1 day apart with neither platelet count $\geq 100 \times 10^9$/L in subjects without CLD and $\geq 75 \times 10^9$/L in subjects with CLD. The mean of these 2 platelet counts (mean baseline platelet count) will be used for entry criteria;

3. Subject is scheduled to undergo operations to critical sites (eg, eye surgery, neurosurgery) or operations with a high risk of bleeding (eg, major abdominal surgery), ~~and~~ ***OR***, in the opinion of the Investigator, would otherwise require a ***pre-operative*** platelet transfusion ~~aiming for a platelet count of at least 100 x 10^9/L~~ to prevent bleeding;

6. Subject ***(or legally authorized representative)*** must provide written informed consent.

4.2 Exclusion Criteria

1. Subject has a history of arterial or venous thrombosis ***within the previous 6 months of Baseline***;
2. Known portal vein blood flow velocity rate <10 cm/second or previous occurrence of a portal vein thrombosis within 6 months of ~~screening~~ ***Baseline***
3. Subject plans to have a platelet transfusion or plans to receive blood products containing platelets within 7 days of the ~~Screening~~ ***Baseline*** Visit; however, packed red blood cells are permitted;
4. ***Subject is unable to temporarily withhold*** ~~use of~~ anticoagulant or antiplatelet therapy ~~within 7 days of the Screening Visit~~ ***per local standard of care prior to the operation (low dose aspirin may be continued);***
5. Use of erythropoietin-stimulating agents within 7 days of the ~~Screening~~ ***Baseline*** Visit;
6. Use of moderate or strong inducers of cytochrome P450 (CYP) 2C9 or CYP3A4/5 from 7 days prior to ~~Screening~~ ***Baseline*** through the end of the dosing regimen (see Appendix C);
8. Subject has an active infection requiring systemic antibiotic therapy within 7 days of the ~~Screening~~ ***Baseline*** Visit; however, prophylactic use of antibiotics is permitted;
9. Subject with alcohol abuse, alcohol dependence syndrome, drug abuse, or drug dependence within 6 months of the ~~Screening~~ ***Baseline*** Visit (unless participating in a controlled rehabilitation program) or alcoholic hepatitis within 6 months of the Screening Visit;
10. Subject has a surgery between the ~~Screening~~ ***Baseline*** Visit and Visit 4 (Procedure Day);
12. Subject has any clinically significant bleeding at the ~~Screening~~ ***Baseline*** Visit;
14. Subject has a ***recent*** history ***(within the previous 6 months)*** of significant cardiovascular disease (eg, ***exacerbation of*** congestive heart failure ~~New York Heart Association Grade III/IV~~, arrhythmia known to increase the risk of thromboembolic events [eg, atrial fibrillation], coronary or peripheral artery stent placement or angioplasty, and coronary or peripheral artery bypass graft);
15. Female subjects who are lactating or pregnant at the ~~Screening Visit or the~~ Baseline Visit (as documented by a positive serum beta-human chorionic gonadotropin [β-hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG) or are planning to become pregnant during the study;

17. Subject has hemoglobin levels ≤8.0 g/dL or ≥18.0 g/dL for males and >15 g/dL for females at the ~~Screening~~ ***Baseline*** Visit, with hematocrit ≥54% for males and ≥45% for females;

19. Subject with a current malignancy including solid tumors and hematologic malignancies whose thrombocytopenia may be attributed to chemotherapy ~~during the study~~;

23. Subject is currently enrolled in another clinical study with any investigational drug or device within 30 days of the ~~Screening~~ ***Baseline*** Visit; however, participation in observational studies is permitted.

5.1 Treatment Groups

At the Screening ***or Baseline*** Visit, site personnel will contact the interactive response technology (IRT) to register the subject.

5.6.1 Excluded Medications and/or Procedures

The following medications and/or procedures are excluded:

- **Platelet transfusion or receipt of blood products containing platelets within 7 days of the ~~Screening~~ *Baseline* Visit; however, packed red blood cells are permitted;**
- Use of anticoagulant or antiplatelet therapy ***(other than low dose aspirin) on*** ~~between 7 days prior to the Screening Visit and~~ Visit 4 (Procedure Day)
- Use of erythropoietin-stimulating agents within 7 days of the ~~Screening~~ ***Baseline*** Visit;
- Use of moderate or strong inducers of CYP2C9 or CYP3A4/5 from 7 days prior to ~~Screening~~ ***Baseline*** through the end of the dosing regimen (see Appendix C);
- Use of systemic antibiotic therapy within 7 days of the ~~Screening~~ ***Baseline*** Visit; however, prophylactic use of antibiotics is permitted;
- **A surgery between the ~~Screening~~ *Baseline* Visit and Visit 4 (Procedure Day); and**
- Currently enrolled in another clinical study with any investigational drug or device within 30 days of the ~~Screening~~ ***Baseline*** Visit; however, participation in observational studies is permitted.

6. STUDY PROCEDURES

Two platelet counts collected on different days must be used to calculate the mean baseline platelet count to determine eligibility as described in Inclusion Criterion #2. If a platelet count obtained per standard of care within 14 days of Baseline (Visit 2) is not available, a platelet count must be obtained at Screening (Visit 1) and then repeated at Baseline (Visit 2) to confirm eligibility. If an eligible platelet count obtained per standard of care is available from this time period, Visit 1 is not required and all Screening and Baseline procedures can be performed at Visit 2.

6.1 Informed Consent

Prior to conducting any study-related activities, written informed consent must be signed and dated by the subject ***(or legally authorized representative)***. See Section 11.3 for additional information on informed consent.

6.2 Screening

6.2.1 Visit 1 – Screening Visit (optional)

If an eligible platelet count obtained per standard of care within 14 days of the Baseline visit is available, this visit is not required and study procedures may commence as described for Visit 2. The following procedures will be performed at the Screening Visit at Visit 1 (Day -14 to Day -1):

- ~~Conduct eligibility assessment based on inclusion/exclusion criteria;~~
- ~~Record concomitant medications;~~
- ~~Assess adverse events;~~
- ~~Perform physical examination;~~
- ~~Record vital signs (includes height, weight, body temperature, blood pressure, and pulse rate);~~
- Collect blood samples for the following assessments:
  - ~~Hematology (local and central laboratories),~~
  - Platelet count (local and central laboratories),
  - ~~Serum chemistry (central laboratory only), and~~
  - ~~Serum pregnancy test for female subjects of childbearing potential only (central laboratory only);~~
- ~~Collect procedure-related information; and~~

6.2.2 Visit 2 - Baseline Visit

The following procedures will be performed prior to study drug administration at the Baseline Visit at Visit 2 (Day 1):

- ***Obtain informed consent prior to screening procedures, if Visit 1 not performed;***
- Conduct eligibility assessment based on inclusion/exclusion criteria;
- ***Obtain demographics and medical history (including etiology of thrombocytopenia), if Visit 1 not performed;***
- ***Collect procedure-related information;***
- Record concomitant medications;
- Assess adverse events;
- ***Perform physical examination;***
- Record vital signs (includes weight, body temperature, blood pressure, and pulse rate);
- ***Record an eligible platelet count collected within the previous 14 days, if available;***
- Collect blood samples for the following assessments (-1 Day permitted):
  - Hematology (local and central laboratories),

- Platelet count (local and central laboratories);
- Coagulation (local and central laboratories);
- ***Serum chemistry (central laboratory only); and***
- ***Pregnancy test for female subjects of childbearing potential only (serum or urine);***

- ~~Perform pregnancy test for female subjects of childbearing potential only (serum or urine);~~
- ~~Assess whether subject required any rescue procedures for bleeding;~~
- ~~Perform International Society on Thrombosis and Haemostasis (ISTH) non-surgical bleeding assessment (see Appendix D);~~
- Contact IRT;

6.3.1 Visit 3

- ***If any bleeding,*** perform ISTH non-surgical bleeding assessment (see Appendix D),

6.4 *Visit 4* - Procedure Day

The following procedures will be performed pre-operatively on Procedure Day at Visit 4 (Day 10 [+3 days]):

- ~~Perform physical examination~~
- ~~Assess~~ ***Record*** whether subject required a platelet transfusion;
- ***If any bleeding,*** perform ISTH non-surgical bleeding assessment (see Appendix D);

The following procedures will be performed post-operatively on Procedure Day at Visit 4 (Day 10 [+3 days]):

- ~~Assess~~ ***Record*** adverse events,
- ~~Assess~~ ***Record*** whether subject required any rescue procedure for bleeding, and
- ***If any bleeding***, perform ISTH surgical bleeding assessment (see Appendix D).

6.5 Follow-Up Period

6.5.1 Visit 5

The following procedures will be performed at Visit 5 (7 days post-procedure [+3 days]):

- ***If any bleeding***, perform ISTH surgical and non-surgical bleeding assessment (see Appendix D); and

6.5.2 Visit 6

The following procedures will be performed at Visit 6 (Day 35 [±3 days]):

- ***If any bleeding,*** perform ISTH surgical and non-surgical bleeding assessment (see Appendix D); and

6.6 Early Termination Visit and Withdrawal Procedures

For subjects who are withdrawn from the study prior to completion, all Visit 6 procedures will be performed at an Early Termination Visit. These procedures include the following:

- ***If any bleeding,*** perform ISTH surgical and/or non-surgical bleeding assessment (see Appendix D); and

8.1 Adverse Events

Adverse events, which include clinical laboratory test variables, will be monitored and documented from the time of informed consent until study participation is complete. Subjects should be instructed to report any adverse event that they experience to the Investigator. ~~Beginning with the Screening Visit,~~ Investigators should make an assessment for adverse events at each visit and record the event on the appropriate adverse event eCRF.

Any medical condition already present at the ~~Screening~~ ***Baseline*** Visit should not be reported as an adverse event unless the medical condition or signs or symptoms present at baseline change in severity or seriousness at any time during the study. In this case, it should be reported as an adverse event.

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

8.7 Vital Signs

Vital sign measurements will include height (at the ~~Screening~~ ***Baseline*** Visit only), weight, body temperature, blood pressure, and pulse rate and will be measured after resting for 5 minutes as indicated in Appendix A.

8.8 Physical Examination

Physical examinations will consist of the following ***at a minimum***: ~~general appearance, head and neck, eyes and ears, nose and throat,~~ chest, lungs, heart, and abdomen ~~extremities and joints, lymph nodes, skin, and neurology~~. Physical examinations will be performed as indicated in Appendix A.

8.9 Demographic and Medical History

Demographic information (date of birth, gender, race, and ethnic group) and relevant medical history will be recorded at the Screening ***or Baseline*** Visit.

11.3 Informed Consent

The Investigator must ensure that each study subject ***(or legally authorized representative)*** 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 ***(or legally authorized representative)*** before any study-specific activity is performed and should document in the source

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

Table 1 Schedule of Procedures

Period	**Screening**		**Treatment**	**Procedure Day**	**Follow-Up**	
Visit	**1** ***(optional)***	**2 (Baseline Visit)**	**3**	**4**	**5**	**6 (ET Visit)**
Day	**Day -14 to -1**	**Day 1 [1]**	**Day 5**	**Day 10 [2]**	**7 Days Post-Procedure**	**Day 35**
Window			**(-2 days)**	**(+3 days)**	**(+3 days)**	**(±3 days)**
Procedures						
Subject informed consent	X	***X [11]***				
Inclusion/exclusion criteria	~~X~~	X				
Demographics	X	***X [11]***				
Medical history [10]	~~X~~	***X***				
Concomitant medications	~~X~~	X	X	X	X	X
Adverse events	X	X	X	X	X	X
Physical examination [3]	~~X~~	***X***		X	X	X
Vital signs [4]	~~X~~	X		X	X	X
Hematology	~~X~~[5]	X [5]	X	X	X	X
Platelet count [5]	X	X	X	X	X	X
Coagulation	~~X~~[5]	X [5]	X	X	X	X
Serum chemistry	~~X~~	***X***		X	X	X
Pregnancy testing [6]	~~X~~	X [7]				X [7]
Assessment of platelet transfusion				X	X	X
Assessment of any rescue procedure for bleeding		~~X~~	X	X	X	X
Procedure-related information (type, risk, etc.)	~~X~~	***X***				
Contact IRT	X	X	X	X	X	X
Dispense study drug [8]		X				
Study drug dosing [8]		X	X			
Bleeding assessment (ISTH) [9]		~~X~~	X	X	X	X
Collect study drug				X		

Note: Prior to conducting any study-related activities, written informed consent must be signed and dated by the subject. Local laboratories will be used to determine eligibility; however, for study analysis and reporting purposes, only values determined at a central laboratory will be used with the exception of platelet count. Local laboratories may be used if immediate results are clinically needed.

1. All assessments will be performed prior to study drug dosing.
2. The following procedures will be performed pre-operatively on Procedure Day: ~~physical examination,~~ vital signs, hematology, platelet count, coagulation, serum chemistry, ~~assess~~ ***record*** whether subject required a platelet transfusion, ISTH non-surgical bleeding assessment ***(if any bleeding),*** contact IRT, and collect study drug. The following procedures will be performed post-operatively on Procedure Day: concomitant medications, adverse events, ~~assess~~ ***record*** any rescue procedure for bleeding, and ISTH surgical bleeding assessment ***(if any bleeding).***
3. Physical examinations will consist of the following ***at a minimum***: ~~general appearance, head and neck, eye and ears, nose and throat,~~ chest, lungs, heart, and abdomen ~~extremities and joints, lymph nodes, skin, and neurology~~.
4. Vital sign measurements will include height (at the ~~Screening~~ ***Baseline*** Visit only), weight, body temperature, blood pressure, and pulse rate and will be measured after resting for 5 minutes.

5. Local and central laboratories. Baseline hematology, platelet count and coagulation laboratories may be collected up to one day prior to the Baseline visit (Visit 2).
6. For female subjects of childbearing potential only. A serum ***or urine*** pregnancy test will be performed at the ~~Screening~~ ***Baseline*** Visit ~~At the Baseline Visit, the pregnancy test will be performed~~ prior to study drug administration.
7. Either a serum or urine pregnancy test may be used.
8. Subjects will receive 60 mg oral avatrombopag once daily for 5 days beginning on Day 1. For study site visits during the Treatment Period, study drug may be administered at the site or the subject may self-dose. Subjects will self-dose at all other times and be instructed to take study drug with food. The Investigator or designee will provide subjects with sufficient study drug to complete the 5-day regimen.
9. Bleeding will be evaluated, ***if present***, by the Investigator using the non-surgical and surgical ISTH bleeding definitions described in Appendix D. The non-surgical ISTH bleeding definitions (Table 3) will be used when evaluating subjects prior to surgery on Procedure Day, and the surgical ISTH bleeding definitions (Table 4) will be used when evaluating subjects after surgery on Procedure Day. Both the non-surgical and surgical ISTH bleeding definitions will be used to evaluate subjects during the Follow-up Period. For an Early Termination Visit where a subject withdraws from the study prior to surgery on Procedure Day, the non-surgical ISTH bleeding definitions will be used. If a subject withdraws after surgery on Procedure Day, both the non-surgical and surgical ISTH bleeding definitions will be used.
10. Document etiology of thrombocytopenia.
11. If Visit 1 not performed

ET = Early Termination; IRT = Interactive Response Technology; ISTH = International Society on Thrombosis and Haemostasis.

Amendment #1 – 09 April 2018

Rationale for Amendment

Amendment 1 has been introduced to include patients with thrombocytopenia due to chronic liver disease. In the original protocol, exclusion criterion #2 excluded patients whose thrombocytopenia was due to chronic liver disease as an appropriate dosing regimen had not yet been established for these patients. PK/PD modeling efforts have since been completed to evaluate the predicted platelet responses in patients with chronic liver disease who would require a platelet count >100 × 10^9/L for a surgical procedure. Several different daily doses and platelet count cutoffs were evaluated to balance efficacy (achieving a platelet count >100 × 10^9/L) and safety concerns (minimizing the number of patients with a platelet count >200 × 10^9/L). By limiting the baseline platelet count for patients with chronic liver disease to between 50 × 10^9/L and <75 × 10^9/L, a 60 mg × 5 days dosing regimen is predicted to achieve platelet counts above 100 × 10^9/L but below 200 × 10^9/L for the majority of patients.

Chronic liver disease patients with additional risk factors for thrombosis are excluded for safety reasons. Additional exclusion criteria have been added to exclude patients with a history of portal vein thrombosis in the previous 6 months, known portal vein blood flow velocity rate <10 cm/sec, hepatic encephalopathy which cannot be effectively treated, and hepatocellular carcinoma (BCLC staging classification C or D).

Exclusion criterion #7 (use of dual moderate inhibitors of CYP2C9 and CYP3A4/5) has been removed based upon the minimal pharmacodynamic impact of this interaction during short-term administration of avatrombopag. An additional exclusion criterion has been added excluding current use of another thrombopoietin receptor agonist for safety reasons and to decrease the potential for confounding of the primary endpoint.

Summary of Significant Changes in Amendment 1

- Patients with thrombocytopenia due to chronic liver disease can now be enrolled, with a lower baseline platelet count between 50 × 10^9/L and <75 × 10^9/L
- Three additional exclusion criteria, related to chronic liver disease, have been added
- Use of dual moderate inhibitors of CYP2C9 and CYP3A4/5 (eg, fluconazole) are now allowed
- Current use of other thrombopoietin receptor agonists (eg, eltrombopag and romiplostim) is excluded

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

SYNOPSIS

POPULATION:

The population for this study is subjects ≥18 years of age at the time of informed consent who are scheduled to undergo operations to critical sites (eg, eye surgery, neurosurgery) or operations with a high risk of bleeding (eg, major abdominal surgery) who, in the opinion of the Investigator, would otherwise require a platelet transfusion aiming for a platelet count of at least 100×10^9/L to prevent bleeding. Subjects ***without chronic liver disease*** must have a mean baseline platelet count between 50×10^9/L and $<100 \times 10^9$/L, measured on 2 separate occasions (the Screening Visit and the Baseline Visit), with neither platelet count $\geq 100 \times 10^9$/L. ***Subjects with chronic liver disease (CLD) must have a mean baseline platelet count between 50×10^9/L and $<75 \times 10^9$/L, measured on 2 separate occasions (the Screening Visit and the Baseline Visit), with neither platelet count $\geq 75 \times 10^9$/L.***

STUDY DESIGN AND DURATION:

Subjects must be screened prior to the Baseline Visit. Mean baseline platelet count ***in subjects without CLD*** must be between 50×10^9/L and $<100 \times 10^9$/L***; between 50×10^9/L and $<75 \times 10^9$/L in subjects with CLD.*** Platelet counts must be measured on 2 separate occasions (the Screening Visit and the Baseline Visit), and must be performed at least 1 day apart with neither platelet count $\geq 100 \times 10^9$/L ***in subjects without CLD and $\geq 75 \times 10^9$/L in subjects with CLD***. The mean of these 2 platelet counts (mean baseline platelet count) will be used for entry criteria.

3.1 Summary of Study Design

Subjects must be screened prior to the Baseline Visit. Mean baseline platelet count ***in subjects without CLD*** must be between 50×10^9/L and $<100 \times 10^9$/L***; between 50×10^9/L and $<75 \times 10^9$/L in subjects with CLD***. Platelet counts must be measured on 2 separate occasions (the Screening Visit and the Baseline Visit), and must be performed at least 1 day apart with neither platelet count $\geq 100 \times 10^9$/L ***in subjects without CLD and $\geq 75 \times 10^9$/L in subjects with CLD***. The mean of these 2 platelet counts (mean baseline platelet count) will be used for entry criteria.

4.1 Inclusion Criteria

24. Subject has a mean baseline platelet count between:

    a. 50×10^9/L and $<100 \times 10^9$/***L in subjects without a diagnosis of chronic liver disease. or***

    b. 50×10^9/L and $<75 \times 10^9$/L in subjects with diagnosed chronic liver disease.

    Platelet counts must be measured on 2 separate occasions (the Screening Visit and the Baseline Visit), and must be performed at least 1 day apart with neither platelet count $\geq 100 \times 10^9$/L ***in subjects without CLD and $\geq 75 \times 10^9$/L in subjects with CLD.*** The mean of these 2 platelet counts (mean baseline platelet count) will be used for entry criteria;

4.2 Exclusion Criteria

~~2. Subject has a diagnosis of thrombocytopenia due to chronic liver disease~~

25. Known portal vein blood flow velocity rate <10 cm/second or previous occurrence of a portal vein thrombosis within 6 months of screening

6. Use of moderate or strong inducers of cytochrome P450 (CYP) 2C9 or CYP3A4/5 ***from 7 days prior to Screening through the end of the dosing regimen*** (see Appendix C);

~~7. Use of dual moderate inhibitors of CYP2C9 and CYP3A4/5 (ie, fluconazole);~~

7. Current use of a thrombopoietin receptor agonist (eg, eltrombopag or romiplostim);

8. Subject with a current malignancy including solid tumors and hematologic malignancies ~~undergoing or planned for treatment~~ ***whose thrombocytopenia may be attributed to*** chemotherapy during the study;

9. Hepatic encephalopathy that cannot be effectively treated;

10. Subjects with hepatocellular carcinoma (HCC) and Barcelona Clinic Liver Cancer (BCLC) staging classification C or D

5.2 Rationale for Dosing

A PK/PD model was developed to simulate platelet response to avatrombopag administration in order to select a dose regimen for this study. Using data from healthy volunteers and patients with chronic liver disease, the PK/PD model evaluated the relationship of avatrombopag concentrations to increases in platelet counts. Simulations were performed assuming the baseline platelet count ranged between 50 and $<100 \times 10^9$/L with a requirement to increase the platelet count to levels $\geq 100 \times 10^9$/L prior to the procedure. Simulations suggested that 60 mg avatrombopag administered once daily for 5 days with the procedure scheduled 5 to 8 days after the last dose of study drug would result in approximately 85% of subjects having platelet counts that exceed 100×10^9/L. ***Simulations were also performed for subjects with CLD. In order to limit the number of subjects with a platelet count >200 × 10^9/L after treatment yet still have the majority of subjects with a platelet count ≥100 × 10^9/L on the day of surgery, subjects with CLD must have a platelet count between 50 and <75 × 10^9/L at Baseline.***

5.6.1 Excluded Medications and/or Procedures

- Use of anticoagulant or antiplatelet therapy ~~within~~ ***between*** 7 days ~~of~~ ***prior to*** the Screening Visit ***and Visit 4 (Procedure Day)***
- Use of moderate or strong inducers of cytochrome P450 (CYP) 2C9 or CYP3A4/5 ***from 7 days prior to Screening through the end of the dosing regimen*** (see Appendix C);
- ~~Use of dual moderate inhibitors of CYP2C9 and CYP3A4/5 (ie, fluconazole);~~

6.2 Screening Visit

- Obtain demographics and medical history ***(including etiology of thrombocytopenia)***;

6.3.1 Baseline Visit

- Collect blood samples for the following assessments ***(-1 Day permitted):***

12.2.3 Drug Safety

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

[redacted]

SAEs should be reported directly to [redacted] by email or fax:

- [redacted]
- [redacted]

Table 1. Schedule of Procedures

5. Local and central laboratories. ***Baseline hematology, platelet count and coagulation laboratories may be collected up to one day prior to the Baseline visit (Visit 2).***
10. Document etiology of thrombocytopenia.

~~Table 5. CYP450 Inhibitors~~

	~~Strong~~	~~Moderate~~
~~CYP2C9 inhibitors~~	~~NA~~	~~Amiodarone, felbamate, fluconazole, miconazole, piperine~~
~~CYP3A4 inhibitors~~	~~Boceprevir, cobicistat, conivaptan, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole, clarithromycin, diltiazem, idelalisib, nefazodone, nelfinavir~~	~~Aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil~~
~~CYP = cytochrome P450; NA = not applicable.~~ ~~Source:~~ ~~https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#inVivo~~		