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Statistical Analysis Plan

SPONSOR:	Dova Pharmaceuticals, Inc.
PROTOCOL 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
STUDY CODE:	AVA-CIT-330
VERSION:	1.0 (31AUG2020)

The undersigned certify that they have read, reviewed and approved this document.

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Change History

Version – Date	Author	Summary of Changes
0.4 – 19 July 2019	[redacted]	N/A – First Version
0.5 – 30 August 2019	[redacted]	Updated to clarify that unscheduled platelet counts may be used in assessment of the nadir value within a time window Updated to clarify that any lab values containing "<" or ">" symbols would be analyzed as the value associated with the symbol
0.6 – 15 July 2020	[redacted]	Added clarification regarding partial date rules, normality assumption, categorical exposure tables, COVID-19 listings Additional editorial comments
1.0 – 31 August 2020	[redacted]	Final Version 1.0 – Added Region to Demographic and subgroup analysis Added LTFU summary table/listing and PK section Added multiple imputation for Cycle X+1 nadir Editorial comments

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1. List of Abbreviations and Definition of Terms

Abbreviation	Term
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
BMI	Body Mass Index
CIT	Chemotherapy-Induced Thrombocytopenia
CMH	Cochran-Mantel-Haenszel
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
ICH	International Conference on Harmonization
IP	Investigational Product
ISTH	International Society on Thrombosis and Haemostasis
IWRS	Interactive Web Response System
LTFU	Long Term Follow Up
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
OLE	Open-Label Extension
PD	Pharmacodynamics
PK	Pharmacokinetics
PPS	Per-Protocol Analysis Set
PT	MedDRA Preferred Term
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SMQ	Standardized MedDRA Query
SOC	MedDRA System Organ Class
TEAE	Treatment-Emergent Adverse Event
WHO	World Health Organization

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2. Introduction

This Statistical Analysis Plan (SAP) describes the statistical methodology and data handling for the clinical trial for Dova Pharmaceuticals with Protocol Number: AVA-CIT-330 (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).

The ICH guideline E3 "Structure and Content of Clinical Study Reports" was used as a guide to the writing of the plan.

This SAP is based on the following study document(s):

- Clinical Study Protocol V2.0 (Amendment 1), 04 April 2019
- Electronic Case Report Form, dated 28 April 2020

3. Study Design and Objectives

3.1 Study Objectives

3.1.1 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 Chemotherapy-Induced Thrombocytopenia (CIT).

3.1.2 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.

3.2 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 Open-Label Extension (OLE) Period, and a Long-Term Follow-Up Period, as described in Figure 1.

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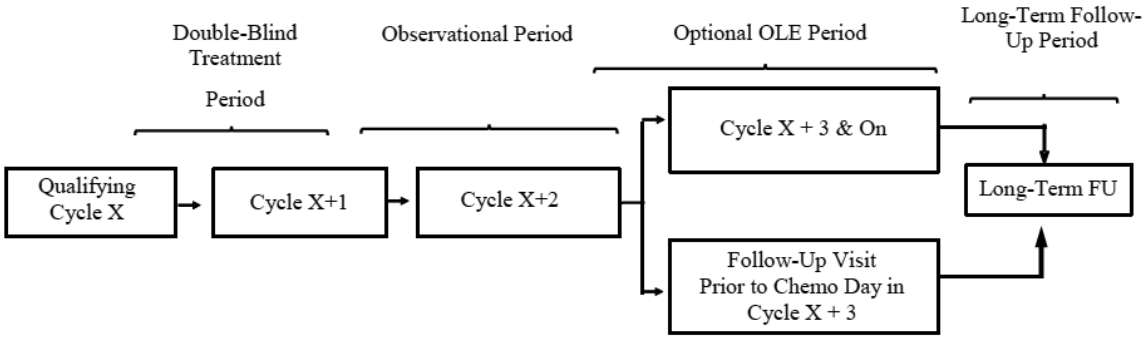
Figure 1. Study Design



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

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.

3.2.1 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.

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

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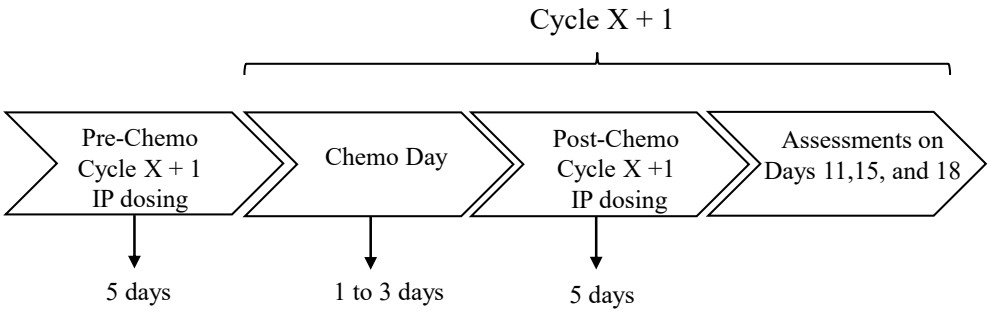
Figure 2. Treatment Schedule for Double-Blind Treatment Period



Chemo = chemotherapy; IP = investigational product.

3.2.2 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 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 (LTFU).

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.

3.2.3 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 do not meet any exclusion criteria for the optional OLE Period. Subjects must continue to fulfill the inclusion criteria and to not meet any 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 x 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.

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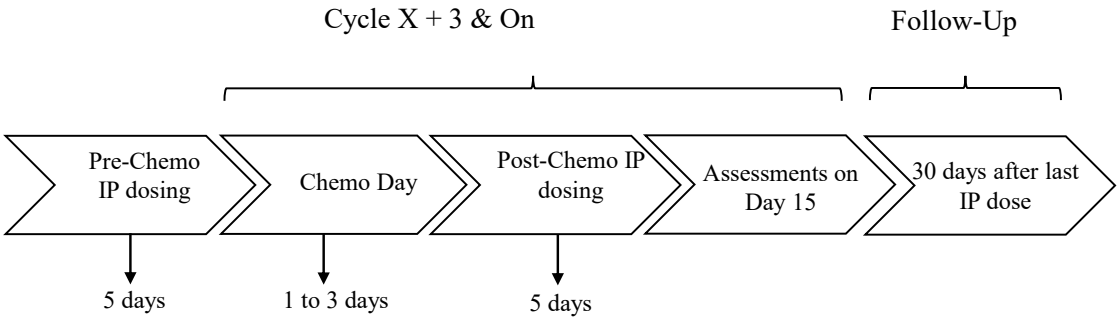
Subjects will have a Follow-Up Visit at 30 days (±3 days) after the last dose of IP treatment of the subject's last chemotherapy cycle.

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



Chemo = chemotherapy; IP = investigational product.

3.2.4 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 LTFU Period for documentation of vital status (if death occurred, record of date of death) and occurrence of secondary malignancies.

3.2.5 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 LTFU Period.

The study data will be cleaned and locked after the last subject finishes the Optional OLE Period. The study will then be unblinded and final analysis will be conducted. The data for LTFU Period will be reported once available.

3.3 Sample Size Justification

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

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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.

4. General Analysis Definitions

4.1 Study Period and Visit Window Definitions

4.1.1 Study Periods

The study periods are defined as follows:

Screening Period: Starting the day of signature of informed consent up to and including the day before randomization. For subjects who are not randomized, the screening period will end on the day the subject is determined to be a screen failure.

Double-Blind Period: Starting the day of randomization up to and including the day before the start of chemotherapy in Cycle X + 2.

Observational Period: Starting the first day of chemotherapy in Cycle X + 2 up to and including the day before the pre-chemotherapy IP administration of Cycle X + 3 (if entering the OLE period) or the day of the Follow-Up visit (if not entering the OLE period).

OLE Period: Starting the first day of the pre-chemotherapy IP administration of Cycle X + 3 up to and including the day of the Follow-Up visit in the OLE Period.

Long-Term Follow-Up Period (LTFU): Starting the day after the Follow-Up visit, up to and including a period of 5 years or death, whichever occurs first.

4.1.2 Visit Windows

No formal visit windowing will be conducted. For by-visit/by-cycle tabular summaries, the scheduled visits or actual chemotherapy cycles will be used in the analyses. The exception to this is for nadir platelet counts; both scheduled and unscheduled platelet counts will be considered for designation of the nadir value within a cycle.

For analyses considering the worst post-baseline grade (laboratory shift tables) or post-baseline liver tests, all post-baseline values will be considered.

4.2 Definition of Populations

The analysis and reporting of the data from this study will be performed using the following analysis populations:

4.2.1 Full Analysis Set (FAS)

The FAS will include all randomized subjects.

4.2.2 Per-Protocol Analysis Set (PPS)

The PPS will include the subset of subjects from the FAS who do not meet the criteria that would potentially impact the evaluation of the efficacy endpoints. A full list of the criteria will be finalized prior to database lock and unblinding. Examples of these criteria may include:

- Use of certain prohibited concomitant medications
- Selected Inclusion/Exclusion criteria not met for the Double-Blind period

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- Lack of compliance with study medication during the Double-Blind period
- Study Discontinuation resulting in an inability to assess the primary efficacy endpoint
- Assigned to incorrect treatment (mis-randomization) or receiving incorrect study medication

4.2.3 Safety Analysis Set (SAF)

The SAF will include all subjects who receive at least one dose of IP.

4.3 Data Handling Conventions

4.3.1 General Conventions

Data will be analyzed using SAS (Version 9.4 or later). Descriptive analyses will be performed on baseline, safety, and efficacy data.

Descriptive statistics will be tabulated as follows:

- Categorical data will be summarized in contingency tables presenting frequencies and percentages, and
- Continuous data will be summarized using number of non-missing values (n), mean, standard deviation, median, minimum, and maximum values.

4.3.2 Platelet Counts

Platelet counts are collected at local laboratories for eligibility and efficacy assessments. Platelet count is also included in the hematology panel sent to the central laboratory as a safety evaluation. For the efficacy analyses, only platelet counts assessed by the local laboratories will be included in the calculations and summaries. For the safety analyses, only platelet counts assessed by the central laboratory will be included in the summaries.

4.3.3 Definition of Study Day

The first day of study treatment with avatrombopag or placebo will be Study Day 1. There is no Study Day 0. The day before the first day of study treatment will be Study Day -1. If an event occurs on or after the first day of study treatment, Study Day will be calculated as (Date of Event - Date of first study treatment + 1). If the event occurs prior to the first day of study treatment, Study Day will be calculated as (Date of Event - Date of first study treatment).

4.3.4 Definition of Baseline

For data displays for the Double-Blind/Observational Period, a baseline value will be the last non-missing value taken prior to the start of study treatment in the Double-Blind Period, unless otherwise indicated. For the efficacy analyses of platelet count, baseline will be defined as the lowest platelet count collected during the qualifying period in Cycle X and prior to the first dose of study drug.

For data displays for the OLE Period, a baseline value is the last non-missing value taken prior to the start of the pre-chemotherapy IP of Cycle X+3, unless otherwise indicated. For the efficacy analyses of platelet count, baseline will be defined as the lowest platelet count collected during Cycle X+2 and prior to the pre-chemotherapy IP of Cycle X+3.

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For data displays for the entire study (avatrombopag group only), a baseline value will be the last non-missing value taken prior to the start of study treatment in the Double-Blind Period, unless otherwise indicated. For the efficacy analyses of platelet count, baseline will be defined as the lowest platelet count collected during the qualifying period in Cycle X and prior to the first dose of study drug.

4.3.5 Handling Missing Data

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.

For efficacy summaries where the proportion of responders meeting certain criteria is calculated, data will be presented in Yes, No, and Missing categories. In the statistical testing (e.g., CMH test), subjects in the Missing category will be treated as non-responders.

4.3.6 Partial Dates

For the purpose of inclusion of appropriate data records in the analysis, some partially missing dates will have date imputation performed. However, these imputations will be limited to table summaries; listings will retain the date as entered in the database. The following imputations will be performed:

Time since Primary Cancer Diagnosis: Prior to calculating this variable, missing month and day will be set to June 15th. If only day is missing, the day will be set to the 15th of the month. If a date is completely missing, no imputation will be performed.

Medications:

- If a start date is missing the day
  - Set to the 1st of the month
- If a start date is missing the day and month
  - Set to January 1st if study treatment began the year prior to the year of medication start
  - Set to January 1st if the medication is known to start in a year prior to study treatment
  - If the medication and the study treatment start the same year, the medication start date will be set to the study treatment start date.
- No medication end dates will be imputed
- No completely missing dates will be imputed. If, after imputation, it cannot be determined whether a medication was taken prior or concomitantly, it will be considered a concomitant medication.

In general, the assumptions about the missing or partially missing dates, when needed, are made conservative to avoid overestimation of treatment effect and underestimation of adverse effects.

4.3.7 Clinical Laboratory Values

Clinical laboratory values collected as below or above a limit of quantitation (e.g. containing "<" or ">" in the laboratory value) will be analyzed according to the numeric value associated with the ">" or "<" symbol.

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4.4 Treatment Groups

Data displays for the Double-Blind Treatment period/Observational period will have columns for avatrombopag 60 mg dose and placebo groups, unless otherwise specified. Data displays for the optional OLE period will have 3 columns: subjects randomized to avatrombopag 60 mg dose, subjects randomized to placebo, and a total column (all subjects in the optional OLE period receive avatrombopag 60 mg). Data displays for the entire study will include subjects randomized to avatrombopag 60 mg only.

Data listings will generally include Subject ID, Age/Sex/Race, and an indicator of whether the applicable record occurred during the Screening, Double-Blind, Observational, or OLE periods.

5. Study Patients

5.1 Disposition of Patients

Disposition will be summarized by treatment group and overall for the FAS population.

A summary table will include the total number of subjects screened and randomized. The number and percentage of subjects in each analysis set will be presented by treatment group.

The summary table will also contain the number and percentage of subjects who completed the Double-Blind/Observational period, discontinued the study during the Double-Blind/Observational period (along with reason), entered the OLE period, completed the OLE period, and discontinued the study during the OLE period (along with reason).

Details of "Other" reason for discontinuation will be included in a disposition listing.

A separate table summary and listing will also indicate the reasons subjects were screen failures for the Double-Blind period as well as the reasons subjects did not enter the OLE period.

5.2 Protocol Deviations

The number and percentage of subjects with major protocol deviations will be summarized by category by treatment group and overall for the FAS. Details of the major protocol deviations will be provided in a listing.

The number and percentage of subjects who are excluded from the PPS will be summarized by treatment group, along with reasons for exclusion. Subjects excluded from PPS will also be presented in a data listing.

5.3 Inclusion and Exclusion Criteria Not Met

Details of inclusion/exclusion criteria not met for subjects in the FAS will be provided in a listing. The listing will separately note whether the inclusion/exclusion criteria not met was for the Double-Blind period or for the OLE period.

5.4 Randomization

For subjects in the FAS, a listing will be provided which details randomization information (including treatment group, date/time, number of eligible

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chemotherapy agents) as collected in the Interactive Web Response System (IWRS), and kit number of the study drug assigned.

6. Demographic and other Baseline Characteristics

Demographics and Baseline Characteristics will be summarized for subjects in the FAS for the Double-Blind period. If necessary, summaries will be repeated for subjects in the PPS.

6.1 Demographics and Baseline Characteristics

Descriptive statistics with respect to subject characteristics at baseline will be displayed by treatment group for the FAS. The variables to be summarized are:

Demographics

- Age at enrollment (years)
- Age group at enrollment: <65 years, 65-<75 years, 75-<85 years, 85+ years
- Sex
- Race
- Ethnicity
- ECOG Performance Status
- Region (United States, Europe, China)

Baseline subject characteristics

- Height (cm)
- Weight (kg)
- Body Mass Index (BMI) (kg/m^2)
- Baseline platelet count ($10^9/L$) (defined as the lowest platelet count collected during the qualifying period in Cycle X and prior to first dose of study drug)
- Platelet count prior to study treatment start (i.e., the last platelet count collected prior to the first dose of study drug)
- Number of eligible chemotherapy agents recorded in IWRS

A listing of demographic and baseline characteristics will also be provided.

6.2 Medical and Surgical History

Medical and surgical history will be coded using the Medical Dictionary for Regulatory Authorities (MedDRA) version 23.0. The coding version may be updated prior to database lock if a newer version is available.

Medical and surgical history will be tabulated by MedDRA System Organ Class (SOC) and Preferred Term (PT) for the FAS. Subjects with more than one medical history event in a SOC or PT will only be counted once per SOC or PT.

Medical history details will also be provided in a data listing.

6.3 Oncology History

Descriptive statistics with respect to oncology history and cancer characteristics will be displayed by treatment group for the FAS. The variables to be summarized are:

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- Primary Cancer Diagnosis: Ovarian, Non-small cell lung cancer, Small cell lung cancer, Bladder cancer
- Stage (I, II, III, IV)
- Time since diagnosis (years), defined as (Date of randomization – Date of Diagnosis)/365.25
- Cycle length of current regimen: 21-day or 28-day
- Cycle of Chemotherapy at Study Entry, both continuous and categorical
- Prior Surgery for Current Cancer (Yes/No)
- Prior Radiation for Current Cancer (Yes/No)
- Prior Chemotherapeutic Regimens for Current Cancer (Yes/No) and number of prior chemotherapy regimens (1 or 2)
- Number of Eligible Chemotherapy Agents recorded on eCRF (1, 2, 3, or 4)

A listing of oncology history will be provided.

7. Prior and Concomitant Treatment

Prior and Concomitant medications will be classified according to the World Health Organization (WHO) Drug Dictionary (March 2020, B3). The coding version may be updated prior to database lock if a newer version is available. Medications will be coded per the Anatomical Therapeutic Classification (ATC). All medications will be documented from the time of informed consent up to the Follow-up visit.

Prior medications are those which start and stop before the first day of study treatment in the Double-Blind period. Concomitant medications for the Double-Blind/Observational period are those which start on or after the first day of study treatment and prior to the first dose of the study drug in the OLE period. A medication which begins before the start of study treatment in the Double-Blind period and continues into the Double-Blind period will be considered as concomitant for the Double-Blind/Observational period.

Concomitant medications for the OLE period are those which begin prior to the OLE period and continue into the OLE period or those which start on or after the first day of study treatment in the OLE period.

Tabular summaries will display the number and percentage of subjects with at least one medication in ATC Level 2 and preferred term categories and overall. Subjects who have taken a medication more than once will only be summarized once per ATC Level 2 or preferred term.

The tabular summaries to be provided are as follows:

- Prior Medications
- Concomitant Medications (Double-Blind/Observational period)
- Concomitant Medications (OLE period)
- Concomitant Medications taken as rescue for a bleeding event (Double-Blind/Observational period)
- Concomitant Medications taken as rescue for a bleeding event (OLE period)

An overall listing of medications will be provided. The listing will designate whether a medication is considered prior or concomitant. A separate listing will also be produced for concomitant medications taken as rescue for a bleeding event.

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A data listing for the concomitant radiation therapy procedures will also be provided.

Chemotherapy agents that the subjects received during Cycle X + 1 will be summarized by preferred name for FAS. The study chemotherapy data will also be provided in a data listing.

8. Efficacy Evaluation

All primary and secondary efficacy endpoints will be analyzed using the FAS.

8.1 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.

Chemotherapy Day is defined as the latest among Day 1 to 3 of the subject's chemotherapy regimen (eg, if chemotherapy is given on Day 1 and Day 2, Day 2 will be the Chemotherapy Day). For subjects whose chemotherapy is on an intermittent schedule (eg, Days 1, 8, 15), Day 1 will be the Chemotherapy Day.

If subjects had no post-chemotherapy IP dosing in Cycle X+1, the assessment period of the primary efficacy endpoint will start from the day after Chemotherapy Day in Cycle X+1 through Chemotherapy Day in Cycle X+2.

If subjects had any post-chemotherapy IP dosing in Cycle X+1, the assessment period of the primary efficacy endpoint will start from the day after post-chemotherapy IP dosing in Cycle X+1 through Chemotherapy Day in Cycle X+2.

If the information on platelet transfusion or chemotherapy dose reduction or delay is missing (eg, due to early drop-out), the subject will be treated as a non-responder in the primary analysis.

The primary efficacy endpoint will be tested between avatrombopag and placebo using the Cochran-Mantel-Haenszel (CMH) 2-sided test at α=0.05, adjusting for number of eligible chemotherapy agents as collected in the IWRS (1 or ≥2 permissible chemotherapy agents). The numbers and percentages of responders in each treatment group with the associated unadjusted exact (Clopper-Pearson) 95% CI, and the difference in proportion of responders between avatrombopag and placebo with the associated unadjusted exact (Clopper-Pearson) 95% CI will be calculated. The primary analysis will be performed based on the FAS and repeated on the PPS as a supportive analysis.

8.2 Secondary Efficacy Analysis

8.2.1 Secondary Efficacy Endpoints

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

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Duration of severe thrombocytopenia will be assessed as the total number of days with platelet count <50 x 10^9/L based on platelet counts taken from the day after the last post-chemotherapy IP in Cycle X + 1 through the Chemotherapy Day in Cycle X + 2. Platelet counts collected through the expected date of Cycle X+2 Chemotherapy Day (based on 21- or 28-day cycle length after Cycle X+1 Chemotherapy Day) or the end of study date, whichever is earliest, will be considered for this endpoint.

The days between a platelet count <50 x 10^9/L and a subsequent platelet count assessment will be assumed to show severe thrombocytopenia and contribute to the duration, and days between a platelet count ≥50 x 10^9/L and a subsequent platelet count within Cycle X+1 will not contribute to the duration. If a scheduled platelet count assessment is missing, it will be considered that the platelet count was <50 × 10^9/L at that visit.

- Change in platelet count from baseline (qualifying chemotherapy cycle [Cycle X]) (nadir) to Cycle X + 1 (nadir)

Change in platelet count from baseline is the difference between the lowest platelet value prior to the first dose of study treatment and the lowest value during Cycle X+1 (i.e., the lowest platelet value during the day after the last post-chemotherapy IP dose in Cycle X + 1 through the Chemotherapy Day of Cycle X + 2).

Multiple imputation methods using a "jump to control" procedure will be implemented to address missing Cycle X+1 (nadir). In this procedure, multiply imputed datasets will be produced using SAS PROC MI which assume that the subjects with missing Cycle X+1 (nadir) have platelet counts following a similar pattern of those subjects receiving placebo. The multiply imputed datasets are then combined using SAS PROC MIANALYZE to create a p-value for the assessment of the difference between avatrombopag and placebo groups in the mean change in platelet count from baseline. This p-value will be used in the hierarchical testing strategy defined in Section 8.2.2.

- 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

Subjects will be considered to NOT have major or non-major clinically relevant bleeding if no bleeding events were reported on the ISTH Non-surgical Bleeding Assessment CRF page that were classified as "Major Bleeding" or "Non-major clinically relevant bleeding" from the day after the last post-chemotherapy IP in Cycle X + 1 through the Chemotherapy Day in Cycle X+2. If information on the bleeding events is missing, subjects will be assumed to have had major or non-major clinically relevant bleeding during that period.

- 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

Subjects will be considered to have not required a platelet transfusion if subjects did not require a platelet transfusion after taking the last post-chemotherapy IP in Cycle X + 1 through the Chemotherapy Day in Cycle X + 2. If information on platelet transfusion is missing, subjects will be assumed to have had a platelet transfusion during that period.

The categorical variables (eg, proportion) will be summarized and analyzed in the same manner as the primary efficacy endpoint. If the data is sparse where the

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approximative methods cannot be applied, the Fisher's Exact test will be used instead.

For continuous variables (eg, change from baseline in platelet count, duration of severe thrombocytopenia), the normality assumption of an analysis of covariance will be evaluated analytically using the Shapiro-Wilk test and visually using the residual plot.

Plots will be created displaying platelet count values over time separately for the Double-Blind/Observational period, the OLE period, and the entire study.

8.2.2 Hierarchical Testing Strategy for 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 the following step-down closed testing procedure to maintain the family-wise Type I error rate at significance level α = 0.05 (2-sided):

- Step 1: Test the treatment effect at a significance 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 significance 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 significance 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 significance 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.

8.3 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 (i.e., subjects with the lowest platelet count <10, <25, <50, <75, <100, and ≥100 x 10^9/L at any time);

• Proportion of subjects achieving a pre-defined post-baseline maximum platelet count (i.e., subjects with the highest platelet count ≤400, >400, and >600 x 10^9/L at any time).

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Categorical variables (eg, proportion) will be summarized and analyzed in the similar manner as the primary efficacy endpoint. If the data is sparse where the approximative methods cannot be applied, the Fisher's Exact test will be used instead.

8.4 Sensitivity Analysis of Primary Efficacy Endpoint

The following sensitivity analyses will be performed for the primary efficacy endpoint:

- The difference in the proportion of responders between the avatrombopag and placebo groups will be tested using the Fisher's Exact test;
- The primary efficacy analysis will be repeated using the observed case, i.e. missing data will be excluded from the analysis.

8.5 OLE Period Efficacy Analysis

For the OLE period (start of pre-chemotherapy IP dosing of Cycle X+3 and onward), the following efficacy endpoints will be summarized descriptively for subjects randomized to avatrombopag and subjects randomized to placebo separately and overall:

- Proportion of subjects who meet the primary efficacy criteria (i.e., no platelet transfusion, no chemotherapy delay by ≥4 days due to thrombocytopenia, no chemotherapy dose reduction by ≥15% due to thrombocytopenia) overall and in each cycle
- Proportion of subjects who do not receive a platelet transfusion overall and in each cycle
- Proportion of subjects who do not have a chemotherapy dose reduction (≥15%) due to thrombocytopenia overall and in each cycle
- Proportion of subjects who do not have a chemotherapy delay (≥4 days) due to thrombocytopenia overall and in each cycle
- Proportion of subjects who do not have major or non-major clinically relevant bleeding overall and in each cycle
- Duration of severe thrombocytopenia (i.e., platelet count $<50 \times 10^9$/L) overall and in each cycle
- Actual and change from baseline values of platelet count in each cycle (nadir)

These analyses and summaries will be provided in a similar manner to the Double-Blind/Observational period.

Similar analyses and summaries will be provided for the entire study (Double Blind/Observational Period + OLE) for subjects randomized to avatrombopag 60 mg group only.

8.6 Subgroup Analyses

The primary efficacy analysis will be repeated for the following subgroups:

- Age (<65 years, 65-<75 years, 75-<85 years, 85+ years)
- Sex
- Race (White vs Non-White)
- Number of eligible chemotherapy agents (1 vs ≥2)
- Tumor type (ovarian cancer, lung cancer, bladder cancer)
- Previous chemotherapy regimens (0 vs 1 vs 2)
- Region (United States, Europe, China)

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8.7 Interim Analysis

No formal interim efficacy analysis is planned for this study. An independent Data Safety and Monitoring Board (DSMB) has been convened for this study to monitor safety on a periodic basis. A separate DSMB charter describes the scope of the DSMB's data review as well as rules governing the DSMB.

9. Safety Evaluation

Safety and tolerability will be assessed by examining exposure/treatment compliance, the incidence of adverse events, clinical laboratory parameters, vital signs, and other pertinent safety data using the SAF.

9.1 Exposure and Treatment Compliance

Exposure and treatment compliance will be separately summarized for the Double-Blind period, the OLE period, and the entire study.

The number of doses (both descriptively and categorically) will be summarized for each study period.

Treatment compliance during the relevant study period per subject will be calculated as (number of tablets taken/number of tablets expected)*100. The treatment compliance will be summarized descriptively and also presented categorically (e.g. number and percentage of subjects with <80%, 80-100%, and >100%). Number of tablets taken will be determined as the number of tablets dispensed minus the number of tablets returned that are recorded in the eCRF.

Duration of exposure (in days) will also be summarized descriptively per study period and computed as the last dose day – the first dose day +1. For the OLE period and entire study, duration will also be summarized by categories (≤10 days, 11-20 days, 21-30 days, 31-40 days, etc.)

The number and percentage of subjects receiving Cycle X+1 chemotherapy, Cycle X+2 chemotherapy, etc. will be summarized in the relevant study period tables.

A data listing will provide details of subject exposure for the Double-Blind, the OLE periods, and the entire study. Listings of study drug administration for the Double-Blind period and study drug accountability for the OLE period will also be provided.

9.2 Adverse Events

Adverse events (AEs) will be coded using MedDRA version 23.0. The coding may be updated according to newly released versions of the dictionary.

Severity of AEs is categorized according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.

For investigator determined relationship to study drug, AEs are classified as "Related" or "Not Related".

AEs leading to discontinuation of avatrombopag/placebo are AEs where action taken is designated as "Drug Withdrawn" in the eCRF.

Two categories for Adverse Events of Special Interest (AESI) will be summarized and are defined as:

1. Thromboembolic events - All adverse events with MedDRA PT belonging to SMQ 'Embolic and thrombotic events'

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2. Bleeding Events - MedDRA PT belonging to 2nd level SMQ 'Haemorrhage terms (excl laboratory terms)'

Tabular summaries of adverse events will be provided for the Double-Blind/Observational period, OLE period, and the entire study separately and will only include treatment-emergent adverse events (TEAE). TEAEs are defined as AEs occurring after the first dose of study treatment.

Listings will include all adverse events reported after the consent form is signed (both TEAE and non-TEAE). A flag will be included in the listings to designate whether an adverse event is treatment-emergent.

Overview summary tables by treatment group will include the number and percentage of subjects with at least one:

- TEAE
- TEAE related to study drug
- Serious TEAE
- Grade 3+ TEAEs
- TEAE leading to study drug discontinuation
- TEAE of special interest
- Deaths

Summary tables of TEAEs by System Organ Class (SOC) and Preferred Term (PT) will be provided for:

- TEAE (by SOC and PT and by descending frequency of PT)
- TEAEs related to study drug
- Grade 3+ TEAEs
- Serious TEAE
- TEAE of special interest
- TEAE leading to study drug discontinuation

Listings of all adverse events by treatment group will be provided and will include information such as the patient identifier, SOC, PT, reported term, date of onset/stop, duration of the event, TEAE, seriousness, severity, action taken, outcome, causality and relationship.

Listings of adverse events will be provided for the following categories:

- All Adverse Events
- AEs related to study drug
- Grade 3+ AEs
- Serious AEs
- AEs of special interest
- AEs leading to study drug discontinuation

A listing of deaths will be provided which will include any death details available in the eCRF.

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9.3 Clinical Laboratory Determination

Clinical safety laboratory assessments will include tests from the serum chemistry, hematology, and coagulation categories. Where applicable, laboratory values will be graded according to the NCI-CTCAE v5.0.

Local laboratories will be used to determine eligibility or when clinically needed; however, for the safety analysis of laboratory assessments, only laboratory values evaluated at a central laboratory will be used. Unless otherwise specified, all the summaries of the laboratory tests will be presented by the Double-blind period, OLE period, and entire study.

Shift tables of Baseline CTCAE grade to worst post-baseline CTCAE grade will be presented separately for gradable Hematology Parameters and Serum Chemistry Parameters. In the case of bi-directional toxicities, parameters will be presented separately (eg Calcium High, Calcium Low). For the purposes of tabulation, laboratory values which are not assigned NCI-CTCAE Grades 1, 2, 3, or 4 due to a toxicity will be assigned Grade 0 (within the normal range).

All laboratory data (including Hematology parameters, Chemistry parameters, Coagulation parameters, and pregnancy tests) will be included in separate laboratory listings.

A separate summary table for liver tests (ALT, AST, Alkaline Phosphatase, Direct Bilirubin, and Total Bilirubin) will be created. This table will indicate the number and percentage of subjects (presented by lab test) who have a highest post-baseline lab value for the test that is CTCAE Grades 1, 2, 3, or 4.

Observed values and changes from baseline for continuous Hematology and Serum Chemistry laboratory tests will be presented over time in box plots. Reference lines for the LLN and ULN will be included in the plots.

9.4 Other Safety Measures

9.4.1 Vital Signs

By-visit summary tables will be created displaying the observed values and changes from baseline for vital sign parameters, separately for the Double-Blind/Observational period and the OLE period.

A listing of all vital signs entered in the eCRF will also be provided.

9.4.2 ISTH Bleeding Information

A tabular summary of ISTH Bleeding Information will be provided and will include the number and percentage of subjects in the Double-Blind/Observational period, OLE period, and entire study who have experienced bleeding in the following categories: any bleeding, major bleeding, non-major clinically relevant bleeding, and minor bleeding.

A data listing of ISTH Bleeding information will also be provided which will include the criteria for major classification, major bleeding at a critical site, and non-major clinically relevant bleeding.

9.4.3 Blood Transfusions

A summary table will be created to display the frequency and percentage of subjects, separately for the Double-Blind/Observational period, OLE period, and

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entire study who have blood transfusions (yes/no). The type of blood product (Red Blood Cells, Platelets, Cryoprecipitate) will be summarized (subjects may appear in more than one category) and the reason for transfusion (Thrombocytopenia, Bleeding Event, Adverse Event other than Bleeding Event, Other) will be summarized (subjects may appear in more than one category). The total number of packs/units received per transfusion will be summarized as a continuous variable.

Details of any blood product transfusions occurring during the study will be presented in a listing.

9.4.4 ECOG Performance Status

The ECOG performance status will be presented in a listing.

9.4.5 Long Term Follow-Up (LTFU) Period

The number and percentage of subjects who entered (Yes vs No), completed (Yes vs No), and remain ongoing during the 5-year LTFU period will be summarized. The reasons for not entering the LTFU and the reasons for not completing the LTFU period will also be tabulated. The number and percentage of subjects who developed a secondary malignancy (Yes vs No), and the number and percentage of deaths occurring during the LTFU period along with the cause of death (if known) will be tabulated for all subjects who participated in the LTFU period. A data listing, with details of any secondary malignancies reported, will also be provided for all subjects in the LTFU period.

9.4.6 COVID-19 Impact

In April 2020, the eCRF was updated to add a page for collecting the extent to which study visits may have been affected by the COVID-19 global pandemic. This page collects a Yes/No answer of whether there was any impact. If the answer was yes, additional data as to the type of impact (Visit not done, Visit delay, Study drug not taken as planned, Study discontinuation, Lab sample collection, Study procedures, Other), visit impacted, cycle impacted, and description of impact were collected.

The details of the COVID-19 Impact will be presented in a listing.

9.5 Pharmacokinetics

A listing of drug concentrations from pharmacokinetic (PK) samples will be provided.

Further analysis relating to PK/PD modelling will be provided in a separate analytical plan.

10. References

International Conference on Harmonization (ICH) guideline "Statistical principles for Clinical trials": E9, 1998.

11. List of Tables, Listings, and Figures

A separate document will detail the list of the planned tables, listings, and figures for the final statistical analysis. The document will also include the mock tables, listings, and figures.

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Appendix A: Time and Events Schedule

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.

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b. Screening Visit 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 (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 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.

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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	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 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.

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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.

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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 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.