CLINICAL STUDY PROTOCOL

A Randomized, Double-Blind, Placebo-Controlled Study With an Open-Label Extension to Evaluate the Efficacy and Safety of Avatrombopag for the Treatment of Chemotherapy-Induced Thrombocytopenia in Subjects With Active Non-Hematological Cancers

Investigational Product: Avatrombopag tablets
Protocol Number: AVA-CIT-330
NCT Number: 03471078

Sponsor:
Dova Pharmaceuticals
240 Leigh Farm Rd, Suite 245
Durham, NC 27707
United States
Telephone: +1 919-748-5975
Fax: +1 919-748-5976

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SIGNATURE PAGE

STUDY TITLE: A Randomized, Double-Blind, Placebo-Controlled Study With an Open-Label Extension to Evaluate the Efficacy and Safety of Avatrombopag for the Treatment of Chemotherapy-Induced Thrombocytopenia in Subjects With Active Non-Hematological Cancers

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

Signature | Date

[redacted] — 04 APR 2019

[redacted]dent, Medical Development
& Pharmacovigilance
Dova Pharmaceuticals

[redacted] — 04 Apr 2019

[redacted]
Senior Vice President, Product Development
Dova Pharmaceuticals

[redacted] — 04APR 2019

[redacted]
Senior Director, Biostatistics
Dova Pharmaceuticals

[redacted] — 04 Apr 2019

[redacted]
Associate Vice President, Regulatory and Quality
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 Institutional Review Board/Ethics Committee Regulations and International Council for Harmonisation (ICH) Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

TITLE: A Randomized, Double-Blind, Placebo-Controlled Study With an Open-Label Extension to Evaluate the Efficacy and Safety of Avatrombopag for the Treatment of Chemotherapy-Induced Thrombocytopenia in Subjects With Active Non-Hematological Cancers

PROTOCOL NUMBER: AVA-CIT-330

INVESTIGATIONAL PRODUCT: Avatrombopag tablets

PHASE: 3

INDICATION(S): Treatment of chemotherapy-induced thrombocytopenia (CIT)

OBJECTIVES:

The primary objective of this study is to evaluate the efficacy of avatrombopag in increasing platelet counts and therefore preventing the need for a platelet transfusion or chemotherapy dose reduction or delay in subjects with CIT.

The secondary objectives of this study are the following:

- To evaluate the safety of avatrombopag in subjects with CIT, and
- To investigate the effect of avatrombopag on bleeding in subjects with CIT.

POPULATION:

Inclusion Criteria for All Subjects

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 with a diagnosis with ovarian cancer, lung cancer (small cell or non-small cell), or bladder cancer, requiring systemic chemotherapy;
3. Subject is currently receiving a chemotherapy regimen given in a 21-day or 28-day cycle (other chemotherapy cycle lengths are not allowed), including 1 or more of the following agents or class of agents:
    - Nucleoside analog, including gemcitabine and fluorouracil;
    - Carboplatin or cisplatin;
    - Anthracycline; or
    - Alkylating agent;
4. Subject experienced severe thrombocytopenia, defined as 2 platelet counts $<50 \times 10^9$/L measured at least 24 hours apart, during the qualifying chemotherapy cycle (Cycle X), of their current chemotherapy regimen. Platelet counts obtained per standard of care during Cycle X prior to consent may be used;

5. Subject is planned to receive the same chemotherapy regimen and the same dose(s) on Chemotherapy Day (Days 1-3) of Cycle X+1 as was given in the qualifying chemotherapy Cycle X;
6. Subject has an Eastern Cooperative Oncology Group (ECOG) performance status ≤2;
7. Subject has a life expectancy >12 weeks at Screening and is able to receive at least 2 additional cycles of the current chemotherapy regimen;
8. Females of childbearing potential must agree to use a highly effective method of contraception (eg, total abstinence; an intrauterine device; hormonal contraceptive given orally, by injection, or by implant; double barrier contraception (i.e., condom + diaphragm); or has a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 30 days after investigational product (IP) discontinuation. If currently abstinent, the subject must agree to use an effective method as described above if she becomes sexually active during the study period or for 30 days after IP discontinuation.

   Male subjects must be either surgically sterile or agree to use a double barrier contraception method (combination of male condom with either cap, diaphragm, or sponge with a spermicide) throughout the entire study period and for 30 days after IP discontinuation;

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

Exclusion Criteria for All Subjects

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

1. Subject has experienced ≥ Grade 2 CIT with a platelet count $<75 \times 10^9$/L (other than during the current chemotherapy treatment regimen) within 6 months of Screening;
2. Subject has a platelet count $>175 \times 10^9$/L at Visit 2 (-1 day);
3. Subject with any history of hematologic malignancies, including leukemia, myeloma, myeloproliferative disease, lymphoma, or myelodysplastic diseases;
4. Subject who received >2 previous lines of chemotherapy (adjuvant/neoadjuvant therapy is considered a previous line; immunotherapy alone is not considered a previous line) or is receiving whole brain radiation during the study treatment period;
5. Subject with an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5 × upper limit of normal or total bilirubin ≥3 × upper limit of normal;
6. Subject has a known medical history of human immunodeficiency virus;
7. Subject has any known clinically significant acute or active bleeding (eg, gastrointestinal or central nervous system) within 7 days of Screening;

8. Subject has a known medical history of genetic prothrombotic syndromes (eg, Factor V Leiden, prothrombin G20210A, or ATIII deficiency);
9. Subject has a recent history (within 3 months of Screening) of significant cardiovascular disease (eg, congestive heart failure exacerbation, arrhythmia known to increase the risk of thromboembolic events [eg, atrial fibrillation], coronary artery stent placement, angioplasty, or coronary artery bypass graft);
10. Subject has a history of arterial or venous thrombosis within 3 months of Screening;
11. Subject has used vitamin K antagonists within 7 days of Screening (use of low molecular weight heparin, Xa inhibitors, or thrombin inhibitors is allowed);
12. Subject has a history of chronic platelet or bleeding disorders or thrombocytopenia due to an etiology other than CIT (eg, chronic liver disease or immune thrombocytopenia purpura);
13. Subject has used moderate or strong inducers of cytochrome P450 (CYP)2C or CYP3A4/5 (see Appendix C) within 7 days of Screening;
14. Subject has received a thrombopoietin receptor agonist (eg, eltrombopag or romiplostim) or recombinant human thrombopoietin for the treatment of CIT within 3 months of Screening;
15. Subject received a platelet transfusion within 72 hours of randomization;
16. Subject is unable to take oral medication;
17. 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, such as unstable angina, renal failure requiring hemodialysis, or active infection requiring intravenous antibiotics;
18. Female subjects who are lactating or pregnant at Screening or the Baseline Visit (as documented by a positive serum or urine beta-human chorionic gonadotropin [β-hCG] test);
19. Subject has hypersensitivity to avatrombopag or any of its excipients; or
20. Subject is currently enrolled in another clinical study with any investigational drug or device within 30 days of Screening; however, participation in observational studies is permitted.

Inclusion Criteria for Subjects to Continue Into the Optional Open-Label Extension Period

Subjects who meet all of the following criteria will be eligible to continue into the optional Open-Label Extension (OLE) Period:

1. Subject is currently receiving the same chemotherapy agents as were given in the qualifying chemotherapy Cycle X;
2. Subject has an ECOG performance status ≤2;
3. Females of childbearing potential must agree to use a highly effective method of contraception as previously defined.

   Male subjects must be either surgically sterile or agree to use a double barrier contraception method (combination of male condom with either cap, diaphragm, or sponge with a spermicide) throughout the entire study period and for 30 days after IP 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 have been sterilized surgically (ie, bilateral tubal ligation, hysterectomy, or bilateral oophorectomy) at least 1 month before dosing.

4. Subject is willing and able to comply with all aspects of the protocol; and
5. Subject must provide consent to continue into the OLE Period.

Exclusion Criteria for Subjects to Continue Into the Optional Open-Label Extension Period

Subjects who meet any of the following criteria will be excluded from continuing into the optional OLE Period:

1. Subject has a platelet count $>175 \times 10^9$/L on the scheduled first day of dosing of avatrombopag prior to chemotherapy;
2. Subject with an ALT or AST >5 × upper limit of normal or total bilirubin ≥3 × upper limit of normal;
3. Subject has any known clinically significant acute or active bleeding (eg, gastrointestinal or central nervous system) within 7 days of pre-chemotherapy IP treatment in OLE cycles;
4. Subject has used vitamin K antagonists within 7 days of pre-chemotherapy IP treatment in Cycle X + 3 (use of low molecular weight heparin, Xa inhibitors, or thrombin inhibitors is allowed);
5. Subject has used moderate or strong inducers of CYP2C or CYP3A4/5 (see Appendix C) within 7 days of pre-chemotherapy IP treatment in OLE cycles;
6. Subject is unable to take oral medication;
7. Female subjects who are lactating or pregnant (as documented by a positive urine or serum test)

STUDY DESIGN AND DURATION:

This is a Phase 3 randomized, double-blind, placebo-controlled study of the efficacy and safety of oral avatrombopag in subjects with CIT with active non-hematological cancers. The study consists of 4 periods: a Double-Blind Treatment Period, an Observational Period, an optional OLE Period, and a Long-Term Follow-Up Period.

To be eligible for the study, subjects must have experienced thrombocytopenia during their current chemotherapy regimen as described in the inclusion criteria. The qualifying chemotherapy cycle is defined as "Cycle X". Subjects must be screened ≤28 days prior to the Baseline Visit, unless Screening and Baseline Visits are performed on the same day, and begin treatment during Cycle X.

Double-Blind Treatment Period

At the Baseline Visit, eligible subjects will be randomized in a 2:1 ratio to receive either avatrombopag or placebo in a double-blind manner prior to and during the subsequent chemotherapy cycle, Cycle X + 1. Randomization will be stratified by the number of chemotherapy agents the subject is receiving (1 or ≥2 permissible chemotherapy agents [nucleoside analog, including gemcitabine and fluorouracil; carboplatin or cisplatin;

anthracycline; or alkylating agent]). Subjects will receive either avatrombopag or placebo once daily for 5 days prior to Chemotherapy Day in Cycle X + 1. Subjects will also receive avatrombopag or placebo once daily for 5 days immediately following Chemotherapy Day. Chemotherapy Day is defined per protocol as Day 1 to 3 of the subject's chemotherapy regimen (eg, if chemotherapy is given on Day 1 and Day 2, the second round of avatrombopag or placebo will start on Day 3). Avatrombopag or placebo will not be administered concurrently with chemotherapy on Chemotherapy Day. Chemotherapy regimens requiring dosing beyond Chemotherapy Day within the 21-day or 28-day cycle (eg, gemcitabine on Day 8) are allowed. These mid-cycle chemotherapy doses, after IP treatment, will be part of the assessment of the composite primary endpoint for dose modifications or delays.

Observational Period

Cycle X + 2 will be an Observational Period. The Observational Period is designed to enable assessment of whether the subjects meet the chemotherapy dose modifications or dose delay components of the composite primary endpoint on Chemotherapy Day while reducing decision-making bias for chemotherapy dose modifications or delays. Subjects in the Observational Period will not receive any IP pre- or post-Chemotherapy Day in Cycle X + 2.

For subjects not continuing into the optional OLE Period, a Follow-Up Visit will occur prior to (within 3 days) Chemotherapy Day in Cycle X + 3. For these subjects, their participation in the Observational Period will conclude after they complete the Follow-Up Visit and at that point they will enter the Long-Term Follow-Up Period.

If Cycle X + 2 is the subject's last chemotherapy cycle, a Follow-Up Visit will occur at 30 days (±3 days) after Chemotherapy Day in Cycle X + 2.

Optional Open-Label Extension Period

Subjects who complete the Double-Blind Treatment Period and the Observational Period will be eligible to enter an optional OLE Period at 5 days prior to Cycle X + 3, if they fulfill the inclusion criteria and exclusion criteria for the optional OLE Period and remain on the same chemotherapy agents as prescribed in Cycle X. Subjects must continue to fulfill the inclusion and exclusion criteria prior to pre-chemotherapy avatrombopag treatment in each enrolled open-label cycle to continue in the OLE Period.

All subjects will receive avatrombopag once daily for 5 days prior to Chemotherapy Day in Cycle X + 3. Subjects will also receive avatrombopag once daily for 5 days immediately following Chemotherapy Day. Avatrombopag will not be administered concurrently with chemotherapy on Chemotherapy Day.

Subjects may repeat this treatment sequence and continue in the optional OLE Period until the end of their current chemotherapy regimen.

Subjects will have a Follow-Up Visit at 30 days (±3 days) after the last dose of avatrombopag treatment of the subject's last chemotherapy cycle.

Long-Term Follow-Up Period

After the Follow-Up Visit, all subjects will be contacted approximately every 6 months for up to 5 years by telephone during the Long-Term Follow-Up Period for documentation of vital status (if death occurred, record of date of death) and occurrence of secondary malignancies.

End of Study

The end of study ("study completion") is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last subject in the Long-Term Follow-Up Period.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

Subjects randomized to the investigational arm will receive 60 mg avatrombopag (3 × 20 mg tablets) for oral administration once daily for 5 days prior to Chemotherapy Day and for 5 days immediately following Chemotherapy Day during the Double-Blind Treatment Period. Subjects randomized to the control arm will receive matching placebo tablets.

Subjects in the optional OLE Period will receive 60 mg avatrombopag (3 × 20 mg tablets) for oral administration once daily for 5 days prior to Chemotherapy Day and for 5 days after Chemotherapy Day.

EFFICACY VARIABLES:

The primary efficacy endpoint is the proportion of responders who meet all of the following criteria during the period after post-chemotherapy IP treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2:

- Not requiring a platelet transfusion;
- Not requiring a chemotherapy dose reduction by ≥15% due to thrombocytopenia; and
- Not requiring a chemotherapy delay by ≥4 days due to thrombocytopenia.

The key secondary efficacy endpoints include the following:

- Duration of severe thrombocytopenia defined as a platelet count $<50 \times 10^9$/L during the period after post-chemotherapy IP treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2;
- Change in platelet count from baseline (qualifying chemotherapy cycle [Cycle X]) (nadir) to Cycle X + 1 (nadir);
- Proportion of subjects who do not have major or non-major clinically relevant bleeding during the period after post-chemotherapy IP treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2; and
- Proportion of subjects who do not receive platelet transfusion during the period after post-chemotherapy IP treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2.

The other efficacy endpoints include the following during the period after post-chemotherapy IP treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2:

- Proportion of subjects who do not have a chemotherapy dose reduction that is ≥15% due to thrombocytopenia;
- Proportion of subjects who do not have a chemotherapy delay that is ≥4 days due to thrombocytopenia;
- Proportion of subjects with a pre-defined post-baseline nadir platelet count; and

- Proportion of subjects achieving a pre-defined post-baseline maximum platelet count.

PHARMACOKINETIC AND PHARMACODYNAMIC VARIABLES:

Blood samples for pharmacokinetic and pharmacodynamics analysis will be collected. Pharmacokinetic sampling will occur twice during the study with 4 samples collected on each day. Pharmacodynamic samples (ie, platelet counts) will be collected throughout each cycle of the study including Cycle X + 1, Cycle X + 2, and each enrolled open-label cycle.

SAFETY VARIABLES:

Safety variables will include adverse events, adverse events of special interest (AESI), clinical laboratory parameters, physical examination findings, and vital signs.

STATISTICAL ANALYSES:

Analysis of Efficacy

All primary and secondary efficacy endpoints will be analyzed using the Full Analysis Set (FAS). The primary efficacy analysis will be repeated for the Per-Protocol Analysis Set (PPS) as the supportive analysis.

Analysis of the Primary Efficacy Endpoint

The treatment effect on the primary efficacy endpoint will be tested between avatrombopag and placebo using the Cochran-Mantel-Haenszel test, adjusting for number of chemotherapy agents (1, or ≥2 permissible chemotherapy agents [nucleoside analog, including gemcitabine and fluorouracil; carboplatin or cisplatin; anthracycline; or alkylating agent]). The numbers and percentages of responders in each treatment group, the associated 95% confidence intervals (CI), and the 95% CI for the difference between avatrombopag and placebo will be calculated. The primary analysis will be performed based on the FAS and repeated on the PPS. Other sensitivity analyses of the primary efficacy endpoint may be performed as appropriate.

Analysis of the Key Secondary Efficacy Endpoints

If the test of the treatment effect on the primary efficacy endpoint is statistically significant, the analysis of the key secondary efficacy endpoints will proceed using step-down closed testing procedure in the following order to maintain the family-wise Type I error rate at significance level alpha = 0.05 (2-sided):

Step 1: Test the treatment effect at a significant level of 0.05 on duration of severe thrombocytopenia defined as a platelet count $<50 \times 10^9$/L during the period after post-chemotherapy IP treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2; if successful, proceed to Step 2; otherwise stop at Step 1.

Step 2: Test the treatment effect at a significant level of 0.05 on change in platelet count from baseline (qualifying chemotherapy cycle [Cycle X]) (nadir) to Cycle X + 1 (nadir); if successful, proceed to Step 3; otherwise stop at Step 2.

Step 3: Test the treatment effect at a significant level of 0.05 on proportion of subjects who do not have major or non-major clinically relevant bleeding during the period after post-chemotherapy

IP treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2; if successful, proceed to Step 4; otherwise stop at Step 3.

Step 4: Test the treatment effect at a significant level of 0.05 on proportion of subjects who do not receive platelet transfusion during the period after post-chemotherapy IP treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2.

Analysis of Other Efficacy Endpoints:

The categorical variables (eg, proportion) will be summarized and analyzed in the same manner as the primary efficacy endpoint. The continuous variables (eg, change from baseline in platelet count) will be analyzed using analysis of covariance models with treatment and the randomization stratification factor as main effects and the baseline measurement as a covariate, and Wilcoxon Rank Sum tests if the normality assumption is violated.

The efficacy variables collected during the optional OLE Period will be summarized descriptively.

Analysis of Safety

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

SAMPLE SIZE DETERMINATION:

Assuming there is a 40% response rate in the active group and 10% in the placebo group, and using a 2:1 randomization, a 10% premature termination rate, and 90% power with 2-sided alpha = 0.05, the sample size is 120 subjects (80 active subjects and 40 placebo subjects).

SITES: Approximately 75 sites globally

SPONSOR:

Dova Pharmaceuticals
240 Leigh Farm Rd, Suite 245
Durham, NC 27707
United States
Telephone: +1 919-748-5975
Fax: +1 919-748-5976

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
21 CFR	Title 21 of the Code of Federal Regulations
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
β-hCG	Beta-human chorionic gonadotropin
CI	Confidence interval
CIT	Chemotherapy-induced thrombocytopenia
CLD	Chronic liver disease
CRA	Clinical research associate
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DSMB	Data and Safety Monitoring Board
eCRF	Electronic case report form
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
FAS	Full Analysis Set
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IP	Investigational product
IRB	Institutional Review Board
IRT	Interactive response technology
ISTH	International Society on Thrombosis and Haemostasis
ITP	Idiopathic/immune thrombocytopenic purpura
OLE	Open-label extension
PD	Pharmacodynamic
PK	Pharmacokinetic(s)
PPS	Per-Protocol Analysis Set
RDI	Relative dose intensity
SAE	Serious adverse event
SUSAR	Suspected unexpected serious adverse reaction
TPO	Thrombopoietin

1 INTRODUCTION AND BACKGROUND INFORMATION

1.1 Thrombocytopenia

Thrombocytes or 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.

1.2 Chemotherapy-Induced Thrombocytopenia

Chemotherapy-induced thrombocytopenia (CIT) is a common toxicity of myelosuppressive chemotherapy. Occurrence of thrombocytopenia has the potential to create significant complications. At platelet counts <10,000/µL, spontaneous bleeding risk is increased. At platelet counts <50,000/µL, procedures are often complicated by bleeding. At platelet counts <100,000/µL, chemotherapy is administered with caution for fear of worsening the thrombocytopenia and increasing the risk of bleeding.[1]

Clinicians' responses to thrombocytopenia in a cancer patient vary: reduction of the dose intensity of chemotherapy is common, more effective regimens with thrombocytopenic toxicity may be avoided, and treatment may even be precluded. Platelet transfusions are often the only treatment;[1,2] however, platelet transfusions create the additional risk of transfusion reactions or infections, and may lead to the development of platelet refractoriness with repeated platelet transfusions. The latter importantly eliminates platelets as an option for future emergent needs in these patients during their chemotherapy regimen or for other emergent conditions that may develop.

The incidence, severity, and duration of thrombocytopenia vary with the chemotherapy regimen. Kuter, 2015 provides an overview of the reported frequencies of severe thrombocytopenia (Grade 3 = 25,000 to <50,000/µL, Grade 4 ≤25,000/µL) associated with various chemotherapy regimens.[1]

The reasons that some patients experience more severe or prolonged thrombocytopenia after chemotherapy are not well understood and can be difficult to predict. The mechanisms by which chemotherapy regimens result in thrombocytopenia also differ and include the following:

- Alkylating agents such as busulfan affect pluripotent stem cells;
- Cyclophosphamide spares hematopoietic stem cells, but affects later megakaryocyte progenitors;
- Bortezomib has no effect on stem cells or megakaryocyte maturation but does inhibit nuclear factor kappa B, a critical regulator of platelet shedding; and
- Chemotherapy may enhance platelet clearance by immune mechanisms, as occurs with fludarabine.

There has been one approved product for the treatment of CIT, oprelvekin (Neumega®, Pfizer); however, due to the toxicity profile associated with this product (anaphylaxis, fluid retention including pulmonary edema, arrhythmias), physicians continue to rely on platelet transfusions in this patient population. As a result, CIT remains a condition that is not adequately treated with existing pharmacological agents.

1.3 Avatrombopag

Avatrombopag maleate 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.

1.4 Nonclinical Studies

The toxicity of avatrombopag has been extensively evaluated in single- and repeated-dose oral toxicity studies in mice, rats, dogs, and cynomolgus monkeys (for up to 13 weeks in mice, 26 weeks in rats, 4 weeks in dogs, and 52 weeks in cynomolgus monkeys). The genotoxicity of avatrombopag was evaluated in vitro and in vivo. Two-year carcinogenicity studies have been conducted in mice and rats. Reproductive and developmental toxicity was evaluated by conducting male and female fertility studies in rats, embryo-fetal development toxicity studies in rats and rabbits, pre- and post-natal development studies in rats, and a juvenile 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 CIT.

1.5 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-treated subjects includes

1107 subjects in the completed clinical studies. This includes 520 healthy volunteers, 395 subjects with thrombocytopenia associated with chronic liver disease (CLD) prior to scheduled surgical or diagnostic procedures, 64 subjects with chronic hepatitis C virus-related thrombocytopenia to enable initiation and maintenance of antiviral treatment, and 128 subjects with chronic immune thrombocytopenic purpura (ITP).

1.5.1 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 520 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.[3]

1.5.2 Phase 2 Studies

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

In the combined CL-003 and CL-004 studies, the most common treatment-emergent adverse events (TEAEs), occurring in 5% or more of subjects treated with avatrombopag were (by decreasing order of frequency) fatigue, headache, epistaxis, contusion, arthralgia, diarrhea, thrombocytopenia, gingival bleeding, back pain, edema peripheral, petechiae, platelet count increased, vomiting, dyspnea, nausea, upper respiratory tract infection, pain in extremity, ecchymosis, cough, insomnia, dizziness, pharyngolaryngeal pain, hyperlipidemia, nasopharyngitis, and platelet count decreased. Most TEAEs were Grade 1 or Grade 2, transient, and completely resolved.

A total of 130 subjects with thrombocytopenia associated with CLD who were scheduled to undergo elective surgical or diagnostic procedures were enrolled in a Phase 2, randomized, placebo-controlled, double-blind, parallel-group study (Study 202). The subjects were split into 2 cohorts and received either avatrombopag (Cohort A: first generation formulation; Cohort B: second generation formulation) or placebo. The primary analysis of the responder rate in the overall combined avatrombopag group was statistically significant compared with the overall combined placebo group. A similar statistical significance was again noted when the data were

adjusted for the etiology of liver disease by a Cochran-Mantel-Haenszel test. Within Cohort B, the response rate in platelet counts by Day 8 increased significantly in subjects receiving treatment with avatrombopag compared with placebo. In addition, a statistically significant reduction was achieved in the proportion of subjects receiving platelet transfusion before elective invasive procedures in Cohort B compared with placebo. The most commonly reported TEAEs, occurring in 5% or more of subjects treated with avatrombopag were (by decreasing order of frequency) nausea, fatigue, headache, portal hypertensive gastropathy, diarrhea, dizziness, muscle spasms, procedural pain, varices esophageal, vomiting, abdominal pain upper, and edema peripheral.

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

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

1.5.3 Phase 3 Studies

Four Phase 3 efficacy and safety studies (Studies 302, 305, 310, and 311) were conducted.

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

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

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

Studies 310 and 311 enrolled adults with CLD 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 patients/48 placebo patients) or Cohort 2 (59 avatrombopag patients/34 placebo patients). Patients had a median age of 57 years with 68% of patients being male and a baseline median platelet count of 38×10^9/L. The CLD etiology of patients was 14% alcohol, 62% viral hepatitis, and 23% other. Study 311 randomized 204 patients to 1 of 2 possible cohorts: Cohort 1 (70 avatrombopag patients/43 placebo patients) or Cohort 2 (58 avatrombopag patients/33 placebo patients). Patients had a median age of 59 years with 62% of patients being male and a baseline median platelet of 39×10^9/L. The CLD etiology of patients was 15% alcohol, 53% viral hepatitis, and 33% other. Significantly greater proportions of avatrombopag-treated patients across all cohorts did not require platelet transfusion or bleeding rescue procedures compared with placebo: Study 310: Cohort 1, 66% versus 23%; Cohort 2, 88% versus 38%; each $p<0.0001$; Study 311: Cohort 1, 69% versus 35%, $p=0.0006$; Cohort 2, 89% versus 33%, $p<0.0001$. Avatrombopag was also superior to placebo for both secondary endpoints, increasing mean platelet counts on Procedure Day to 64×10^9/L in Cohort 1 and 85×10^9/L in Cohort 2. The most common TEAEs were pyrexia,

abdominal pain, nausea, and headache, which were similar for placebo and avatrombopag arms in both studies. Most TEAEs were mild to moderate in severity; however, 1 thrombotic TEAE occurred in Cohort 2 (40 mg avatrombopag) in Study 311. The studies concluded avatrombopag given over 5 days significantly reduced the need for platelet transfusions or rescue procedures for bleeding, and it was well tolerated with a safety profile similar to placebo.

1.6 Rationale

Data in subjects with CLD and ITP suggest that avatrombopag is a promising candidate for use in the treatment of thrombocytopenia of diverse etiologies. Avatrombopag is being developed to potentially address the unmet medical need of CIT. The study aims to evaluate the efficacy of avatrombopag in increasing platelet counts post-chemotherapy to avoid platelet transfusions and chemotherapy dose delays or dose reductions. The safety of avatrombopag in this subject population will also be assessed through monitoring of adverse events, adverse events of special interest (AESI), clinical laboratory parameters, physical examination findings, and vital signs.

Thrombocytopenia occurs at various grades of severity in subjects undergoing chemotherapy with myelosuppressive agents. Frequently, it is the major dose-limiting hematologic toxicity. This is becoming increasingly important given the recent trend toward the use of dose-intensive combination chemotherapy regimens facilitated by supportive hematopoietic colony-stimulating factors to prevent chemotherapy-induced febrile neutropenia. The standard treatment during the cycle of chemotherapy to correct platelets is a therapeutic platelet transfusion, especially in the setting of an active bleeding event. The standard preventive measure against chemotherapy-induced depression of platelets in subsequent treatment cycles has been dose reduction and/or dose delay.

While platelet transfusions often rescue subjects with very low platelet levels, they are associated with the risk of viral and bacterial infections, as well as alloimmunization. Platelet donor recruitment can also be difficult and platelet transfusion can be very expensive depending on the source of platelets. Cancer patients receiving intensive chemotherapy or myeloablative regimens may require multiple platelet transfusions. For these patients, alternate strategies are needed so that platelet transfusions can be significantly reduced or eliminated. As a result, for the purposes of this study, one component of the primary endpoint will classify a responder as a subject who did NOT require the administration of a platelet transfusion.

Relative dose intensity (RDI) is a term that refers to the amount of a particular chemotherapy given over a specific time in relation to what was ordered (or is considered standard). Dose delays and dose reductions can decrease RDI and potentially increase the risk of disease progression and mortality. Retrospective analyses of randomized controlled clinical trials have suggested a strong association between RDI and disease-free and overall survival, especially for lymphoma and cancers of the breast, lung, ovary, and colon. Data show increased survival for subjects who receive ≥85% RDI and, conversely, mortality curves similar to untreated populations when this threshold RDI is not administered. As a result, for the purposes of this study, one component of the primary endpoint will classify a responder as a subject who did NOT have a dose reduction of chemotherapy of ≥15% (to maintain the RDI >85%).[5-9, 11-20]

In addition, chemotherapy dose delay (or total duration of chemotherapy) also contributes to the overall outcomes of subjects receiving chemotherapy. While there are fewer studies investigating the impact of chemotherapy dose delay on outcomes, one study indicated that an extension of the

time to complete the entire chemotherapy regimen resulted in poorer outcomes.[10,21] In that study, the total delay of treatment across 5 cycles was 9 days. While a delay in chemotherapy initiation of 7 days is a common duration of delay described in the literature, mainly due to convenience of re-scheduling a chemotherapy infusion, the aforementioned study suggests multiple shorter duration delays may result in clinically relevant alterations in outcomes. As a result, for the purposes of this study, one component of the primary endpoint will classify a responder as a subject who did NOT have a dose delay of chemotherapy of ≥4 days (to maintain the overall duration of chemotherapy as short as possible to maintain outcomes).

1.7 Risk/Benefit

Current treatment options for patients with CIT include chemotherapy dose reductions, chemotherapy dose delays, and platelet transfusions. 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.

An orally administered thrombopoietic agent that can prevent significant thrombocytopenia due to chemotherapy and avoid any reductions in dosage or delays in chemotherapeutic regimens 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 and therefore preventing the need for a platelet transfusion or chemotherapy dose reduction or delay in subjects with CIT.

2.2 Secondary Objectives

The secondary objectives of this study are the following:

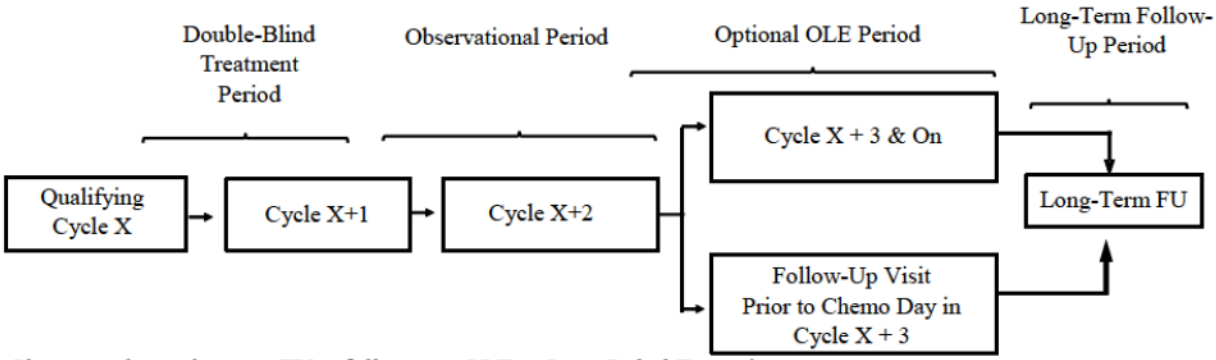
- To evaluate the safety of avatrombopag in subjects with CIT, and
- To investigate the effect of avatrombopag on bleeding in subjects with CIT.

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is a Phase 3 randomized, double-blind, placebo-controlled study of the efficacy and safety of oral avatrombopag in subjects with CIT with active non-hematological cancers. The study consists of 4 periods: a Double-Blind Treatment Period, an Observational Period, an optional OLE Period, and a Long-Term Follow-Up Period, as described in Figure 1.

Figure 1. Study Design



Chemo = chemotherapy; FU = follow-up; OLE = Open-Label Extension.

3.1.1 Screening/Qualifying Chemotherapy Regimen (Cycle X)

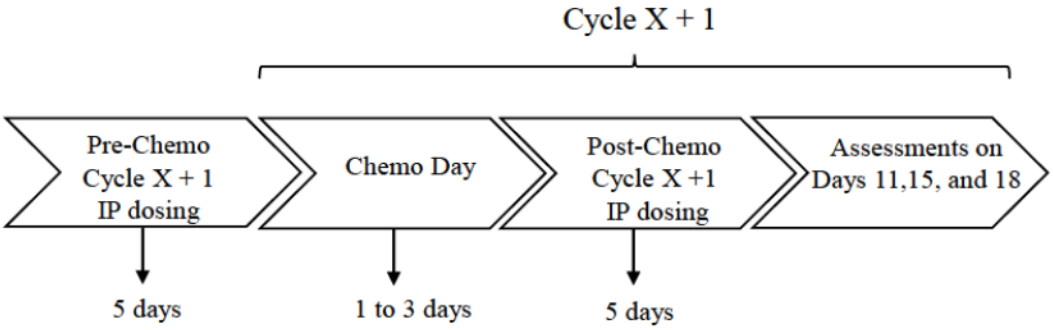
To be eligible for the study, subjects must have experienced thrombocytopenia during their current chemotherapy regimen as described in the inclusion criteria in Section 4.1. The qualifying chemotherapy cycle is defined as "Cycle X". Subjects must be screened ≤28 days prior to the Baseline Visit, unless Screening and Baseline Visits are performed on the same day, and begin treatment during Cycle X.

3.1.2 Double-Blind Treatment Period

At the Baseline Visit, eligible subjects will be randomized in a 2:1 ratio to receive either avatrombopag or placebo in a double-blind manner prior to and during the subsequent chemotherapy cycle, Cycle X + 1. Randomization will be stratified by the number of chemotherapy agents the subject is receiving (1 or ≥2 permissible chemotherapy agents [nucleoside analog, including gemcitabine and fluorouracil; carboplatin or cisplatin; anthracycline; or alkylating agent]). Subjects will receive either avatrombopag or placebo once daily for 5 days prior to Chemotherapy Day in Cycle X + 1. Subjects will also receive avatrombopag or placebo once daily for 5 days immediately following Chemotherapy Day. Chemotherapy Day is defined per protocol as Day 1 to 3 of the subject's chemotherapy regimen (eg, if chemotherapy is given on Day 1 and Day 2, the second round of avatrombopag or placebo will start on Day 3). Avatrombopag or placebo will not be administered concurrently with chemotherapy on Chemotherapy Day. Chemotherapy regimens requiring dosing beyond Chemotherapy Day within the 21-day or 28-day cycle (eg, gemcitabine on Day 8) are allowed. These mid-cycle chemotherapy doses, after IP treatment, will be part of the assessment of the composite primary endpoint for dose modifications or delays.

During the study, if the subject has a platelet count >400 × 10^9/L, IP dosing will be stopped temporarily. Dosing may be restarted following discussion with the Medical Monitor.

Figure 2. Treatment Schedule for Double-Blind Treatment Period



Chemo = chemotherapy; IP = investigational product.

3.1.3 Observational Period

Cycle X + 2 will be an Observational Period. The Observational Period is designed to enable assessment of whether the subjects meet the chemotherapy dose modifications or dose delay components of the composite primary endpoint on the Chemotherapy Day while reducing decision making bias for chemotherapy dose modifications or delays. Subjects in the Observational Period will not receive any IP pre- or post-Chemotherapy Day in Cycle X + 2.

For subjects not continuing into the optional OLE Period, a Follow-Up Visit will occur prior to (within 3 days) Chemotherapy Day in Cycle X + 3. For these subjects, their participation in the Observational Period will conclude after they complete the Follow-Up Visit and at that point they will enter the Long-Term Follow-Up Period.

If Cycle X + 2 is the subject's last chemotherapy cycle, a Follow-Up Visit will occur at 30 days (±3 days) after Chemotherapy Day in Cycle X + 2.

3.1.4 Optional Open-Label Extension Period

Subjects who complete the Double-Blind Treatment Period and the Observational Period will be eligible to enter an optional OLE Period at 5 days prior to Cycle X + 3, if they fulfill the inclusion criteria and exclusion criteria for the optional OLE Period. Subjects must continue to fulfill the inclusion and exclusion criteria prior to pre-chemotherapy IP treatment in each enrolled open-label cycle to continue in the OLE Period.

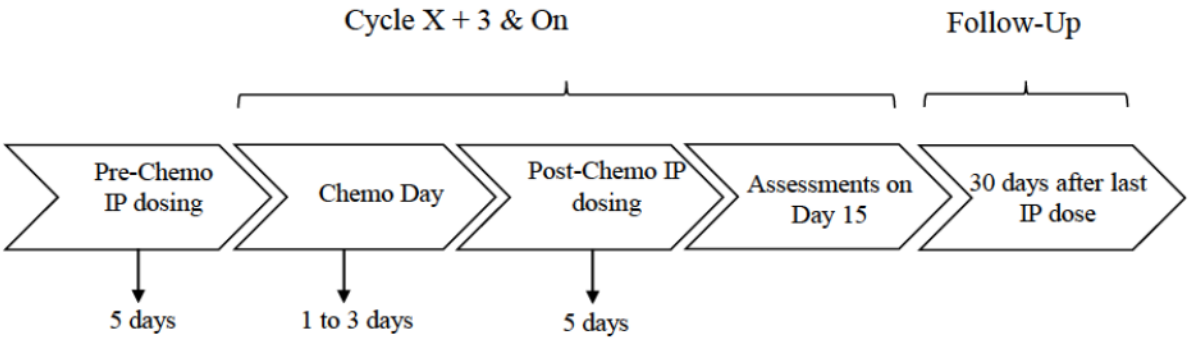
All subjects will receive avatrombopag once daily for 5 days prior to Chemotherapy Day in Cycle X + 3. Subjects will also receive avatrombopag once daily for 5 days immediately following Chemotherapy Day. Avatrombopag will not be administered concurrently with chemotherapy on Chemotherapy Day.

During the study, if the subject has a platelet count >400 × 10^9/L, IP dosing will be stopped temporarily. Dosing may be restarted following discussion with the Medical Monitor.

Subjects may repeat this treatment sequence and continue in the optional OLE Period until the end of their current chemotherapy regimen.

Subjects will have a Follow-Up Visit at 30 days (±3 days) after the last dose of IP treatment of the subject's last chemotherapy cycle.

Figure 3. Treatment Schedule for Optional Open-Label Extension Period



Chemo = chemotherapy; IP = investigational product.

3.1.5 Long-Term Follow-Up Period

After the Follow-Up Visit, all subjects will be contacted approximately every 6 months for up to 5 years by telephone during the Long-Term Follow-Up Period for documentation of vital status (if death occurred, record of date of death) and occurrence of secondary malignancies. If a secondary malignancy has occurred, the following information will be collected: date of onset and type of malignancy, as well as a written narrative from the clinical site summarizing the course of events leading up to diagnosis of the secondary malignancy.

3.2 Study Duration and End of Study

The study will consist of the following periods:

- Double-Blind Treatment Period and Observational Period of approximately 8 to 9 weeks,
- Optional OLE Period until the subject's current chemotherapy regimen changes or the subject completes chemotherapy, and
- Long-Term Follow-Up Period of up to 5 years.

The end of study ("study completion") is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last subject in the Long-Term Follow-Up Period.

3.3 Data and Safety Monitoring Board

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

3.4 Study Indication

The indication for this study is the treatment of CIT.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria for All Subjects

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 with a diagnosis with ovarian cancer, lung cancer (small cell or non-small cell), or bladder cancer, requiring systemic chemotherapy;
3. Subject is currently receiving a chemotherapy regimen given in a 21-day or 28-day cycle (other chemotherapy cycle lengths are not allowed), including 1 or more of the following agents or class of agents:
   - Nucleoside analog, including gemcitabine and fluorouracil;
   - Carboplatin or cisplatin;
   - Anthracycline; or
   - Alkylating agent;
4. Subject experienced severe thrombocytopenia, defined as 2 platelet counts $<50 \times 10^9$/L measured at least 24 hours apart, during the qualifying chemotherapy cycle (Cycle X), of their current chemotherapy regimen. Platelet counts obtained per standard of care during Cycle X prior to consent may be used;
5. Subject is planned to receive the same chemotherapy regimen and the same dose(s) on Chemotherapy Day (Days 1-3) of Cycle X+1 as was given in the qualifying chemotherapy Cycle X;
6. Subject has an Eastern Cooperative Oncology Group (ECOG) performance status ≤2;
7. Subject has a life expectancy >12 weeks at Screening and is able to receive at least 2 additional cycles of the current chemotherapy regimen;
8. Females of childbearing potential must agree to use a highly effective method of contraception (eg, total abstinence; an intrauterine device; hormonal contraceptive given orally, by injection, or by implant; double barrier contraception (i.e., condom + diaphragm); or has a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 30 days after investigational product (IP) discontinuation. If currently abstinent, the subject must agree to use an effective method as described above if she becomes sexually active during the study period or for 30 days after IP discontinuation.

   Male subjects must be either surgically sterile or agree to use a double barrier contraception method (combination of male condom with either cap, diaphragm, or sponge with a spermicide) throughout the entire study period and for 30 days after IP discontinuation;

   Note: All female subjects are considered to be of childbearing potential unless they are postmenopausal (at least 12 months consecutive amenorrhea and without another known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, hysterectomy, or bilateral oophorectomy) at least 1 month before dosing.
9. Subject is willing and able to comply with all aspects of the protocol; and

10. Subject must provide written informed consent.

4.2 Exclusion Criteria for All Subjects

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

1. Subject has experienced ≥ Grade 2 CIT with a platelet count $<75 \times 10^9$/L (other than during the current chemotherapy treatment regimen) within 6 months of Screening;
2. Subject has a platelet count $>175 \times 10^9$/L at Visit 2 (-1 day);
3. Subject with any history of hematologic malignancies, including leukemia, myeloma, myeloproliferative disease, lymphoma, or myelodysplastic diseases;
4. Subject who received >2 previous lines of chemotherapy (adjuvant/neoadjuvant therapy is considered a previous line; immunotherapy alone is not considered a previous line) or is receiving whole brain radiation during the study treatment period;
5. Subject with an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5 × upper limit of normal or total bilirubin ≥3 × upper limit of normal;
6. Subject has a known medical history of human immunodeficiency virus;
7. Subject has any known clinically significant acute or active bleeding (eg, gastrointestinal or central nervous system) within 7 days of Screening;
8. Subject has a known medical history of genetic prothrombotic syndromes (eg, Factor V Leiden, prothrombin G20210A, or ATIII deficiency);
9. Subject has a recent history (within 3 months of Screening) of significant cardiovascular disease (eg, congestive heart failure exacerbation, arrhythmia known to increase the risk of thromboembolic events [eg, atrial fibrillation], coronary artery stent placement, angioplasty, or coronary artery bypass graft);
10. Subject has a history of arterial or venous thrombosis within 3 months of Screening;
11. Subject has used vitamin K antagonists within 7 days of Screening (use of low molecular weight heparin, Xa inhibitors, or thrombin inhibitors is allowed);
12. Subject has a history of chronic platelet or bleeding disorders or thrombocytopenia due to an etiology other than CIT (eg, chronic liver disease or immune thrombocytopenia purpura);
13. Subject has used moderate or strong inducers of cytochrome P450 (CYP)2C or CYP3A4/5 (see Appendix C) within 7 days of Screening;
14. Subject has received a thrombopoietin receptor agonist (eg, eltrombopag or romiplostim) or recombinant human thrombopoietin for the treatment of CIT within 3 months of Screening;
15. Subject received a platelet transfusion within 72 hours of randomization;
16. Subject is unable to take oral medication;
17. 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, such as unstable angina, renal failure requiring hemodialysis, or active infection requiring intravenous antibiotics;

18. Female subjects who are lactating or pregnant at Screening or the Baseline Visit (as documented by a positive serum or urine beta-human chorionic gonadotropin [β-hCG] test) ;
19. Subject has hypersensitivity to avatrombopag or any of its excipients; or
20. Subject is currently enrolled in another clinical study with any investigational drug or device within 30 days of Screening; however, participation in observational studies is permitted.

4.3 Inclusion Criteria for Subjects to Continue Into the Optional Open-Label Extension Period

Subjects who meet all of the following criteria will be eligible to continue into the optional OLE Period:

1. Subject is currently receiving the same chemotherapy agents as were given in the qualifying chemotherapy Cycle X;
2. Subject has an ECOG performance status ≤2;
3. Females of childbearing potential must agree to use a highly effective method of contraception as previously defined.

   Male subjects must be either surgically sterile or agree to use a double barrier contraception method (combination of male condom with either cap, diaphragm, or sponge with a spermicide) throughout the entire study period and for 30 days after IP 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 have been sterilized surgically (ie, bilateral tubal ligation, hysterectomy, or bilateral oophorectomy) at least 1 month before dosing.
4. Subject is willing and able to comply with all aspects of the protocol; and
5. Subject must provide consent to continue into the OLE Period.

4.4 Exclusion Criteria for Subjects to Continue Into the Optional Open-Label Extension Period

Subjects who meet any of the following criteria will be excluded from continuing into the optional OLE Period:

1. Subject has a platelet count >175 × 10^9/L on the scheduled first day of dosing of avatrombopag prior to chemotherapy;
2. Subject with an ALT or AST >5 × upper limit of normal or total bilirubin ≥3 × upper limit of normal;
3. Subject has any known clinically significant acute or active bleeding (eg, gastrointestinal or central nervous system) within 7 days of pre-chemotherapy IP treatment in OLE cycles;
4. Subject has used vitamin K antagonists within 7 days of pre-chemotherapy IP treatment in Cycle X + 3 (use of low molecular weight heparin, Xa inhibitors, or thrombin inhibitors is allowed);

5. Subject has used moderate or strong inducers of CYP2C or CYP3A4/5 (see Appendix C) within 7 days of pre-chemotherapy IP treatment in OLE cycles;
6. Subject is unable to take oral medication;
7. Female subjects who are lactating or pregnant (as documented by a positive urine or serum test).

4.5 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 serious adverse event (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 Visit 13 (for subjects not in the optional OLE Period) or Visit 17 (for subjects participating in the optional OLE Period). All subjects should continue into the Long-Term Follow-Up Period unless consent has been withdrawn. 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.

4.5.1 Subjects with Investigational Product Interruption or Discontinuation

Subjects who discontinue study drug will be followed for the entire study duration through the Long-term Follow-Up Period (unless the subject withdraws consent), 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 3 randomized, double-blind, placebo-controlled study of the efficacy and safety of oral avatrombopag in subjects with CIT with active non-hematological cancers. The study consists of 4 periods: a Double-Blind Treatment Period, an Observational Period, an optional OLE Period, and a Long-Term Follow-Up Period.

Subjects in the Double-Blind Treatment Period will be randomized to one of 2 study arms: 60 mg avatrombopag (3 × 20 mg tablets) once daily or placebo (3 tablets).

Subjects in the Observational Period will not receive any IP.

Subjects in the optional OLE Period will receive 60 mg avatrombopag (3 × 20 mg tablets) once daily.

Subjects in the Long-Term Follow-Up Period will not receive any IP.

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 subjects with CLD, the PK/PD model evaluated the relationship of avatrombopag concentrations to increases in platelet counts. As a part of this model, the effect of carboplatin dose on platelet count obtained from population PK/PD modeling of eltrombopag in subjects with advanced solid tumors with CIT was also incorporated.[4] Simulations were performed assuming the baseline platelet count ranged between 25 and 150 × 10^9/L with a goal to increase the platelet count to levels >100 × 10^9/L for the duration of chemotherapy treatment to prevent platelet transfusion and to allow the subject to receive the same dose and schedule of chemotherapy as prescribed in Cycle X. Simulations suggested that 60 mg avatrombopag administered once daily for 5 days prior to chemotherapy and once daily for 5 days following chemotherapy was the most appropriate for maintaining platelet counts above this threshold while preventing platelet counts from elevating above the upper limit of normal.

To ensure the accuracy of the predictions, platelet response data will be reviewed by the DSMB as described in Section 3.3, and if necessary, dosage adjustments may be made following these data reviews.

5.3 Randomization and Blinding

This is a randomized, double-blind, placebo-controlled study. For the Double-Blind Treatment Period, subjects who meet the inclusion criteria and exclusion criteria will be randomized to receive either avatrombopag 60 mg or placebo in a 2:1 ratio at the Baseline Visit. Randomization will be stratified by the number of chemotherapy agents the subject is receiving (1, ≥2 permissible chemotherapy agents [nucleoside analog, including gemcitabine and fluorouracil; carboplatin or cisplatin; anthracycline; or alkylating agent]). Randomization assignment will be performed using interactive response technology (IRT). Following randomization, IP will be dispensed in a double-blind manner. The Sponsor and designated clinical site personnel (Investigator and study coordinator) will be blinded to the treatment group for each subject. Subjects will also be blinded to the treatment they receive.

5.4 Breaking the Blind

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

5.5 Drug Supplies

5.5.1 Formulation and Packaging

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

Matching placebo tablets, containing lactose monohydrate (23.6 mg), will be provided.

Investigational product will be packaged in blinded blister packages, each containing 15 tablets.

For the optional OLE Period, avatrombopag will be packaged in open-label blister packages, each containing 15 tablets of avatrombopag.

5.5.2 Investigational Product Dispensing

The Investigator or designee will provide subjects with sufficient IP to complete each 5-day course of study drug during the Double-Blind Treatment Period (each 5-day course to be dispensed on separate occasions as appropriate). If subjects continue into the optional OLE Period, the Investigator or designee will provide subjects with additional IP to complete the optional OLE Period.

5.5.3 Investigational Product Administration

Subjects randomized to the investigational arm will receive 60 mg avatrombopag (3 × 20 mg tablets) for oral administration once daily for 5 days prior to Chemotherapy Day and for 5 days immediately following Chemotherapy Day during the Double-Blind Treatment Period. Subjects randomized to the control arm will receive matching placebo tablets.

Subjects in the optional OLE Period will receive 60 mg avatrombopag (3 × 20 mg tablets) for oral administration once daily for 5 days prior to Chemotherapy Day and for 5 days after Chemotherapy Day.

At scheduled study visits, IP may be administered at the site or the subject may self-dose except for Visits 3 and 5 when subjects will be dosed at the site and serial PK samples will be collected pre- and post-dose of IP. Subjects will self-dose at all other times. Subjects will be instructed to take IP with food.

During the study, if the subject has a platelet count >400 × 10^9/L, IP dosing will be stopped temporarily. Dosing may be restarted following discussion with the Medical Monitor.

The number of tablets to be taken will be three 20 mg avatrombopag tablets or 3 matching placebo tablets once daily.

Actual date and time of chemotherapy doses will also be captured.

5.5.4 Treatment Compliance

At scheduled study visits, IP may be administered at the site or the subject may self-dose except for Visits 3 and 5 when subjects will be dosed at the site and serial PK samples will be collected pre- and post-dose of IP. Subjects will self-dose at all other times. When taking IP at home for the double-blind phase of the study, subjects will be asked to record the date and time of each IP dose in the dosing diary.

Compliance with IP administration will be assessed by counting returned IP packages and any unused IP in addition to reviewing the dosing diary entries of IP intake. Any discrepancies between returned IP number and dosing in the dosing diary will be discussed with the subject for whom a discrepancy was seen and recorded in the source documents. Number of tablets dispensed and number of tablets returned will be recorded on the appropriate drug accountability eCRF.

5.5.5 Storage and Accountability

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

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

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:

- Use of vitamin K antagonists;
- Use of thrombopoietin receptor agonists or recombinant human thrombopoietin;
- Use of moderate or strong inducers of CYP2C or CYP3A4/5 (see Appendix C); and
- Currently enrolled in another clinical study with any investigational drug or device within 30 days of Screening; however, participation in observational studies is permitted.

5.6.2 Allowed Medications and/or Procedures

- Use of packed red blood cell transfusions, erythropoietin, or granulocyte-colony stimulating factor, as ordered by the managing oncology service, is acceptable and does not preclude participation; and
- Use of low molecular weight heparin, Xa inhibitors, or thrombin inhibitors is allowed.

5.6.3 Documentation of Prior and Concomitant Medication Use

All concomitant medications (including concurrent therapies and concurrent procedures) will be documented from the time of informed consent to the Follow-Up Visit. 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, Table 2, and Table 3 in Appendix A.

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

6.1 Informed Consent

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

6.2 Cycle X (Qualifying Chemotherapy Cycle)

6.2.1 Screening (Visit 1, Day -28 to Day -1)

The Screening Visit may be combined with the Baseline Visit on the day prior to IP treatment (Day -1).

The following procedures will be performed at the Screening Visit:

- Obtain informed consent prior to screening procedures;
- Contact IRT to register the subject in the study
- Conduct eligibility assessment based on inclusion/exclusion criteria;
- Obtain demographics (including race), and medical history (to include chemotherapy and cancer history);
- Assess functional status using the ECOG Performance Status Scale;
- Record concomitant medications;
- Assess adverse events;
- Perform full physical examination;
- Record vital signs (includes height, weight, body temperature, blood pressure, and pulse rate); and
- Perform pregnancy test (serum or urine) for female subjects of childbearing potential only;
- Collect blood samples for the following assessments (if Screening Visit occurs on the same day as the Baseline Visit, only the Baseline laboratory assessments should be performed):
    - Hematology (including platelet counts). Local platelet counts may be repeated as needed; and
    - Serum chemistry

6.2.2 Baseline Visit (Visit 2, First Day [or -1 Day] of the 5-day Investigational Product Treatment)

The Baseline Visit may occur one day prior to IP treatment, and may be combined with the Screening Visit.

Eligible subjects will receive either avatrombopag or placebo once daily for 5 days prior to Chemotherapy Day in Cycle X + 1. The following procedures will be performed at the Baseline Visit prior to IP dosing:

- Conduct eligibility assessment based on inclusion/exclusion criteria;
- Contact IRT to randomize the subject;
- Perform International Society on Thrombosis and Haemostasis (ISTH) bleeding assessment (see Appendix D);
- Record concomitant medications;
- Assess adverse events;
- Perform symptom-directed physical examination (if not previously performed within 1 week of Baseline Visit);
- Record vital signs (includes weight, body temperature, blood pressure, and pulse rate). Only Screening vital signs will be recorded if combined with the Screening Visit;
- Collect blood samples for the following assessments:
  - Hematology (including platelet counts);
  - Coagulation; and
  - Serum chemistry;
- Perform pregnancy test (serum or urine) for female subjects of childbearing potential only;
- Assess chemotherapy dose modifications/schedule;
- Dispense IP;
- Dispense dosing diary; and
- Administer or self-dose IP with food, if the Baseline Visit occurs on the first day of the 5-day IP treatment.

6.2.3 Pre-Chemotherapy Investigational Product Treatment (Visit 3, Last Day of the 5-day Investigational Product Treatment)

The following procedures will be performed on the last day of the 5-day pre-chemotherapy IP treatment at Visit 3:

- Contact IRT;
- Perform ISTH bleeding assessment (see Appendix D);
- Record concomitant medications;
- Assess adverse events;

- Collect blood samples for the following assessments:
  - Hematology (including platelet counts); and
  - PK sampling at pre-dose (within 30 minutes of IP dosing) and 0.5 to 2, 2 to 4, and 4 to 6 hours post-dose. Each sample must be collected at least one hour apart from adjacent samples.
- Assess chemotherapy dose modifications/schedule;
- Assess whether subject required platelet transfusion;
- Administer IP in the clinic with food after the first PK sampling;
- Review dosing diary; and
- Collect unused IP, if applicable.

6.3 Double-Blind Treatment Period (Cycle X + 1)

6.3.1 Chemotherapy Day (Visit 4, Cycle X + 1 Day 1 to 3)

The following procedures will be performed on Cycle X + 1, Day 1 at Visit 4 prior to chemotherapy dosing:

- Perform ISTH bleeding assessment (see Appendix D);
- Record concomitant medications;
- Assess adverse events;
- Perform symptom-directed physical examination;
- Record vital signs (includes blood pressure and pulse rate);
- Collect blood samples for the following assessments:
  - Hematology (including platelet counts); and
  - Serum chemistry;
- Assess chemotherapy dose modifications/schedule; and
- Assess whether subject required platelet transfusion.

The following procedures will be performed post-chemotherapy dosing (these procedures will be performed on the last Chemotherapy Day of the cycle):

- Dispense IP; and
- Dispense dosing diary.

6.3.2 Post-Chemotherapy Investigational Product Treatment (Visit 5)

Subjects will also receive avatrombopag or placebo once daily for 5 days immediately following Chemotherapy Day. The following procedures will be performed on the last day of the 5-day post-chemotherapy IP treatment at Visit 5:

- Contact IRT;

- Perform ISTH bleeding assessment (see Appendix D);
- Record concomitant medications;
- Assess adverse events;
- Collect blood samples for the following assessments:
  - Hematology (including platelet counts); and
  - Serum Chemistry;
  - Coagulation; and
  - PK sampling at pre-dose (within 30 minutes of IP dosing) and 0.5 to 2, 2 to 4, and 4 to 6 hours post-dose. Each sample must be collected at least one hour apart from adjacent samples.
- Assess chemotherapy dose modifications/schedule;
- Assess whether subject required platelet transfusion;
- Administer IP in the clinic with food after the first PK sampling;
- Review dosing diary; and
- Collect unused IP, if applicable.

6.3.3 Cycle X + 1 Days 11 (±1 day), 15 (±1 day), and 18 (±1 day) (Visits 6, 7, and 8)

The following procedures will be performed on Cycle X + 1, Days 11, 15, and 18 at Visits 6, 7, and 8:

- Record concomitant medications;
- Assess adverse events;
- Collect blood samples for platelet counts;
- Assess chemotherapy dose modifications/schedule; and
- Assess whether subject required platelet transfusion.

6.4 Observational Period (Cycle X + 2)

If Chemotherapy Day in Cycle X+2 is delayed, record the reason for delay in the eCRF. If the delay is due to laboratory results, record the relevant results in the eCRF.

6.4.1 Chemotherapy Day in Cycle X + 2 (Visit 9)

The following procedures will be performed on Cycle X + 2, Day 1 at Visit 9 prior to chemotherapy dosing:

- Perform ISTH bleeding assessment (see Appendix D);
- Record concomitant medications;
- Assess functional status using the ECOG Performance Status Scale;

- Assess adverse events;
- Collect blood samples for the following assessments prior to chemotherapy dosing:
  - Hematology (including platelet counts);
  - Coagulation; and
  - Serum chemistry;
- Assess chemotherapy dose modifications/schedule; and
- Assess whether subject required platelet transfusion.

6.4.2 Cycle X + 2 Days 11 (±1 day), 15 (±1 day), and 18 (±1 day) (Visits 10, 11, and 12)

The following procedures will be performed on Cycle X + 2, Days 11, 15, and 18 at Visits 10, 11, and 12:

- Record concomitant medications;
- Assess adverse events;
- Collect blood samples for the following assessments:
  - Platelet counts;
- Assess chemotherapy dose modifications/schedule; and
- Assess whether subject required platelet transfusion.

6.4.3 Follow-Up Visit (For subjects not continuing into the optional Open-Label Extension Period)

6.4.3.1 Prior to Chemotherapy Day in Cycle X + 3 (Visit 17)

For subjects not continuing into the optional OLE Period, a Follow-Up Visit will occur prior to (within 3 days) Chemotherapy Day in Cycle X + 3. If Cycle X + 2 is the subject's last chemotherapy cycle, a Follow-Up Visit will occur at 30 days (±3 days) after Chemotherapy Day in Cycle X + 2. Subjects will complete Visit 17 procedures in Section 6.5.5.

6.5 Optional Open-Label Extension Period (Cycle X + 3 and On)

6.5.1 Pre-Chemotherapy Avatrombopag Treatment (Visit 13)

Subjects will receive avatrombopag once daily for 5 days prior to Chemotherapy Day in Cycle X + 3 (Visit 13). For Cycle X + 4, this visit will be denoted Visit 13.1 and for Cycle X + 5, this visit will be denoted Visit 13.2. This numbering scheme will continue for subsequent enrolled open-label cycles.

The following procedures will be performed on the first day of pre-chemotherapy avatrombopag treatment at Visit 13 prior to avatrombopag dosing:

- Conduct eligibility assessment based on OLE inclusion/exclusion criteria;
- Assess functional status using the ECOG Performance Status Scale;

- Contact IRT;
- Perform ISTH bleeding assessment (see Appendix D);
- Record concomitant medications;
- Assess adverse events;
- Record vital signs (includes blood pressure and pulse rate);
- Collect blood samples for the following assessments prior to IP dosing:
  - Hematology (including platelet counts);
  - Coagulation; and
  - Serum chemistry;
- Perform pregnancy test (urine or serum) for female subjects of childbearing potential only;
- Assess chemotherapy dose modifications/schedule;
- Assess whether subject required platelet transfusion;
- Dispense avatrombopag;
- Administer or self-dose avatrombopag with food.

6.5.2 Chemotherapy Day (Visit 14, Cycle X + 3 Day 1 to 3)

For Cycle X + 4, this visit will be denoted Visit 14.1 and for Cycle X + 5, this visit will be denoted Visit 14.2. This numbering scheme will continue for subsequent enrolled open-label cycles.

The following procedures will be performed on Cycle X + 3, Day 1 at Visit 14 prior to chemotherapy dosing:

- Perform ISTH bleeding assessment (see Appendix D);
- Record concomitant medications;
- Assess adverse events;
- Perform symptom-directed physical examination;
- Record vital signs (includes blood pressure and pulse rate);
- Collect blood samples for the following assessments:
  - Hematology (including platelet counts)
- Assess chemotherapy dose modifications/schedule;
- Assess whether subject required platelet transfusion; and
- Collect unused avatrombopag, if applicable.

The following procedures will be performed on post-chemotherapy dosing (these procedures will be performed on the last Chemotherapy Day of the cycle):

- Dispense avatrombopag

6.5.3 Post-Chemotherapy Avatrombopag Treatment (Visit 15)

For Cycle X + 4, this visit will be denoted Visit 15.1 and for Cycle X + 5, this visit will be denoted Visit 15.2. This numbering scheme will continue for subsequent enrolled open-label cycles.

The following procedures will be performed on the last day of the 5-day post-chemotherapy avatrombopag treatment at Visit 15:

- Contact IRT;
- Perform ISTH bleeding assessment (see Appendix D);
- Record concomitant medications;
- Assess adverse events;
- Collect blood samples for the following assessments:
  - Hematology (including platelet counts);
  - Coagulation; and
  - Serum chemistry;
- Assess chemotherapy dose modifications/schedule;
- Assess whether subject required platelet transfusion;
- Administer or self-dose avatrombopag with food; and
- Collect unused avatrombopag, if applicable.

6.5.4 Cycle X + 3 Day 15 (±1 day) (Visit 16)

For Cycle X + 4, this visit will be denoted Visit 16.1 and for Cycle X + 5, this visit will be denoted Visit 16.2. This numbering scheme will continue for subsequent enrolled open-label cycles. The following procedures will be performed on Cycle X + 3, Day 15 at Visit 16:

- Record concomitant medications;
- Assess adverse events;
- Perform ISTH bleeding assessment (see Appendix D);
- Collect blood samples for platelet counts;
- Assess chemotherapy dose modifications/schedule; and
- Assess whether subject required platelet transfusion.

6.5.5 Follow-Up Visit

6.5.5.1 Thirty days after last avatrombopag dose (Visit 17) in the OLE Period

The following procedures will be performed 30 days (±3 days) after last avatrombopag dose at Visit 17:

- Contact IRT;
- Perform ISTH bleeding assessment (see Appendix D);

- Assess functional status using the ECOG Performance Status Scale;
- Record concomitant medications;
- Assess adverse events;
- Perform full physical examination;
- Record vital signs (includes blood pressure and pulse rate);
- Collect blood samples for the following assessments:
  - Hematology (including platelet counts);
  - Coagulation; and
  - Serum chemistry;
- Perform pregnancy test (urine) for female subjects of childbearing potential only; and
- Assess whether subject required platelet transfusion.

6.6 Early Termination Visit and Withdrawal Procedures

For subjects who are withdrawn from the study prior to the Follow-Up Visit, all Visit 13 (for subjects not continuing into the optional OLE Period) or Visit 17 (for subjects continuing into the optional OLE Period) procedures will be performed at an Early Termination Visit. These procedures include the following:

- Contact IRT;
- Perform ISTH bleeding assessment (see Appendix D);
- Assess functional status using the ECOG Performance Status Scale;
- Record concomitant medications;
- Assess adverse events;
- Perform full physical examination;
- Record vital signs (includes blood pressure and pulse rate);
- Collect blood samples for the following assessments:
  - Hematology (including platelet counts);
  - Coagulation; and
  - Serum chemistry;
- Perform pregnancy test (urine) for female subjects of childbearing potential only;
- Assess whether subject required platelet transfusion; and
- Collect unused IP, if applicable.

6.7 Long-Term Follow-Up

After the Follow-Up Visit, all subjects will be contacted approximately every 6 months for up to 5 years by telephone during the Long-Term Follow-Up Period for documentation of vital status (if death occurred, record of date of death) and occurrence of secondary malignancies. If a secondary malignancy has occurred, the following information will be collected: date of onset and type of malignancy, as well as a written narrative from the clinical site summarizing the course of events leading up to diagnosis of the secondary malignancy.

7 EFFICACY ASSESSMENTS

The primary efficacy endpoint is the proportion of responders who meet all of the following criteria during the period after post-chemotherapy IP treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2:

- Not requiring a platelet transfusion;
- Not requiring a chemotherapy dose reduction by ≥15% due to thrombocytopenia; and
- Not requiring a chemotherapy delay by ≥4 days due to thrombocytopenia.

The key secondary efficacy endpoints include the following:

- Duration of severe thrombocytopenia defined as a platelet count $<50 \times 10^9$/L during the period after post-chemotherapy IP treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2;
- Change in platelet count from baseline (qualifying chemotherapy cycle [Cycle X]) (nadir) to Cycle X + 1 (nadir);
- Proportion of subjects who do not have major or non-major clinically relevant bleeding during the period after post-chemotherapy IP treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2; and
- Proportion of subjects who do not receive a platelet transfusion during the period after post-chemotherapy IP treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2.

The other efficacy endpoints include the following during the period after post-chemotherapy IP treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2:

- Proportion of subjects who do not have a chemotherapy dose reduction that is ≥15% due to thrombocytopenia;
- Proportion of subjects who do not have a chemotherapy delay that is ≥4 days due to thrombocytopenia;
- Proportion of subjects with a pre-defined post-baseline nadir platelet count; and
- Proportion of subjects achieving a pre-defined post-baseline maximum platelet count

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

Bleeding will be evaluated by the Investigator using the non-surgical ISTH bleeding definitions described in Appendix D.

8 PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENTS

8.1 Pharmacokinetic Assessments

Blood samples for PK analysis will be collected as indicated in Appendix A. Additional time points may be collected as necessary.

Pharmacokinetic sampling will occur twice during the study with 4 samples collected on each day.

8.2 Pharmacodynamic Assessments

Blood samples for PD analysis will be collected as indicated in Appendix A.

Pharmacodynamic samples (ie, platelet counts) will be collected throughout each cycle of the study including Cycle X + 1, Cycle X + 2, and each enrolled open-label cycle.

9 SAFETY ASSESSMENTS

9.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An 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 the Follow-Up Visit occurring prior to (within 3 days) Chemotherapy Day in Cycle X + 3 (for subjects not continuing into the optional OLE Period) and the Follow-Up Visit occurring 30 days after last dose of IP (for subjects continuing into the optional OLE Period). 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. Events associated with disease progression should not be reported as adverse events/SAEs. However, if in the Investigator's opinion the disease progression is manifesting in an unusual or uncharacteristic manner, the associated events should be reported as adverse events/SAEs, as appropriate.

Wherever possible, a specific disease or syndrome (ie, diagnosis) rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate 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 Screening Visit should not be reported as an adverse event unless the medical condition or signs or symptoms present at baseline changes in severity, frequency, or seriousness at any time during the study. In this case, it should be reported as an adverse event.

Clinically significant abnormal laboratory or other examination findings that are detected during the study or are present at the Screening Visit and significantly worsen during the study should be reported as 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. Laboratory abnormalities are not considered adverse events unless they are associated with clinical signs or symptoms, or require medical intervention. Any abnormal test that is determined to be an error does not require reporting as an adverse event.

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

9.1.1 Assessment of Adverse Events by the Investigator

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

Assessment of Severity:

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

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

Causality Assessment:

The relationship of an adverse event to the administration of the IP is to be assessed according to the following definitions:

- No (unrelated, not related, no relation) – The time course between the administration of IP 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 IP 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 IP. 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 IP administration-
  - The event should occur after the IP is given. The length of time from IP 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 IP-
  - 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 IP-
  - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the IP should be considered.

9.1.2 Adverse Events of Special Interest

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

The AESI defined in this protocol include:

- Thromboembolic events (any thrombotic or embolic event, whether arterial or venous); and
- Bleeding events (any clinically significant blood loss).

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

9.1.3 Efficacy Endpoints

Efficacy endpoints, as described in Section 7, should not be reported as adverse events unless in the opinion of the Investigator the event is causally associated with the IP. For example, thrombocytopenia, platelet transfusions for thrombocytopenia, and chemotherapy dose reductions or delays should not be reported as adverse events; however, clinically significant bleeding events (a secondary endpoint) should be always be reported as an AESI.

9.2 Method of Detecting Adverse Events and Serious Adverse Events

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

9.3 Serious Adverse Events

An adverse event or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death,
- A life-threatening adverse event,
  - NOTE: An adverse event or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires hospitalization or prolongation of existing hospitalization,
  - NOTE: Any hospital admission even if admitted and discharged the same day will be considered an inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent. 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.
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions,
- A congenital anomaly/birth defect,
- An important medical event, or
  - NOTE: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.
- Any suspected transmission via a medicinal product of an infectious agent.

9.4 Serious Adverse Event Reporting – Procedures for Investigators

Initial Reports:

All SAEs occurring from the time of informed consent until prior to (within 3 days) Chemotherapy Day in Cycle X + 3 (for subjects not continuing into the optional OLE Period) and 30 days following the last administration of IP (for subjects continuing into the optional OLE Period) 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 becomes aware of and considers related to IP occurring after the 30-day Follow-Up Period must be reported to the Sponsor.

To report the SAE, complete the SAE Report Form and fax or email as instructed on the form. It is very important that the form be filled out as completely as possible at the time of the initial report. This includes the Investigator's assessment of causality. Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital discharge summaries, autopsy reports, and other documents requested by the Sponsor or designee. The Investigator must notify his/her Institutional Review Board (IRB) or Independent Ethics Committee (IEC) of the occurrence of the SAE, in writing, if required by their institution. A copy of this communication must be forwarded to the Sponsor to be filed in the Sponsor's Trial Master 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), the subject dies, or the subject is lost to follow-up.

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

9.5 Pregnancy Reporting

If the subject becomes pregnant during the study or within 30 days of discontinuing IP, the Investigator will complete the Pregnancy Report Form within 24 hours of being notified and forward it to the Sponsor.

A subject becoming pregnant while on IP 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 by completing and forwarding the Pregnancy Report Form with the updated information within 24 hours of being notified. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE and also update the Pregnancy Report Form.

9.6 Regulatory Reporting Requirements for Serious Adverse Events

Regulatory reporting requirements for SAEs include the following:

- Prompt notification by the Investigator to the Sponsor or designee of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor or designee will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IEC, and Investigators.

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

9.7 Clinical Laboratory Evaluations

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

9.8 Vital Signs

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

9.9 Physical Examinations

Physical examinations will consist of the following: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurology. Full and symptom-directed physical examinations will be performed as indicated in Appendix A.

10 STATISTICS

10.1 Analysis Populations

Full Analysis Set (FAS): The FAS will include all randomized subjects.

Per-Protocol Analysis Set (PPS): The PPS will include the subset of subjects from the FAS who do not have any major deviations. A full list of major protocol deviations will be finalized prior to database lock and unblinding.

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

10.2 Statistical Methods

The study data will be cleaned and locked after the last subject finishes the Optional Open-Label Extension Period. The study will then be unblinded and final analysis will be conducted. The data for Long-Term Follow-Up Period will be reported once available.

10.2.1 Analysis of Efficacy

All primary and secondary efficacy endpoints will be analyzed using the FAS. The primary efficacy analysis will be repeated for the PPS as the supportive analysis.

10.2.1.1 Primary efficacy analysis

The primary efficacy endpoint is the proportion of responders who meet all of the following criteria during the period after post-chemotherapy IP treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2:

- Not requiring a platelet transfusion;
- Not requiring a chemotherapy dose reduction by ≥15% due to thrombocytopenia; and
- Not requiring a chemotherapy delay by ≥4 days due to thrombocytopenia

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

The treatment effect on the primary efficacy endpoint will be tested between avatrombopag and placebo using the Cochran-Mantel-Haenszel test, adjusting for number of chemotherapy agents (1 or ≥2 permissible chemotherapy agents [nucleoside analog, including gemcitabine and fluorouracil; carboplatin or cisplatin; anthracycline; or alkylating agent]). The numbers and percentages of responders in each treatment group, the associated 95% confidence intervals (CI), and the 95% CI for the difference between avatrombopag and placebo will be calculated. The primary analysis will be performed based on the FAS and repeated on the PPS. Other sensitivity analyses of the primary efficacy endpoint may be performed as appropriate.

10.2.1.2 Key secondary efficacy analysis

The key secondary efficacy endpoints include the following:

- Duration of severe thrombocytopenia defined as a platelet count $<50 \times 10^9$/L during the period after post-chemotherapy IP treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2;
- Change in platelet count from baseline (qualifying chemotherapy cycle [Cycle X]) (nadir) to Cycle X + 1 (nadir);
- Proportion of subjects who do not have major or non-major clinically relevant bleeding during the period after post-chemotherapy IP treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2; and
- Proportion of subjects who do not receive platelet transfusion during the period after post-chemotherapy IP treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2.

If the test of the treatment effect on the primary efficacy endpoint is statistically significant, the analysis of the key secondary efficacy endpoints will proceed using step-down closed testing procedure in the following order to maintain the family-wise Type I error rate at significance level alpha = 0.05 (2-sided):

- Step 1: Test the treatment effect at a significant level of 0.05 on duration of severe thrombocytopenia defined as a platelet count $<50 \times 10^9$/L during the period after post-chemotherapy IP treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2; if successful, proceed to Step 2; otherwise stop at Step 1.
- Step 2: Test the treatment effect at a significant level of 0.05 on change in platelet count from baseline (qualifying chemotherapy cycle [Cycle X]) (nadir) to Cycle X + 1 (nadir); if successful, proceed to Step 3; otherwise stop at Step 2.
- Step 3: Test the treatment effect at a significant level of 0.05 on proportion of subjects who do not have major or non-major clinically relevant bleeding during the period after post-chemotherapy IP treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2; if successful, proceed to Step 4; otherwise stop at Step 3.
- Step 4: Test the treatment effect at a significant level of 0.05 on proportion of subjects who do not receive platelet transfusion during the period after post-chemotherapy IP treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2.

10.2.1.3 Other efficacy analysis

The other efficacy endpoints include the following during the period after post-chemotherapy IP treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2:

- Proportion of subjects who do not have a chemotherapy dose reduction that is ≥15% due to thrombocytopenia;
- Proportion of subjects who do not have a chemotherapy delay that is ≥4 days due to thrombocytopenia;
- Proportion of subjects with a pre-defined post-baseline nadir platelet count; and
- Proportion of subjects achieving a pre-defined post-baseline maximum platelet count.

The categorical variables (eg, proportion) will be summarized and analyzed in the same manner as the primary efficacy endpoint. The continuous variables (eg, change from baseline in platelet count) will be analyzed using analysis of covariance models with treatment and the randomization stratification factor as main effects and the baseline measurement as a covariate, and Wilcoxon Rank Sum tests if the normality assumption is violated.

The efficacy variables collected during the optional OLE Period will be summarized descriptively.

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.

10.2.2 Analysis of Safety

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

10.2.3 Interim Analysis

No formal interim analysis is planned for this study. A DSMB will be convened for this study, primarily to monitor safety at regular intervals. A DSMB charter, detailing all aspects of the DSMB's scope of review and procedures will be described in a separate document.

10.2.4 Sample Size Determination

Assuming there is a 40% response rate in the active group and 10% in the placebo group, and using a 2:1 randomization, a 10% premature termination rate, and 90% power with 2-sided alpha = 0.05, the sample size is 120 subjects (80 active subjects and 40 placebo subjects).

The assumptions for the response rates for the null and alternative hypotheses were based upon results from a study in CIT completed with oprelvekin (Neumega, Pfizer). The study design for oprelvekin was similar in that subjects were randomized to active or placebo following occurrence of severe thrombocytopenia (platelet count $\leq 20 \times 10^9$/L in a previous cycle [Cycle X]). The primary endpoint of the study assessed the ability of oprelvekin to eliminate the need for platelet transfusions. In the placebo group (n=30), 93% of subjects required a platelet transfusion (7% responder rate) and 72% of active subjects (n=29) required a platelet transfusion (28% responder rate). The responder rates assumed for the null and alternative hypotheses in the AVA-CIT-330 study were based upon the responder rates in this similarly designed study with an assumption for a slightly higher response rate due to the inclusion of subjects with a platelet count in Cycle X of $<50 \times 10^9$/L, rather than $\leq 20 \times 10^9$/L.

11 DATA MANAGEMENT AND RECORD KEEPING

11.1 Data Management

11.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the clinical research associate (CRA) on an ongoing basis and during monitoring visits. The CRAs will verify data recorded in the electronic data capture (EDC) system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for and reconciliation between other databases (eg, safety, IRT) is complete.

11.1.2 Computer Systems

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

11.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure 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.

11.1.4 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.

11.1.5 Data Validation

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

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

11.2 Record Keeping

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

12 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

12.1 Ethical Conduct of the Study

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

12.2 Institutional Review Board/Independent Ethics Committee

The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of subjects. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, 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/IEC by the Investigator.

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

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

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

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

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

12.3 Protocol Amendments

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

12.4 Informed Consent

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

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

12.5 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Declaration of Helsinki, ICH GCP, Directive 2001/20/EC, and applicable regulatory requirements, and that valid data are entered into the eCRFs.

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

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

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

12.6 Disclosure of Data

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

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

12.7 Retention of Records

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

source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

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

12.8 Publication Policy

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

12.9 Financial Disclosure

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

12.10 Insurance and Indemnity

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

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APPENDIX A: SCHEDULE OF PROCEDURES

Table 1. Schedule of Procedures (Double-Blind Treatment Period)

	Chemotherapy Cycle X[a]			Chemotherapy Cycle X + 1		
Day	Screening D -28 to D -1	Baseline	Pre-Chemo IP Treatment (5D)	Chemo Day (D1 up to D3)	Post-Chemo IP Treatment (5D)	D11 (±1D), D15 (±1D), and D18 (±1D)
Visit	1[b]	2	3[c]	4[d]	5[e]	6, 7, 8
Subject informed consent	X					
I/E criteria	X	X				
Randomization		X[f]				
Demographics (incl. race)	X					
Medical history[g]	X					
ECOG performance status	X					
Concomitant medications[h]	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X
Physical examination	X	X[i]		X[i]		
Vital signs[j]	X	X		X		
PK[k]			X		X	
Hematology (incl. platelet counts)[l]	X[b]	X	X	X	X	X
Coagulation panel (central lab)		X			X	
Serum chemistry[m]	X[b]	X		X	X	
Pregnancy testing[n]	X[b]	X[o]				
Bleeding assessment (ISTH)		← continuous → [p]				
Contact IRT	X	X	X		X	
IP dosing[q]		X	X[r]		X[r]	
Dispense IP and dosing diary		X		X[s]		
Collect dosing diary and IP package			X		X	

Chemo = chemotherapy; D = day(s); ECOG = Eastern Cooperative Oncology Group; I/E = inclusion/exclusion; incl. = including; IP = investigational product; IRT = Interactive Response Technology; ISTH = International Society on Thrombosis and Haemostasis; PK = pharmacokinetic.

Note: Prior to conducting any study-related activities, written informed consent must be signed and dated by the subject. Throughout the double-blind treatment period, all subjects will be assessed for platelet transfusions and chemotherapy dose reductions or delays.

a. The qualifying chemo cycle is defined as Cycle X.
b. Screening Visit may occur on the same day as the Baseline Visit, if one day prior to IP treatment. If these bs occur on the same day, only the Baseline (Visit 2) laboratory samples should be sent to the central lab. Local platelet counts may be repeated as needed.
c. Visit 3 will occur on the last day of the 5-day pre-chemo IP treatment.

d. Chemotherapy Day may be 1 to 3 days depending on the subject's chemotherapy regimen (eg, if chemotherapy is given on Day 1 and Day 2, subjects will receive avatrombopag or placebo on Day 3). Avatrombopag or placebo will not be administered concurrently with chemotherapy on Chemotherapy Day. All assessments will occur on the first day of chemotherapy prior to chemotherapy dosing.
e. Visit 5 will occur on the last day of the 5-day post-chemo IP treatment.
f. Randomization must occur prior to IP dosing.
g. Medical history to include tumor type, date of cancer diagnosis, and prior chemotherapeutic regimens (numbers of cycles, dates).
h. Concomitant medications to include details of chemotherapeutic regimen (doses, schedule)
i. Symptom-directed physical examination; full physical examination only required at Screening.
j. Includes height (at the Screening Visit only), weight (Screening and Baseline Visits only), body temperature (Screening and Baseline Visits only), blood pressure, and pulse rate, and will be measured after resting for 5 minutes. Only screening vital signs will be recorded if screening and baseline visits occur the same day.
k. Blood samples for PK analysis will be collected at the following time points: pre-dose and 0.5-2, 2-4, and 4-6 hours post-dose. A pre-dose PK sample will be collected within 30 minutes of IP dosing. Each PK sample must be separated by at least one hour from adjacent samples. Pharmacokinetic samples do not need to be collected at identical times for pre- and post-chemo visits.
l. Hematology samples should be sent to the central lab in addition to local lab platelet counts at Visits 1, 2, 3, 4, and 5. Platelet counts at Baseline (Visit 2) may be performed prior (-1 day) to randomization. Only local lab platelet counts will be assessed at Visits 6, 7, and 8.
m. Screening chemistries can be performed locally to determine eligibility. Chemistry samples will be sent to the central lab at Visits 1, 2, 4, and 5.
n. For females of childbearing potential only. A serum or urine pregnancy test will be performed at the Screening Visit. At the Baseline Visit, the pregnancy test will be performed prior to IP administration.
o. Urine or serum pregnancy test will be performed at the Baseline Visit.
p. Assessment of bleeding will be performed if a subject has an unscheduled study visit.
q. Following randomization, IP will be dispensed in a double-blind manner. Subjects will receive either avatrombopag or placebo once daily for 5 days prior to Chemotherapy Day in Cycle X + 1. Subjects will also receive avatrombopag or placebo once daily for 5 days following last day of chemotherapy treatment. The first dose of IP may be administered at the site if the Baseline visit occurs on the first day of the 5-day IP treatment, or self-dosed if the Baseline visit occurs the day prior to the first day of IP treatment. At scheduled study visits, IP may be administered at the site or the subject may self-dose except for Visits 3 and 5 when subjects will be dosed at the site and serial PK samples will be collected pre- and post-dose of IP. Subjects will self-dose at all other times. Subjects will be instructed to take IP with food. The Investigator or designee will provide subjects with sufficient IP to complete the regimen.
r. Subjects will receive the last dose of IP at the site.
s. These procedures will be performed post chemotherapy dosing on the last Chemotherapy Day of Cycle X + 1.

Table 2. Schedule of Procedures (Observational Period)

	Chemotherapy Cycle X + 2[a]				
Day	**Chemo Day (D1 up to D3)**	**D11 (±1D)**	**D15 (±1D)**	**D18 (±1D)**	**Follow-Up Prior to Chemo Day (-3D) in Cycle X + 3**
Visit	**9[b]**	**10**	**11**	**12[c]**	**17/Early Termination[d]**
ECOG performance status	X				X
Concomitant medication	X	X	X	X	X
Adverse events	X	X	X	X	X
Full physical examination					X
Vital signs[e]					X
Hematology (incl. platelet counts)[f]	X	X	X	X	X
Coagulation (central lab)	X				X
Serum chemistry (central lab)	X				X
Pregnancy testing[g]					X
Bleeding assessment (ISTH)[h]	X				X
Contact IRT					X
Collect unused IP, if applicable					X[i]

Chemo = chemotherapy; D = day(s); ECOG = Eastern Cooperative Oncology Group; incl. = including; IP = investigational product; IRT = Interactive Response Technology; ISTH = International Society on Thrombosis and Haemostasis; OLE = Open-Label Extension.

Note: Throughout the observational period, all subjects will be assessed for platelet transfusions and chemotherapy dose reductions or delays.

a. Cycle X + 2 will be an Observational Period.
b. Chemotherapy Day may be 1 to 3 days depending on the subject's chemotherapy regimen. All assessments will occur on the first day of chemotherapy prior to chemotherapy dosing.
c. Only for subjects receiving a 28-day cycle who are not continuing into the optional OLE Period.
d. Only for subjects not continuing into the optional OLE Period. For subjects not continuing into the optional OLE Period, a Follow-Up Visit will occur prior to (within 3 days) Chemotherapy Day in Cycle X + 3. If Cycle X + 2 is the subject's last chemotherapy cycle, a Follow-Up Visit will occur at 30 days (±3 days) after Chemotherapy Day in Cycle X + 2. For subjects continuing into the optional OLE Period, Visit 13 will occur 5 days prior to Chemotherapy Day in Cycle X + 3.
e. Includes blood pressure and pulse rate, and will be measured after resting for 5 minutes.
f. Hematology samples will be sent to the central lab in addition to local lab platelet counts at Visits 9 and 17. Only local lab platelet counts will be assessed at Visits 10, 11, and 12.
g. Urine pregnancy test may be performed for females of childbearing potential only.
h. Assessment of bleeding will be performed if a subject has an unscheduled study visit.
i. Only for an Early Termination Visit.

Table 3. Schedule of Procedures (Optional Open-Label Extension Period)

		Chemotherapy Cycle X + 3 & On			
Day	Pre-Chemo Avatrombopag Treatment (5D)	Chemo Day (D1 up to D3)	Post-Chemo Avatrombopag Treatment (5D)	D15 (±1D)	Follow-Up 30D (±3D) After Last Avatrombopag Dose
Visit	**13[a]**	**14[b]**	**15[c]**	**16[d]**	**17/Early Termination[e]**
I/E criteria	X				
ECOG performance status	X				X
Concomitant medications	X	X	X	X	X
Adverse events	X	X	X	X	X
Full physical examination					X
Symptom-directed physical examination		X			
Vital signs[f]	X	X			X
Hematology (incl. platelet counts)[g]	X[h]	X	X	X	X
Coagulation panel (central lab)	X		X		X
Serum chemistry (central lab)	X		X		X
Pregnancy testing[i]	X				X
Bleeding assessment (ISTH)	←——— continuous ———→[j]				
Contact IRT	X		X		X
Avatrombopag dosing[k]	X		X		
Dispense avatrombopag	X	X[l]			
Collect unused avatrombopag, if applicable		X	X		X[m]

Chemo = chemotherapy; D = day(s); ECOG = Eastern Cooperative Oncology Group; I/E = inclusion/exclusion; incl. = including; IRT = Interactive Response Technology; ISTH = International Society on Thrombosis and Haemostasis.

Note: Throughout the open-label extension period, all subjects will be assessed for platelet transfusions and chemotherapy dose reductions or delays.

a. Visit 13 will occur on the first day of the pre-chemotherapy avatrombopag treatment. For Cycle X + 4, this visit will be denoted Visit 13.1 and for Cycle X + 5, this visit will be denoted Visit 13.2. This numbering scheme will continue for subsequent enrolled open-label cycles.
b. Chemotherapy Day may be 1 to 3 days depending on the subject's chemotherapy regimen (eg, if chemotherapy is given on Day 1 and Day 2, the second round of avatrombopag will start on Day 3). Avatrombopag will not be administered concurrently with chemotherapy on Chemotherapy Day. All assessments will occur on the first day of chemotherapy prior to chemotherapy dosing. For Cycle X + 4, this visit will be denoted Visit 14.1 and for Cycle X + 5, this visit will be denoted Visit 14.2. This numbering scheme will continue for subsequent enrolled open-label cycles.
c. Visit 15 will occur on the last day of the 5-day post-chemo avatrombopag treatment. For Cycle X + 4, this visit will be denoted Visit 15.1 and for Cycle X + 5, this visit will be denoted Visit 15.2. This numbering scheme will continue for subsequent enrolled open-label cycles.
d. For Cycle X + 4, this visit will be denoted Visit 16.1 and for Cycle X + 5, this visit will be denoted Visit 16.2. This numbering scheme will continue for subsequent enrolled open-label cycles.
e. Subjects will have a Follow-Up Visit at 30 days (±3 days) after the last dose of avatrombopag treatment of the subject's last chemotherapy cycle.
f. Includes blood pressure and pulse rate and will be measured after resting for 5 minutes.
g. Hematology samples will be sent to the central lab in addition to local lab platelet counts for Visits 13, 14, 15, and 17. Only local lab platelet counts will be assessed at Visit 16.
h. Blood sample for platelet counts will be collected prior to avatrombopag dosing. Platelet counts may be performed prior (-1 day) to avatrombopag dosing.

i. For females of childbearing potential only. A serum or urine pregnancy test may be performed at Visit 13.
j. Assessment of bleeding will be performed if a subject has an unscheduled study visit.
k. All subjects will receive avatrombopag once daily for 5 days prior to Chemotherapy Day in Cycle X + 3. Subjects will also receive avatrombopag once daily for 5 days following the last day of chemotherapy treatment. At scheduled study visits, avatrombopag may be administered at the site or the subject may self-dose. Subjects will self-dose at all other times. Subjects will be instructed to take avatrombopag with food. The Investigator or designee will provide subjects with sufficient avatrombopag to complete the regimen.
l. These procedures will be performed post-chemotherapy dosing on the last Chemotherapy Day of the cycle.
m. Only for an Early Termination Visit.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Safety Chemistry Panel

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

Hematology

- Hematocrit
- Hemoglobin
- Platelets
- Red blood cell count
- White blood cell count and differential

Coagulation

- Prothrombin time
- Activated partial thromboplastin time
- International normalized ratio

Pregnancy Test

- Beta-human chorionic gonadotropin

Creatinine Clearance using the Cockcroft-Gault formula

APPENDIX C: CYTOCHROME P450 INDUCERS

Table 4 Cytochrome P450 Inducers

	Strong	Moderate
CYP2C9 inducers	NA	Aprepitant, carbamazepine, enzalutamide, fosaprepitant, 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 5. International Society on Thrombosis and Haemostasis Bleeding Definitions

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.

APPENDIX E: Protocol Amendments

Amendment #1 – 04 April 2019

Rationale for Amendment

Amendment 1 has been introduced to include an additional tumor type, clarify the time period for assessment of the efficacy endpoints, and clarify certain inclusion and exclusion criteria. Additionally, the Screening and Baseline Visits may now be combined and performed on the same day and the window for a separate Screening Visit has been increased to 28 days.

Additional Tumor Type: Due to the similarities in chemotherapy agents used in the treatment of small cell lung cancer compared to non-small cell lung cancer, subjects with small cell lung cancer are eligible for enrollment.

Time Period for Assessment of Endpoints: The time period for efficacy assessments for chemotherapy delays and dose reductions has been clarified to 'the period after post-chemotherapy IP treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2'. If a subject has decreased or delayed doses of a chemotherapeutic agent due to thrombocytopenia during the middle of Cycle X+1 (eg, Day 15 gemcitabine), this could affect whether or not there is a need for a delay or dose reduction at the beginning of Cycle X+2 due to thrombocytopenia. As a result, this time period clarification was warranted to ensure accurate data collection for the assessment of the efficacy endpoints.

Inclusion/Exclusion Criteria Clarification: Inclusion Criterion #5 previously required that the subject would be able to receive the same dose and schedule of chemotherapy in Cycle X+1 as they received in Cycle X. This criterion has now been clarified to "Subject is planned to receive the same chemotherapy regimen and the same dose(s) on Chemotherapy Day (Days 1-3) of Cycle X+1 as was given in the qualifying chemotherapy Cycle X" to align with the clarification in the timing of the efficacy endpoint clarification described above.

Exclusion Criterion #9 has been modified to exclude patients with a recent history (3 months prior to Screening) of significant cardiac disease. There is no evidence that would preclude use of avatrombopag in subjects with stable cardiac disease.

Due to commercial availability of recombinant human TPO in some countries, Exclusion Criterion #14 has been clarified to exclude recombinant human thrombopoietin in addition to the TPO-receptor agonists in the 3 months prior to Screening.

Combined Screening and Baseline: The Baseline Visit may now be conducted one day prior to IP treatment, and may be combined with the Screening Visit. As platelet counts from standard of care laboratory assessments may be used for eligibility, this change should allow for logistical efficiencies and reduce the required number of visits for a potential subject. The window for a separate Screening Visit has been increased to 28 days, from 14 days, to allow for earlier consenting of subjects in order to screen for thrombocytopenia in Cycle X.

Summary of Significant Changes in Amendment 1

- Patients with small cell lung cancer are eligible to be enrolled
- The timeframe for efficacy assessments for dose reductions and delays in chemotherapy has been clarified to include the period after post-chemotherapy IP treatment in Cycle X+1
- Exclusion Criterion #9 has been clarified to exclude only those patients with recent histories of significant cardiac disease in the 3 months prior to Screening; Exclusion Criterion #14 now excludes recombinant human TPO, in addition to eltrombopag and romiplostim
- The Baseline Visit may be performed one day prior to IP treatment, and may be combined with the Screening Visit. The visit window for the Screening Visit has been increased to 28 days.

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

3.1.1 Screening/Qualifying Chemotherapy Regimen (Cycle X)

To be eligible for the study, subjects must have experienced thrombocytopenia during their current chemotherapy regimen as described in the inclusion criteria in Section 4.1. The qualifying chemotherapy cycle is defined as "Cycle X". Subjects must be screened ≤~~14~~ ***28*** days prior to the Baseline Visit, ***unless Screening and Baseline Visits are performed on the same day***, and begin treatment during Cycle X.

3.1.2 Double-Blind Treatment Period

At the Baseline Visit, eligible subjects will be randomized in a 2:1 ratio to receive either avatrombopag or placebo in a double-blind manner prior to and during the subsequent chemotherapy cycle, Cycle X + 1. Randomization will be stratified by the number of chemotherapy agents the subject is receiving (1 or ≥2 permissible chemotherapy agents [nucleoside analog, including gemcitabine and fluorouracil; carboplatin or cisplatin; anthracycline; or alkylating agent]). Subjects will receive either avatrombopag or placebo once daily for 5 days prior to Chemotherapy Day in Cycle X + 1. Subjects will also receive avatrombopag or placebo once daily for 5 days immediately following Chemotherapy Day. Chemotherapy Day is defined per protocol as Day 1 to 3 of the subject's chemotherapy regimen (eg, if chemotherapy is given on Day 1 and Day 2, the second round of avatrombopag or placebo will start on Day 3). Avatrombopag or placebo will not be administered concurrently with chemotherapy on Chemotherapy Day. Chemotherapy regimens requiring dosing beyond Chemotherapy Day within the 21-day or 28-day cycle (eg, gemcitabine on Day 8) are allowed. ***These mid-cycle chemotherapy doses, after IP treatment, will be part of the assessment of the composite primary endpoint for dose modifications or delays.***

3.1.3 Observational Period

Cycle X + 2 will be an Observational Period. The Observational Period is designed to enable assessment of whether the subjects meet the chemotherapy dose modifications or dose delay components of the composite primary endpoint ***on the Chemotherapy Day*** while reducing decision making bias for chemotherapy dose modifications or delays. Subjects in the Observational Period will not receive any IP pre- or post-Chemotherapy Day in Cycle X + 2.

4.1 Inclusion Criteria for All Subjects

2. Subject with a diagnosis with ovarian cancer, ~~non-small cell~~ lung cancer ***(small cell or non-small cell)***, or bladder cancer, requiring systemic chemotherapy;

4. Subject experienced severe thrombocytopenia, defined as 2 platelet counts $<50 \times 10^9$/L measured at least 24 hours apart, during the qualifying chemotherapy cycle (Cycle X), of their current chemotherapy regimen. ***Platelet counts obtained per standard of care during Cycle X prior to consent may be used;***

5. Subject is ~~able~~ ***planned*** to ***receive the same chemotherapy regimen and the same dose(s) on Chemotherapy Day (Days 1-3) of Cycle X+1*** ~~continue to receive the current chemotherapy regimen at the same dose and schedule~~ as was given in the qualifying chemotherapy Cycle X;

4.2 Exclusion Criteria for All Subjects

4. Subject who received >2 previous lines of chemotherapy ***(adjuvant/neoadjuvant therapy is considered a previous line; immunotherapy alone is not considered a previous line)*** or is receiving whole brain radiation during the study treatment period;

6. Subject ***has a known medical history of*** ~~is known to be~~ human immunodeficiency virus ~~positive~~;

9. Subject has a ***recent*** history ***(within 3 months of Screening)*** of significant cardiovascular disease (eg, congestive heart failure ~~New York Heart Association Grade 3/4~~ ***exacerbation***, arrhythmia known to increase the risk of thromboembolic events [eg, atrial fibrillation], coronary artery stent placement, angioplasty, or coronary artery bypass graft);

14. Subject has ~~previously~~ received a thrombopoietin receptor agonist (eg, eltrombopag or romiplostim) ***or recombinant human thrombopoietin*** for the treatment of CIT ***within 3 months of Screening***;

15. Subject received a platelet transfusion within ~~3 days~~ ***72 hours*** of randomization;

18. Female subjects who are lactating or pregnant at Screening ***or the Baseline Visit*** (as documented by a positive serum ***or urine*** beta-human chorionic gonadotropin [β-hCG] test) ~~or the Baseline Visit (urine);~~

4.5 Withdrawal Criteria

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 Visit 13 (for subjects not in the optional OLE Period) or Visit 17 (for subjects participating in the optional OLE Period). ***All subjects should continue into the Long-Term Follow-Up Period unless consent has been withdrawn.*** The reason for subject withdrawal must be documented in the electronic case report form (eCRF).

5.3 Randomization and Blinding

This is a randomized, double-blind, placebo-controlled study. For the Double-Blind Treatment Period, subjects who ~~complete the Screening Visit and~~ meet the inclusion criteria and exclusion criteria will be randomized to receive either avatrombopag 60 mg or placebo in a 2:1 ratio at the Baseline Visit.

5.6.1 Excluded Medications and/or Procedures

The following medications and/or procedures are excluded:

- ***Use of thrombopoietin receptor agonists or recombinant human thrombopoietin;***

6.2.1 Screening (Visit 1, Day ~~-14~~ ***-28*** to Day -1)

The Screening Visit may be combined with the Baseline Visit on the day prior to IP treatment (Day -1).

The following procedures will be performed at the Screening Visit:

- Perform pregnancy test (serum ***or urine***) for female subjects of childbearing potential only;
- Collect blood samples for the following assessments ***(if Screening Visit occurs on the same day as the Baseline Visit, only the Baseline laboratory assessments should be performed):***
  - Hematology (including platelet counts). ***Local platelet counts may be repeated as needed***; and

6.2.2 Baseline Visit (Visit 2, First Day ***[or -1 Day]*** of the 5-day Investigational Product Treatment)

The Baseline Visit may occur one day prior to IP treatment, and may be combined with the Screening Visit.

Eligible subjects will receive either avatrombopag or placebo once daily for 5 days prior to Chemotherapy Day in Cycle X + 1. The following procedures will be performed at the Baseline Visit prior to IP dosing:

- Record vital signs (includes weight, body temperature, blood pressure, and pulse rate). ***Only Screening vital signs will be recorded if combined with the Screening Visit***;
- Perform pregnancy test (***serum or*** urine) for female subjects of childbearing potential only;
- Administer or self-dose IP with food***, if the Baseline Visit occurs on the first day of the 5-day IP treatment.***

6.3.2 Post-Chemotherapy Investigational Product Treatment (Visit 5~~), Last Day of the 5-day Investigational Product Treatment)~~

6.4 Observational Period (Cycle X + 2)

If Chemotherapy Day in Cycle X+2 is delayed, record the reason for delay in the eCRF. If the delay is due to laboratory results, record the relevant results in the eCRF.

7 EFFICACY ASSESSMENTS

The primary efficacy endpoint is the proportion of responders who meet all of the following criteria ***during the period after post-chemotherapy IP treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2***:

- Not requiring a platelet transfusion ~~during Cycle X + 1 through immediately prior to Cycle X + 2~~;
- Not requiring a chemotherapy dose reduction by ≥15% ~~in Cycle X + 2~~ due to thrombocytopenia ~~in Cycle X + 1~~; and
- Not requiring a chemotherapy delay by ≥4 days ~~in Cycle X + 2~~ due to thrombocytopenia ~~in Cycle X + 1.~~

The key secondary efficacy endpoints include the following:

- Duration of severe thrombocytopenia defined as a platelet count <50 × 10^9/L during ***the period after post-chemotherapy IP treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2*** ~~Cycle X + 1 through immediately prior to Cycle X + 2~~;
- Change in platelet count from baseline (qualifying chemotherapy cycle [Cycle X]) (nadir) to Cycle X + 1 (nadir);
- Proportion of subjects who do not have major or non-major clinically relevant bleeding during ***the period after post-chemotherapy IP treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2*** ~~Cycle X + 1 through immediately prior to Cycle X + 2~~; and
- Proportion of subjects who do not receive a platelet transfusion during ***the period after post-chemotherapy IP treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2*** ~~Cycle X + 1 through immediately prior to Cycle X + 2.~~

The other efficacy endpoints include the following ***during the period after post-chemotherapy IP treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2***:

- Proportion of subjects who do not have a chemotherapy dose reduction that is ≥15% ~~in Cycle X + 2~~ due to thrombocytopenia ~~in Cycle X + 1~~;
- Proportion of subjects who do not have a chemotherapy delay that is ≥4 days ~~in Cycle X + 2~~ due to thrombocytopenia ~~in Cycle X + 1~~;
- Proportion of subjects with a pre-defined post-baseline nadir platelet count ~~during Cycle X + 1 and through immediately prior to Cycle X + 2~~; and
- Proportion of subjects achieving a pre-defined post-baseline maximum platelet count ~~during Cycle X + 1 and through immediately prior to Cycle X + 2.~~

9.1 Adverse Events

Adverse events, which include clinical laboratory test variables, will be monitored and documented from the time of informed consent until the Follow-Up Visit occurring prior to (within 3 days) Chemotherapy Day in Cycle X + 3 (for subjects not continuing into the optional OLE Period) and the Follow-Up Visit occurring 30 days after last dose of IP (for subjects continuing into the optional OLE Period). 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. Events associated with disease progression should not be reported as adverse events/SAEs. ~~The events will be captured as an outcome on a separate form for deaths due to disease progression.~~ However, if in the Investigator's opinion the disease progression is manifesting in an unusual or uncharacteristic manner, the associated events should be reported as adverse events/SAEs, as appropriate.

10.2.1.1 Primary efficacy analysis

The primary efficacy endpoint is the proportion of responders who meet all of the following criteria ***during the period after post-chemotherapy IP treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2***:

- Not requiring a platelet transfusion ~~during Cycle X + 1 through immediately prior to Cycle X + 2;~~
- Not requiring a chemotherapy dose reduction by ≥15% ~~in Cycle X + 2~~ due to thrombocytopenia~~in Cycle X + 1~~; and
- Not requiring a chemotherapy delay by ≥4 days ~~in Cycle X + 2~~ due to thrombocytopenia ~~in Cycle X + 1.~~

10.2.1.2 Key secondary efficacy analysis

The key secondary efficacy endpoints include the following:

- Duration of severe thrombocytopenia defined as a platelet count <50 × 10^9/L during ***the period after post-chemotherapy IP treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2*** ~~Cycle X + 1 through immediately prior to Cycle X + 2~~;
- Change in platelet count from baseline (qualifying chemotherapy cycle [Cycle X]) (nadir) to Cycle X + 1 (nadir);
- Proportion of subjects who do not have major or non-major clinically relevant bleeding during ***the period after post-chemotherapy IP treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2*** ~~Cycle X + 1 through immediately prior to Cycle X + 2;~~ and
- Proportion of subjects who do not receive platelet transfusion during ***the period after post-chemotherapy IP treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2*** ~~Cycle X + 1 through immediately prior to Cycle X + 2.~~

If the test of the treatment effect on the primary efficacy endpoint is statistically significant, the analysis of the key secondary efficacy endpoints will proceed using step-down closed testing procedure in the following order to maintain the family-wise Type I error rate at significance level alpha = 0.05 (2-sided):

- Step 1: Test the treatment effect at a significant level of 0.05 on duration of severe thrombocytopenia defined as a platelet count <50 × 10^9/L ***during the period after post-chemotherapy IP treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2*** ~~during Cycle X + 1 through immediately prior to Cycle X + 2~~; if successful, proceed to Step 2; otherwise stop at Step 1.

- Step 2: Test the treatment effect at a significant level of 0.05 on change in platelet count from baseline (qualifying chemotherapy cycle [Cycle X]) (nadir) to Cycle X + 1 (nadir); if successful, proceed to Step 3; otherwise stop at Step 2.
- Step 3: Test the treatment effect at a significant level of 0.05 on proportion of subjects who do not have major or non-major clinically relevant bleeding ***during the period after post-chemotherapy IP treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2*** ~~during Cycle X + 1 through immediately prior to Cycle X + 2~~; if successful, proceed to Step 4; otherwise stop at Step 3.
- Step 4: Test the treatment effect at a significant level of 0.05 on proportion of subjects who do not receive platelet transfusion ***during the period after post-chemotherapy IP treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2*** ~~during Cycle X + 1 through immediately prior to Cycle X + 2.~~

10.2.1.3 Other efficacy analysis

The other efficacy endpoints include the following ***during the period after post-chemotherapy IP treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2***:

- Proportion of subjects who do not have a chemotherapy dose reduction that is ≥15% ~~in Cycle X + 2~~ due to thrombocytopenia ~~in Cycle X + 1~~;
- Proportion of subjects who do not have a chemotherapy delay that is ≥4 days ~~in Cycle X + 2~~ due to thrombocytopenia ~~in Cycle X + 1;~~
- Proportion of subjects with a pre-defined post-baseline nadir platelet count ~~during Cycle X + 1 and through immediately prior to Cycle X + 2~~; and
- Proportion of subjects achieving a pre-defined post-baseline maximum platelet count ~~during Cycle X + 1 and through immediately prior to Cycle X + 2.~~

13 REFERENCES

3. Avatrombopag maleate Global Investigator's Brochure, ~~v12~~*v14*, ~~April 2016~~ ***January 2019***.

APPENDIX A: SCHEDULE OF PROCEDURES

Table 1 Schedule of Procedures (Double-Blind Treatment Period)

	Chemotherapy Cycle X[a]			Chemotherapy Cycle X + 1		
Day	Screening D ~~-14~~ *-28* to D -1	Baseline	Pre-Chemo IP Treatment (5D)	Chemo Day (D1 up to D3)	Post-Chemo IP Treatment (5D)	D11 (±1D), D15 (±1D), and D18 (±1D)
Visit	1[b]	2	3[c]	4[d]	5[e]	6, 7, 8
Subject informed consent	X					
I/E criteria	X	X				
Randomization		X[f]				
Demographics (incl. race)	X					
Medical history[g]	X					
ECOG performance status	X					
Concomitant medications[h]	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X
Physical examination	X	X[i]		X[i]		
Vital signs[j]	X	X		X		
PK[k]			X		X	
Hematology (incl. platelet counts)[l]	X[b]	X[i]	X	X	X	X
Coagulation panel ***(central lab)***		X			X	
Serum chemistry[m]	X[b]	X		X	X	
Pregnancy testing[n]	X[b]	X[o]				
Bleeding assessment (ISTH)		← continuous → [p]				
Contact IRT	X	X	X		X	
IP dosing[q]		X	X[r]		X[r]	
Dispense IP and dosing diary		X		X[s]		
Collect dosing diary and IP package			X		X	

Chemo = chemotherapy; D = day(s); ECOG = Eastern Cooperative Oncology Group; I/E = inclusion/exclusion; incl. = including; IP = investigational product; IRT = Interactive Response Technology; ISTH = International Society on Thrombosis and Haemostasis; PK = pharmacokinetic.

Note: Prior to conducting any study-related activities, written informed consent must be signed and dated by the subject. Throughout the double-blind treatment period, all subjects will be assessed for platelet transfusions and chemotherapy dose reductions or delays.

a. The qualifying chemo cycle is defined as Cycle X.

b. Screening Visit ~~will occur at the discovery of severe thrombocytopenia~~ ***may occur on the same day as the Baseline Visit, if one day prior to IP treatment. If these visits occur on the same day, only the Baseline (Visit 2) laboratory samples should be sent to the central lab. Local platelet counts may be repeated as needed.***

c. Visit 3 will occur on the last day of the 5-day pre-chemo IP treatment.

d. Chemotherapy Day may be 1 to 3 days depending on the subject's chemotherapy regimen (eg, if chemotherapy is given on Day 1 and Day 2, subjects will receive avatrombopag or placebo on Day 3). Avatrombopag or placebo will not be administered concurrently with chemotherapy on Chemotherapy Day. All assessments will occur on the first day of chemotherapy prior to chemotherapy dosing.
e. Visit 5 will occur on the last day of the 5-day post-chemo IP treatment.
f. Randomization must occur prior to IP dosing.
g. Medical history to include tumor type, date of cancer diagnosis, and prior chemotherapeutic regimens (~~doses~~ ***numbers of cycles***, dates).
h. Concomitant medications to include details of chemotherapeutic regimen (doses, schedule)
i. Symptom-directed physical examination; full physical examination only required at Screening.
j. Includes height (at the Screening Visit only), weight (Screening and Baseline Visits only), body temperature (Screening and Baseline Visits only), blood pressure, and pulse rate, and will be measured after resting for 5 minutes. ***Only screening vital signs will be recorded if screening and baseline visits occur the same day.***
k. Blood samples for PK analysis will be collected at the following time points: pre-dose and 0.5-2, 2-4, and 4-6 hours post-dose. A pre-dose PK sample will be collected within 30 minutes of IP dosing. Each PK sample must be separated by at least one hour from adjacent samples. Pharmacokinetic samples do not need to be collected at identical times for pre- and post-chemo visits.
l. ***Hematology samples should be sent to the central lab in addition to local lab platelet counts at Visits 1, 2, 3, 4, and 5.*** Platelet counts ***at Baseline (Visit 2)*** may be performed prior (-1 day) to randomization. Only ***local lab platelet counts will be assessed at Visits 6, 7, and 8.***
m. ~~Only platelet counts will be assessed at Visits 6, 7, and 8.~~ ***Screening chemistries can be performed locally to determine eligibility. Chemistry samples will be sent to the central lab at Visits 1, 2, 4, and 5.***
n. For females of childbearing potential only. A serum ***or urine*** pregnancy test will be performed at the Screening Visit. At the Baseline Visit, the pregnancy test will be performed prior to IP administration.
o. Urine ***or serum*** pregnancy test will be performed at the Baseline Visit.
p. Assessment of bleeding will be performed if a subject has an unscheduled study visit.
q. Following randomization, IP will be dispensed in a double-blind manner. Subjects will receive either avatrombopag or placebo once daily for 5 days prior to Chemotherapy Day in Cycle X + 1. Subjects will also receive avatrombopag or placebo once daily for 5 days following last day of chemotherapy treatment. ***The first dose of IP may be administered at the site if the Baseline visit occurs on the first day of the 5-day IP treatment, or self-dosed if the Baseline visit occurs the day prior to the first day of IP treatment.*** At scheduled study visits, IP may be administered at the site or the subject may self-dose except for Visits 3 and 5 when subjects will be dosed at the site and serial PK samples will be collected pre- and post-dose of IP. Subjects will self-dose at all other times. Subjects will be instructed to take IP with food. The Investigator or designee will provide subjects with sufficient IP to complete the regimen.
r. Subjects will receive the last dose of IP at the site.
s. These procedures will be performed post chemotherapy dosing on the last Chemotherapy Day of Cycle X + 1.

Table 2 Schedule of Procedures (Observational Period)

Day	Chemotherapy Cycle X + 2[a]				
	Chemo Day (D1 up to D3)	**D11 (±1D)**	**D15 (±1D)**	**D18 (±1D)**	**Follow-Up Prior to Chemo Day (-3D) in Cycle X + 3**
Visit	**9[b]**	**10**	**11**	**12[c]**	**17/Early Termination[d]**
ECOG performance status	X				X
Concomitant medication	X	X	X	X	X
Adverse events	X	X	X	X	X
Full physical examination					X
Vital signs[e]					X
Hematology (incl. platelet counts)[f]	X	X[f]	X[f]	X[f]	X
Coagulation ***(central lab)***	X				X
Serum chemistry ***(central lab)***	X				X
Pregnancy testing[g]					X
Bleeding assessment (ISTH)[h]	X				X
Contact IRT					X
Collect unused IP, if applicable					X[i]

Chemo = chemotherapy; D = day(s); ECOG = Eastern Cooperative Oncology Group; incl. = including; IP = investigational product; IRT = Interactive Response Technology; ISTH = International Society on Thrombosis and Haemostasis; OLE = Open-Label Extension.

Note: Throughout the observational period, all subjects will be assessed for platelet transfusions and chemotherapy dose reductions or delays.

a. Cycle X + 2 will be an Observational Period.
b. Chemotherapy Day may be 1 to 3 days depending on the subject's chemotherapy regimen. All assessments will occur on the first day of chemotherapy prior to chemotherapy dosing.
c. Only for subjects ***receiving a 28-day cycle who are*** not continuing into the optional OLE Period.
d. Only for subjects not continuing into the optional OLE Period. For subjects not continuing into the optional OLE Period, a Follow-Up Visit will occur prior to (within 3 days) Chemotherapy Day in Cycle X + 3. If Cycle X + 2 is the subject's last chemotherapy cycle, a Follow-Up Visit will occur at 30 days (±3 days) after Chemotherapy Day in Cycle X + 2. For subjects continuing into the optional OLE Period, Visit 13 will occur 5 days prior to Chemotherapy Day in Cycle X + 3.
e. Includes blood pressure and pulse rate, and will be measured after resting for 5 minutes.
f. ***Hematology samples will be sent to the central lab in addition to local lab platelet counts at Visits 9 and 17.*** Only ***local lab*** platelet counts will be assessed at Visits 10, 11, and 12.
g. Urine ~~or serum~~ pregnancy test may be performed for females of childbearing potential only.
h. Assessment of bleeding will be performed if a subject has an unscheduled study visit.
i. Only for an Early Termination Visit.

Table 3 Schedule of Procedures (Optional Open-Label Extension Period)

		Chemotherapy Cycle X + 3 & On			
Day	Pre-Chemo ~~IP~~ *Avatrombopag* Treatment (5D)	Chemo Day (D1 up to D3)	Post-Chemo *Avatrombopag* ~~IP~~ Treatment (5D)	D15 (±1D)	Follow-Up 30D (±3D) After Last *Avatrombopag* ~~IP~~ Dose
Visit	**13[a]**	**14[b]**	**15[c]**	**16[d]**	**17/Early Termination[e]**
I/E criteria	X				
ECOG performance status	X				X
Concomitant medications	X	X	X	X	X
Adverse events	X	X	X	X	X
Full physical examination					X
Symptom-directed physical examination		X			
Vital signs[f]	X	X			X
Hematology (incl. platelet counts)[g]	X[g,h]	X	X	X[h]	X
Coagulation panel ***(central lab)***	X		X		X
Serum chemistry ***(central lab)***	X		X		X
Pregnancy testing[i]	X				X
Bleeding assessment (ISTH)	←——— continuous ———→[j]				
Contact IRT	X		X		X
Avatrombopag dosing[k]	X		X		
Dispense avatrombopag	X	X[l]			
Collect unused avatrombopag, if applicable		X	X		X[m]

Chemo = chemotherapy; D = day(s); ECOG = Eastern Cooperative Oncology Group; I/E = inclusion/exclusion; incl. = including; ~~IP = investigational product;~~ IRT = Interactive Response Technology; ISTH = International Society on Thrombosis and Haemostasis.

Note: Throughout the open-label extension period, all subjects will be assessed for platelet transfusions and chemotherapy dose reductions or delays.

a. Visit 13 will occur on the first day of the pre-chemotherapy ***avatrombopag*** ~~IP~~-treatment. For Cycle X + 4, this visit will be denoted Visit 13.1 and for Cycle X + 5, this visit will be denoted Visit 13.2. This numbering scheme will continue for subsequent enrolled open-label cycles.
b. Chemotherapy Day may be 1 to 3 days depending on the subject's chemotherapy regimen (eg, if chemotherapy is given on Day 1 and Day 2, the second round of avatrombopag will start on Day 3). Avatrombopag will not be administered concurrently with chemotherapy on Chemotherapy Day. All assessments will occur on the first day of chemotherapy prior to chemotherapy dosing. For Cycle X + 4, this visit will be denoted Visit 14.1 and for Cycle X + 5, this visit will be denoted Visit 14.2. This numbering scheme will continue for subsequent enrolled open-label cycles.
c. Visit 15 will occur on the last day of the 5-day post-chemo ***avatrombopag*** ~~IP~~-treatment. For Cycle X + 4, this visit will be denoted Visit 15.1 and for Cycle X + 5, this visit will be denoted Visit 15.2. This numbering scheme will continue for subsequent enrolled open-label cycles.
d. For Cycle X + 4, this visit will be denoted Visit 16.1 and for Cycle X + 5, this visit will be denoted Visit 16.2. This numbering scheme will continue for subsequent enrolled open-label cycles.
e. Subjects will have a Follow-Up Visit at 30 days (±3 days) after the last dose of ***avatrombopag*** ~~IP~~ treatment of the subject's last chemotherapy cycle.
f. Includes blood pressure and pulse rate and will be measured after resting for 5 minutes.
g. ***Hematology samples will be sent to the central lab in addition to local lab platelet counts for Visits 13, 14, 15, and 17. Only local lab platelet counts will be assessed at Visit 16.***

h. Blood sample for platelet counts will be collected prior to ***avatrombopag*** ~~IP~~ dosing. Platelet counts may be performed prior (-1 day) to ***avatrombopag*** ~~IP~~ dosing.
~~i. Only platelet counts will be assessed at Visit 16.~~
i. For females of childbearing potential only. A serum or urine pregnancy test may be performed at Visit 13.
j. Assessment of bleeding will be performed if a subject has an unscheduled study visit.
k. All subjects will receive avatrombopag once daily for 5 days prior to Chemotherapy Day in Cycle X + 3. Subjects will also receive avatrombopag once daily for 5 days following the last day of chemotherapy treatment. At scheduled study visits, ***avatrombopag*** ~~IP~~ may be administered at the site or the subject may self-dose. Subjects will self-dose at all other times. Subjects will be instructed to take ***avatrombopag*** ~~IP~~ with food. The Investigator or designee will provide subjects with sufficient ***avatrombopag*** ~~IP~~ to complete the regimen.
l. These procedures will be performed post-chemotherapy dosing on the last Chemotherapy Day of the cycle.
m. Only for an Early Termination Visit.

APPENDIX C: CYTOCHROME P450 INDUCERS

Table 4 Cytochrome P450 Inducers

	Strong	Moderate
CYP2C9 inducers	NA	Aprepitant, carbamazepine, enzalutamide, ***fosaprepitant,*** 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