Statistical Analysis Plan

Protocol Title:	RECITE: A Phase 3 Randomized Placebo-controlled Double-blind Study of Romiplostim for the Treatment of Chemotherapy-induced Thrombocytopenia in Patients Receiving **Oxaliplatin**-based Chemotherapy for Treatment of Gastrointestinal, **Pancreatic** or Colorectal Cancer
Short Protocol Title:	Study of Romiplostim for Chemotherapy induced Thrombocytopenia in Adult Subjects with Gastrointestinal, **Pancreatic** or Colorectal Cancer
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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	**16 April 2019**	
v2.0	13 January 2020	• Updated based on protocol amendment 4. Key changes as follows o Adverse Events (CTCAE) version changed from 4.0 to 5.0 o End of Treatment visit renamed to follow-up o For subjects who discontinue investigational product prior to completing 3 cycles of chemotherapy, chemotherapy dose and schedule should be recorded through 3 on-study chemotherapy cycles to the end of the third on-study cycle. o Subjects will be contacted 30 (+5 days) after the last dose of the last on-study cycle of chemotherapy (up to 3 cycles) to collect adverse event, concomitant medication, urine pregnancy test information. o The study will be unblinded at the primary analysis. o Added sensitivity analysis to exclude subject(s) discontinued from treatment due to positive for neutralizing antibodies to romiplostim or TPO for primary endpoint. Treatment emergent adverse event definition split for primary and final analysis and its analysis modified to describe in detail.
v3.0	**12 January 2023**	• Updated based on protocol amendments 5, 6 & 7. Key changes as follows o Added new stratification factor variable o Added sensitivity analysis due to Coronavirus Disease 2019 (COVID-19) in section 9.5.1 o Missing data imputation for primary endpoint in section 8.3 is updated by

		considering COVID-19 epidemic during the trial conduct time. o Summary statistics analysis added to summarize COVID-19 missing data of investigational product. o Removed covariate parameter intent of treatment (curative, non-curative) because the Case Report Form (CRF) is collecting this data directly for prior surgery, but for prior anti-cancer therapy and prior radiotherapy this information is not available. Thus, classification of intention of treatment either as curative or non-curative is not possible by seeing the collected data. o Baseline CTCAE V5.0 grades for aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin is not derivable. Thus, cannot summarize shifts from baseline grades for these analytes and removed it from section 9.6.2. o Section (9.6.1) added for all available safety data by Data Monitoring Committee (DMC) o Study design updated: ▪ platelet count criteria updated for study day 1 from $<75 \times 10^9$/L to $\geq 85 \times 10^9$/L ▪ Pancreatic Cancer included ▪ Investigational product receiving time of subject updated from 7 – 18 week to 7-21 weeks o One interim analysis added approximately 81 subjects (50% of the planned sample size) completing three cycles of chemotherapy. o Protocol section 7.4.1.1 for the treatment responder and non-responder and dose modification for non-investigational products

		○ MedDRA version updated to 25.1 ○ Capitalization of notation in code fragment ○ Added the censoring rules for Andersen Gill Model and SAS code. ○ TEAE for Final analysis removed, and TEAE for Primary analysis modified to include the TEAE in primary and Final.
v4.0	**03 April 2023**	• **Table of contents updated.** ○ **Removed List of Tables from Table of contents – Which are not referred in this document (9-1 – 9-4)**

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List of Abbreviations

Abbreviation	Explanation
5-FU	5-fluorouracil
AC	Adjudication Committee
ADaM	Analysis Data Model
ADPC	Analysis dataset for pharmacokinetics concentrations
ALT	Alanine aminotransferase
AMQ	Amgen MedDRA query
AST	Aspartate aminotransferase
CIT	Chemotherapy-induced thrombocytopenia
CDISC	Clinical data interchange standards consortium
CMH	Cochran-Mantel-Haenszel
[redacted]	[redacted]
COVID-19	Coronavirus Disease 2019
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data monitoring committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
Electronic Source Data (eSource)	source data captured initially into a permanent electronic record used for the reconstruction and evaluation of a trial.
End of Study for Individual Subject	Excluding early termination of the study, the EOS visit for individual subjects will be defined as up to 2 weeks after the last subject in the trial completes their LTFU visit 1 year after the last dose of investigational product.
End of Study (EOS, primary completion)	defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s).
End of Study (end of trial)	defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable
End of Treatment Period (EOTP)	defined as the latest assessment date of the follow-up visit (7 days [$\pm$ 1 day] after the last dose of investigational product). If a subject does not complete an follow-up visit, then EOTP will be 7 days after the last dose of investigational product or the EOS date, whichever is earlier

FOLFOX	Oxaliplatin, 5-FU, leucovorin
GSO-DM	Global Study Operations-Data Management
[redacted]	[redacted]
IBG	Independent Biostatistics Group
ICH	International Council for Harmonisation
IP	Investigational product
LTFU	Long-term follow-up
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
SAP	Statistical analysis plan
SMQ	Standardized MedDRA query
Source Data	Information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
SSAP	Supplemental statistical analysis plan
TPO	Thrombopoietin
ULN	Upper limit of normal

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for study 20140346, Romiplostim dated **7/29/2021**. The scope of this plan includes **the interim analysis**, the primary analysis and the final analysis will be executed by the Amgen Global Biostatistical Science department unless otherwise specified [redacted]. Pharmacokinetics (PK) analyses will be provided by Department of Clinical Pharmacology and Modeling and Simulation.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• to evaluate the efficacy of romiplostim for the treatment of chemotherapy-induced thrombocytopenia (CIT) in patients receiving chemotherapy for the treatment of gastrointestinal, **pancreatic, or colorectal cancer, measured by the ability to administer on-time, full-dose chemotherapy**	• no thrombocytopenia-induced modification of any myelosuppressive treatment agent in the second and third cycles of the planned on-study chemotherapy regimen. • Thrombocytopenia-induced modifications include chemotherapy dose reduction, delay, omission, or chemotherapy treatment discontinuation due to platelet counts below 100 x 10^9/L
Secondary	
• to compare the treatment effect of romiplostim with that of placebo on the depth of platelet nadir	• the depth of the platelet count nadir from the start of the first on-study chemotherapy cycle through the end of the treatment period
• to compare the treatment effect of romiplostim with that of placebo on the time to first platelet response	• the time to first platelet response, defined by platelet count ≥ 100 x 10^9/L in the absence of platelet transfusions during the preceding 7 days
• to compare the treatment effect of romiplostim with that of placebo on the incidence of ≥ grade 2 bleeding events	• the duration-adjusted event rate of ≥ grade 2 bleeding events, as assessed by Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 grading scale

• to compare the treatment effect of romiplostim with that of placebo on overall survival	• overall survival
• to compare the treatment effect of romiplostim with that of placebo on the incidence of platelet transfusions	• platelet transfusion(s) during the treatment period
• to compare the treatment effect of romiplostim with that of placebo on the proportion of patients achieving platelet response	• achieving a platelet count $\geq 100 \times 10^9$/L at any time after study day 1 to week 4 (ie, 7 days after the planned third dose of investigational product) and in the absence of platelet transfusions during the preceding 7 days
• overall safety of romiplostim	• adverse events, including treatment-emergent adverse events, fatal adverse events, serious adverse events, and clinically significant changes in laboratory values. • anti-romiplostim antibodies and antibodies to thrombopoietin (TPO) • myelodysplastic syndromes and secondary malignancies

Exploratory
[redacted]

2.2 Hypotheses and/or Estimations

It is anticipated that romiplostim will raise platelet counts faster than placebo, resulting in more on-time and full-dose delivery of chemotherapy cycles in subjects with CIT and decreasing the incidence of platelet transfusions and bleeding events.

3. Study Overview

3.1 Study Design

This is a phase 3, randomized, placebo-controlled, multicenter, international study for the treatment of CIT in adult subjects receiving **oxaliplatin**-based chemotherapy for the treatment of gastrointestinal, **pancreatic**, or colorectal cancer. Subjects must have a platelet count **≤8**5 x 109/L on day 1 of the study. The study will consist of a screening period of up to 4 weeks, a treatment period long enough to allow for assessment of 3 planned cycles of chemotherapy, a follow-up visit, and long-term follow-up (LTFU). Given that subjects will be assessed for 3 planned cycles of chemotherapy, the **oxaliplatin**-based chemotherapy cycles are 2-**3** weeks in duration, and the investigational product dose adjustment guidelines allow for up to 12 weeks of dosing before a subject is declared a non-responder, the majority of study subjects will receive investigational product (IP) for a range of between 7-**21** weeks.

Once eligibility is confirmed, subjects will be randomized on day 1 of the study in a 2 to 1 ratio to receive either romiplostim or placebo, respectively. Randomization will be stratified by tumor type and by baseline platelet count ($< 50 \times 10^9$/L, $\geq 50 \times 10^9$/L). Baseline platelet count is defined as last platelet count measured prior to the time of the planned investigational product administration. Gastrointestinal cancers, including tumors of the esophagus or stomach, will be included in one stratum**, pancreatic cancers in a second stratum, and colorectal cancers, including adenocarcinomas of the colon or rectum, will be included in a third** stratum. Subjects will then enter the treatment period, during which time they will return to the clinic weekly for local platelet counts, undergo dose titrations as needed, and investigational product administration. If there are multiple platelet values performed on a study visit date, the platelet value from the test performed most immediately prior to the time of the planned investigational product and/or non-investigational product administration will be recorded as the platelet value for that study visit date and will be used to determine the subject's dose of investigational product and, when applicable, chemotherapy dose modifications which include dose reductions, delays, omissions, and discontinuations. Subjects will receive weekly subcutaneous injections of investigational product throughout the treatment period, starting at 2 μg/kg and increasing by

increments of 1 µg/kg to a maximum dose of 10 µg/kg to reach a target platelet count of ≥ 100 x 10^9/**L. Dose adjustment rules will be followed according to protocol Table 7-1. If the subject will be receiving concomitant chemotherapy on a study visit date, investigational product will be administered immediately after the completion of chemotherapy infusion on chemotherapy day 1. If continuous infusion 5 fluorouracil (5-FU) over 46-48 hours is part of the chemotherapy regimen the investigational product may be administered prior to beginning or during the continuous infusion 5-FU.**

Subjects will have a follow-up visit 1 week after the last dose of investigational product. Subjects will have their first in-clinic LTFU visit 30 (+ 5) days after the last dose of investigational product (Safety Follow-up 1). Subjects will be contacted 30 (+5 days) after the last dose of the last on-study cycle of chemotherapy (up to 3 cycles) to collect adverse event information except for females who are in addition required to come to clinic for a highly sensitive urine **or serum** pregnancy test (Safety Follow-up 2). Subjects will remain in LTFU until the last subject in the trial completes the LTFU visit 1 year after the last dose of investigational product. During the LTFU period, all subjects will be followed by phone or in clinic every 12 weeks (± 2 weeks) **from the last dose of investigational product** until the end of study (EOS) visit. All subjects should complete EOS visit up to 2 weeks after the last subject in the trial completes their LTFU visit 1 year after the last dose of investigational product.

During LTFU subjects will be followed for the diagnosis of, or progression to, secondary malignancies (including myeloid malignancies) or myelodysplastic syndromes, as well as vital status and cause(s) of death.

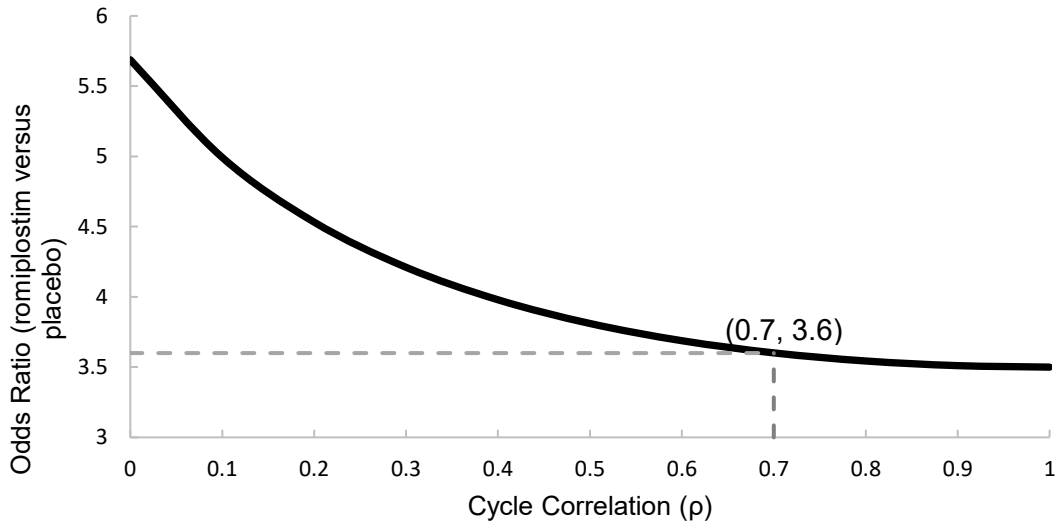
3.2 Sample Size

A sample size of 162 is chosen with 2:1 randomization ratio (108 romiplostim, 54 placebo), stratified by tumor type **(Gastrointestinal, Pancreatic, and Colorectal)** and baseline platelet count (< 50 x 10^9/L, ≥ 50 x 10^9/L). In two small studies (Al Samkari et al, 2018; Soff et al, 2017), few patients with CIT spontaneously recovered their platelet counts to adequate levels: 5 of 22 (23%) and 1 of 8 (13%), respectively. A phase 2 study showed 75% (24 out 32 subjects) subjects resumed chemotherapy after treatment with romiplostim (Soff et al, 2017). From retrospective reviews, between 65% (13 of 20 subjects) and 82% (18 of 22 subjects) subjects did not have any thrombocytopenia-induced chemotherapy dose modifications after treatment with romiplostim (Parameswaran et al, 2014; Al-Samkari et al, 2018).

Thrombocytopenia-induced chemotherapy dose modifications in one cycle may be correlated with the previous cycle outcome. Assume that p is the probability of receiving a planned on-study chemotherapy regimen with no thrombocytopenia-induced chemotherapy dose modifications in a cycle, ρ is the cycle correlation and the correlation is the same in romiplostim group and control group, the probability of receiving the planned chemotherapy regimen with no thrombocytopenia-induced chemotherapy dose modifications in two subsequent cycles, $p_{2,3}$ for Cycle 2 and 3, can be calculated as $p_{2,3} = p^2 + \rho p(1-p)$.

A higher cycle correlation is shown to be associated with a lower odds ratio of treatment effect for romiplostim vs control (Figure 3-1).

Figure 3-1. Relationship Between Cycle Correlation and Treatment Effect[a]



[a] Assume 30% and 60% probability of having no dose modifications in one cycle for placebo and romiplostim respectively.

From conservative considerations, probability of receiving the planned on-study chemotherapy regimen with no thrombocytopenia-induced chemotherapy dose modifications in one cycle for subjects treated in placebo group and romiplostim group is assumed to be 30% and 60% respectively, with a strong cycle correlation of 0.7 between two subsequent cycles. The odds ratio of having no thrombocytopenia-induced chemotherapy dose modifications in two cycles for romiplostim vs placebo is 3.6 (Figure 3-1).

The chosen sample size of 162 (108 romiplostim, 54 placebo) will provide 93% power to detect the treatment effect between the romiplostim group and the placebo group as defined in the

primary endpoint at a two-sided significance level of 0.05 using a Cochran-Mantel-Haenszel (CMH) test. Power calculations were performed in East version 6.4 using a 2-sided CMH test at significance level of 0.05 and stratification by tumor type and baseline platelet count (< 50 x 10^9/L, ≥ 50 x 10^9/L).

One interim analysis will be performed at approximately 81 subjects (50% of the planned sample size) completing three cycles of chemotherapy. The non-binding futility boundary is constructed using Lan-DeMets spending function with the O'Brien-Fleming approach. Assuming an observed 35% of subjects in the control arm with no thrombocytopenia-induced chemotherapy dose modification in one cycle, the power is estimated to be 84% at the interim analysis and the probability of stopping for futility is 2%.

4. Covariates and Subgroups

4.1 Planned Covariates

The following baseline characteristics are specified as potential confounding covariates:

- Stratification factor of tumor type (Gastrointestinal, **Pancreatic**, Colorectal) Stratification factor of baseline platelet count (< 50 x 10^9/L, ≥ 50 x 10^9/L)
- Age (continuous and categorized ≤ 65 years, > 65 years)
- Sex (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Region (United States, Europe, Rest of World)
- Body mass index
- ECOG (0–1, ≥ 2)
- Stage of disease (Stage 1 to 3, Stage 4 or recurrent disease)
- Line of chemotherapy treatment (1, ≥ 2)
- **Type of chemotherapy regimen (FOLFOX, FOLFIRINOX, FOLFOXIRI, CAPEOX)**
- Number of previous chemotherapy cycles (≤ 2, > 2)
- Prior or Concurrent Bevacizumab use (Yes, No)
- Baseline platelet count (continuous)
- Prior bleeding events (Yes, No)

- Prior platelet transfusions (Yes, No)
- Prior use of erythropoiesis-stimulating agent (Yes, No)
- Prior use of granulocyte colony-stimulating factor (Yes, No)
- Prior use of programmed cell death 1 inhibitors or programmed cell death ligand 1 inhibitors (Yes, No)
- Concurrent use of programmed cell death 1 inhibitors or programmed cell death ligand 1 inhibitors (Yes, No)

4.2 Subgroups

The study is not powered to draw conclusions from subgroup analyses. However, exploratory analyses will be conducted to examine the consistency of the treatment effect on the primary and key secondary endpoints. Subgroup analyses will be performed for the following covariates when each subgroup has at least 10% of the subjects in the analysis set:

- Sex (Male vs Female)
- Stage of disease (Stage 1 to 3, Stage 4 or recurrent disease)
- Prior or Concurrent Bevacizumab use (Yes, No)
- Number of previous chemotherapy cycles (≤ 2, > 2)
- **Type of chemotherapy regimen (FOLFOX, FOLFIRINOX, FOLFOXIRI, CAPEOX)**
- Baseline platelet count ($< 50 \times 10^9$/L, $\geq 50 \times 10^9$/L) (stratification factor)
- Tumor type (Gastrointestinal, **Pancreatic,** Colorectal) (stratification factor)

5. Definitions

Baseline

Baseline is defined as the value measured on the randomization date, i.e., study day 1. If measurement was not available on randomization date, the latest measurement before randomization date may be used.

Chemotherapy Cycle Status

Chemotherapy cycle status is information on whether a given on-study chemotherapy cycle was administered as planned or was modified, and the reason for modification. Chemotherapy modifications include dose reduction, dose delay, dose omission and treatment discontinuation.

Concurrent Use of Medication at Baseline

Concurrent use of medication at baseline means the medication has been administered on or after the start of the current chemotherapy regimen.

This derivation will be used to derive efficacy covariates variables of prior or concurrent bevacizumab use (Yes, No), prior use of erythropoiesis-stimulating agent (Yes, No), prior use of granulocyte colony-stimulating factor (Yes, No), prior use of programmed cell death 1 inhibitors or programmed cell death ligand 1 inhibitors (Yes, No), concurrent use of programmed cell death 1 inhibitors or programmed cell death ligand 1 inhibitors (Yes, No).

Duration-Adjusted Event Rate for Adverse Events (AE) during the Treatment Period

The duration-adjusted AE incidence rate within a treatment group is expressed as the number of events per 100 subject-years from the study day 1 until the date of last dose of investigational product plus 30 days or EOS, whichever is earlier:

$$\text{Duration-adjusted event rate} = \frac{\text{Total number of events}}{\text{Total duration in subject-years}} \times 100$$

Duration-Adjusted Event Rate for AE during the Follow-up Period

The duration-adjusted AE incidence rate within a treatment group is expressed as the number of events per 100 subject-years from the 31 days after the date of last dose of investigational product to EOS:

$$\text{Duration-adjusted event rate} = \frac{\text{Total number of events}}{\text{Total duration in subject-years}} \times 100$$

Endpoints: Primary - No Thrombocytopenia-induced Modification of any Myelosuppressive Treatment Agent in the Second and Third Cycles

Subjects will meet the criteria of the primary endpoint if there is no thrombocytopenia-induced modification of any myelosuppressive treatment agent in the second and third cycles of the planned on-study chemotherapy regimen.

A thrombocytopenia-induced modification is defined as any dose reduction, dose delay, dose omission, and/or early chemotherapy treatment discontinuation due to low platelet counts less than 100 x 10^9/L.

For the purposes of determining dose reductions, the actual on-study chemotherapy doses will be compared to the planned chemotherapy dose recorded on study day 1, defined by the dose administered in the chemotherapy cycle immediately prior to study entry.

For the purposes of determining dose delays, the difference between the start date of a given chemotherapy cycle and the start date of the chemotherapy cycle immediately prior to the given cycle will be calculated and compared to the planned cycle length of the regimen.

Delayed, reduced, omitted, and discontinued doses within a cycle will also be counted as dose modifications even if they do not cause the start of the next cycle to be delayed. Note: For subjects who discontinue investigational product prior to completing 3 cycles of chemotherapy, chemotherapy dose and schedule should be recorded through 3 on-study chemotherapy cycles to the end of the third on-study cycle.

An independent adjudicator will periodically verify the reason for chemotherapy dose reduction, dose delay, dose omission and treatment discontinuation during on-study cycles 1-3. For each planned chemotherapy agent, any dose delays, dose reduction, dose omission, and treatment discontinuation at any time during on-study cycle 2 or 3, where the adjudicated reason is thrombocytopenia, will be counted as failure in the primary endpoint analysis. Chemotherapy dose modification in the first cycle of the planned on study chemotherapy regimen will not be counted toward the primary endpoint even if due to CIT. If a chemotherapy dose modification occurs during on-study cycle 1 the new baseline for comparison will reset to the chemotherapy dose modifications that occurred in cycle 1. This will also apply to dose modifications occurring during on study cycle 2 that are not attributable to CIT**.**

Chemotherapy dose delays dose reductions, and dose omissions will be permitted according to chemotherapy dose modification outline in section 7.4.1.2 of the protocol.

Endpoints: Secondary (1) – Platelet Count Nadir from the Start of the First On-study Chemotherapy Cycle through the End of the Treatment Period

The platelet count nadir from the start of the first on-study chemotherapy cycle through the EOTP is defined as the lowest platelet count observed after the date of the earliest myelosuppressive chemotherapy agent delivered in the first on-study cycle through the EOTP day.

For subjects who never started the first on-study chemotherapy cycles or who never have platelet count measured after the first on-study chemotherapy cycle, the platelet count at baseline will be used for the endpoint.

Endpoints: Secondary (2) – Time to First Platelet Response

Time to first platelet response is defined as the number of days from study day **1** to the date of achieving a platelet count $\geq 100 \times 10^9$/L **in the absence of platelet transfusions during the preceding 7 days**. It is calculated as:

Date of first platelet response – study day **1** + 1.

If a platelet transfusion occurred during the 7 days preceding a platelet count then that platelet count will not be considered a response event if it is ≥ 100 x 10^9/L. Subjects who did not achieve a response event during the treatment period are censored at their last platelet count assessment date up to EOTP or at **randomization date** if they did not have any **post-baseline** platelet assessments.

Endpoints: Secondary (3) – Duration-adjusted Event Rate of ≥ Grade 2 Bleeding Events

The duration-adjusted event rate (**events**/100 subject-years) is defined **as** the number of grade ≥ 2 bleeding events, divided by the total duration (in 100 subject-years) that subjects have been on study from study day **1** to the earliest of last dose of IP + 30 days or EOS.

Bleeding events will be recorded on the adverse events case report form (CRF) and graded using the CTCAE version 5.0. Bleeding events will be identified using the narrow search of haemorrhages standardized MedDRA query (SMQ), using the MedDRA version 25.1 or later.

Abbreviations:

- **b.events = Bleeding Events (Haemorrhages)**
- **Status = 1 (recurrence of b.event)**
- **Status = 0 (no b.event)**

Censoring Rules:

- **Subject with at least one or more than one "grade ≥ 2 b.events"**
    - **Subject may report multiple b.events, each b.event will be flagged with "Status = 1".**
    - **Subject may report multiple b.events, if any b.event end date is missing then also "Status = 1".**
    - **The treatment period from last b.event start date to Min(last dose of IP date+30, Study End date) will be considered as no event period, reported as "Status = 0"**
- **The subjects who do not report any "grade ≥ 2 b.events"**
    - **These subjects will be included in analysis with "Status = 0".**

Notes:

Status variable will be assigned considering "Haemorrhages" SMQ only, irrespective of number of other adverse event(s) experienced by subject.

- **Status is the censoring variable which will be utilized into the PHREG.**

Endpoints: Secondary (4) –Overall Survival

Overall survival time will be calculated from study day 1 to death. Subjects who have not died will be censored at their last date of contact.

Endpoints: Secondary (5) – Platelet Transfusion

Platelet transfusions during the treatment period is defined as a subject having at least one platelet transfusion after during study period as recorded on the transfusions CRF.

Endpoints: Secondary (6) – Achieving a platelet count ≥ 100 x 10^9/L

Achieving a platelet count ≥ 100 x 10^9/L at any time after study day 1, up to and including the date of the week 4 visit (ie, 7 days after the third planned dose of investigational product). if a platelet transfusion occurred during the 7 days preceding a platelet count, then that platelet count will not be considered as achieving the endpoint even if it is ≥ 100 x 10^9/L. Subjects who have no platelet counts during this period will be considered as not achieving achieved a platelet count ≥ 100 x 10^9/L. For subjects who never received IP, the subjects are considered as not achieving a platelet count ≥ 100 x 10^9/L. Weeks with no platelet count measurements (missing data) are considered as not achieving a platelet count ≥ 100 x 10^9/L.

Endpoints: Secondary (safety) – Myelodysplastic Syndromes (MDS) Free Time

Myelodysplastic syndromes (MDS) free time is defined as the time from the first dose of IP to the first occurrence of MDS. Subjects who have not had an MDS event will be censored at their last contact date or death date, whichever is later.

It is calculated as:

Date of first occurrence of MDS or censoring date – the date of the first dose of IP + 1.

MDS events will be identified using the narrow search of myelodysplastic syndromes (SMQ), using the MedDRA version **25.1** or later available at the time of the analysis.

Endpoints: Secondary (safety) – Myelodysplastic Syndromes (MDS) Free Survival Time

MDS free survival time is defined as the time from the first dose of IP to the first occurrence of MDS or death, whichever is earlier. Subjects who have not had an MDS event and have not died will be censored at their last contact date. It is calculated as:

Date of first occurrence of MDS, death or censoring – the date of the first dose date of IP + 1.

MDS events will be identified using the narrow search of myelodysplastic syndromes (SMQ), using the MedDRA version **25.1** or later available at the time of the analysis.

Endpoints: Secondary (safety) – Secondary Malignancy Free Time

Secondary malignancy free time is defined as the time from the first dose of IP to the onset of a secondary malignancy. Subjects without an event will be censored at their last contact date or death, whichever is later. It is calculated as:

Date of onset of secondary malignancy or censoring – the date of the first dose IP + 1.

Endpoints: Secondary (safety) – Secondary Malignancy Free Survival Time

Secondary malignancy free survival time is defined as the time from the first dose of IP to the onset of a secondary malignancy or death, whichever is earlier. Subjects without an event will be censored at their last contact date. It is calculated as:

Date of onset of secondary malignancy, death or censoring – the date of the first dose date of IP + 1.

[redacted]

Last Contact Date

The latest date on which a subject is known to alive.

Myelosuppressive Treatment Agents

Myelosuppressive treatment agents are those agents in the on-study chemotherapy regimen that are 5-fluorouracil **or capecitabine and oxaliplatin (plus irinotecan in FOLFIRINOX or FOLFOXIRI)** (**Oxaliplatin**)-based chemotherapy regimen.

On-study Chemotherapy Regimens

The on-study chemotherapy regimen is the chemotherapy regimen planned to be taken after study day 1. It will be the same chemotherapy regimen taken in the last chemotherapy cycle immediately before study day 1.

Platelet Counts

If there are multiple platelet values performed on a study visit date, the platelet value most immediately prior to **non-IP** administration **will be selected**, as the platelet value for that study visit date. **If no platelet value prior to non-IP administration, the platelet value prior to IP administration will be selected.**

Prior Use of Medication at Baseline

Prior use of medication at baseline means the medication has been administered prior to the start of the current chemotherapy regimen.

Randomization Date

Randomization date is defined as the date the subject is randomized to a treatment group. Per protocol, subjects should initiate IP the same day they are randomized.

Study Day 1

Study day 1 is defined as the randomization date. **If the randomization date and the first IP administration date are the same, then study day 1 is the randomization date for both efficacy and safety analysis.**

If randomization date and subject first IP administration date are different then study day 1 will be derived using first IP administration date.

Study Day

For dates occurring on or after the study day 1 date, study day will be calculated as:

Date of interest **- date of first IP administration** + 1.

For dates occurring before the study day 1 date, study day will be calculated as:

Date of interest - **date of first IP administration**.

Treatment-emergent Adverse Event

Events categorized as AEs starting on or after first dose of investigational product as determined by "Did event start before first dose of investigational product" equal to "No" or missing on the Events eCRF; and up to and including 30 days after the last dose of investigational product (excluding events reported after End of Study date).

Any event which has started 30 days after the last dose of IP (i.e., during LTFU period) will not be considered as TEAE.

6. Analysis Sets

6.1 Full Analysis Set

The full analysis set will include all randomized subjects. All subjects will be analyzed according to the treatment to which they are randomized. Full analysis set will be used for all primary analysis for primary and secondary efficacy endpoints.

6.2 Safety Analysis Set

The safety population will include all randomized subjects who received at least 1 dose of investigational product. Subjects in the analyses based on the safety analysis set will be analyzed according to the treatment group corresponding to the actual treatment received.

[redacted]

6.4 Pharmacokinetic/Pharmacodynamic Analyses Set(s)

The PK Concentration Analysis Set will include all subjects who received at least 1 dose of investigational product and have at least 1 PK concentration available for analysis.

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

One interim futility analysis will be performed at approximately 81 subjects completing three cycles of chemotherapy. The primary endpoint, which is the proportion of subjects with no thrombocytopenia-induced chemotherapy dose modification in the second and third cycles of the planned on-study chemotherapy regimen, will be analyzed at the interim analysis. Dose

modification assessments will be based on the central review by the independent adjudication committee. The futility boundary for the primary endpoint is p-value of 0.438, which corresponds to an OR of 1.086. The study may be stopped for futility if the non-binding futility boundary is crossed.

Due to slow enrollment, there will be no enrollment pause during the interim analysis. An independent Data Monitoring Committee (DMC) will perform the futility analysis. The DMC will make recommendation to Amgen regarding the continuation of the study. The DMC will be supported by an independent biostatistics group which is responsible for preparing reports. Details regarding the responsibilities of the DMC and the independent biostatistics group will be described in the DMC Charter.

Records of all meetings will be submitted to the TMF per the DMC Charter and in accordance with SOP-427356. Further details are provided in the DMC charter.

The Data Access Plan (DAP) will be invoked if the DMC recommends early stopping for efficacy. The DAP Team will make the decisions on further conduct of the study and will decide on any further action which may include, for example, external communication to a regulatory agency, study team, unblinding, and/or changes to study conduct. Further details are provided in the DAP.

7.2 Primary Analysis

The primary analysis will be performed at the primary completion date. For this study, the primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint. Based on the definition above, the primary completion date is either the date when the status (information on whether a given on-study chemotherapy cycle was administered as planned, administered at a modified dose, delayed, omitted or discontinued) of the third cycle of the planned on study chemotherapy regimen is assessed on the last subject or the last subject ends the last dose of investigational product plus 30 days, whichever occurs later. The data that are collected up to the primary completion date will be cleaned and locked for the primary analysis purposes. The study will be unblinded at the primary analysis.

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date

when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

Outcomes from the endpoints and assessment below will be evaluated during the primary analysis:

- no thrombocytopenia-induced modification of any myelosuppressive treatment agent in the second and third cycles of the planned on-study chemotherapy regimen.
  Thrombocytopenia-induced modifications include chemotherapy dose reduction, delay, omission, or chemotherapy treatment discontinuation due to platelet counts below 100 x 10^9/L
- the depth of the platelet count nadir from the start of the first on-study chemotherapy cycle through the end of the treatment period
- the time to first platelet response, defined by platelet count $\geq$ 100 x 10^9/L in the absence of platelet transfusions during the preceding 7 days
- the duration-adjusted event rate of $\geq$ grade 2 bleeding events, as assessed by CTCAE version 5.0 grading scale

overall safety of romiplostim up to primary completion date

7.3 Final Analysis

When the last subject in the trial completes LTFU at 1 year after the last dose of investigational product, the final database will be locked for the final analysis. In the final analysis, the following secondary endpoints, assessment, and all the exploratory endpoints will be evaluated:

- overall survival
- platelet transfusion(s) during the treatment period
- achieving a platelet count $\geq$ 100 x 10^9/L at any time after study day 1 to week 4 (ie, 7 days after the planned third dose of investigational product) and in the absence of platelet transfusions during the preceding 7 days
- overall safety of romiplostim

8. Data Screening and Acceptance

8.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

8.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will receive and store all data to be used in the planned analyses. This study will use the database.

8.3 Handling of Missing and Incomplete Data

For primary analysis **on the thrombocytopenia-induced dose modification,** subjects with **complete missing visits (missing chemotherapy and none of the protocol specified assessments are performed) or partial visits (missing chemotherapy but some of the protocol specified assessments are performed) without platelet count assessment** for cycle 2 and/or cycle 3 are imputed as **having thrombocytopenia-induced dose modification in cycle 2 and/or cycle 3. Partial missing visits with platelet count assessment will be recorded following the dose modification rule in protocol section 7.4.1.2. Subjects with missing chemotherapy but having platelet count assessment within two days of the planned chemotherapy start or chemotherapy discontinuation will be determined by the adjudication committee.**

Potential **complete or partial missing or visits** missing assessments may result from below reasons:

- Death
- Early discontinuation of chemotherapy
- Consent withdrawal or lost to follow up

The rules for handling partial dates are described in Appendix B

8.4 Detection of Bias

Placebo subjects might drop out earlier than romiplostim subjects and we would detect this in our summary of disposition and IP exposure tables. Sensitivity analyses for the primary analysis specified in Section 9.5.1 address the potential of early drop out or discontinuation.

8.5 Outliers

Any suspected outliers will be investigated by the study team and will be included in the database unless determined to be an error or there is supporting evidence or explanation to justify the exclusion. Any outliers excluded from the analysis will be discussed in the Clinical Study Report (CSR), including the reasons for exclusion and the impact of their exclusion on the study

Pharmacokinetic (PK) [plasma] concentration data will be evaluated for outliers by visual inspection, and decisions to re-assay individual samples will be made in accordance with standard pharmacokinetic evaluation practice.

8.6 Distributional Characteristics

The statistical assumptions for analysis methods will be assessed. If the assumptions for the distributional characteristics are not met, these will be described and further analyses may be carried out using data transformations or alternative analysis methods. The use of transformations or alternative analysis methods will be justified in the final study report.

8.7 Validation of Statistical Analyses

Programs will be developed and maintained, and output will be verified in accordance with current risk-based quality control procedures.

Tables, figures, and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version 9.4 or later or using R.

9. Statistical Methods of Analysis

9.1 General Considerations

Continuous variables will be summarized descriptively by the n, mean, standard deviation, median, Q1 (25^{th} percentile), Q3 (75^{th} percentile), minimum, and maximum. The confidence interval and standard error for the mean will also be summarized for efficacy variables that are continuous. Categorical variables will be summarized descriptively by the number and percentage in each category. Missing values will be shown as a separate category. The confidence interval will also be summarized for dichotomous efficacy variables.

Time to event variables will be summarized with hazard ratios, Kaplan-Meier curves, Kaplan-Meier quartiles, the number of subjects at risk, the number of subjects censored, and the number of subjects with events.

Where confidence intervals are provided, these will be 2-sided at the 95% level, unless otherwise specified.

The primary efficacy endpoint will be compared between the romiplostim and placebo groups at the significance level of 0.05 using a 2-sided test. If statistical significance is achieved for the primary endpoint in favor of romiplostim, **the following secondary efficacy endpoints will be tested using a fixed sequence hierarchical testing procedure to control the family-wise Type I error rate below 2-sided 0.05 level. The family of hypotheses is ordered as follows:**

- the depth of platelet count nadir from the start of the first on-study chemotherapy cycle through the end of the treatment period
- the time to first platelet response, defined by platelet count ≥ 100 x 10^9/L, in the absence of platelet transfusions during the preceding 7 days.
- the duration-adjusted event rate of ≥ grade 2 bleeding events as assessed per CTCAE version 5.0 grading scale
- overall survival
- platelet transfusion(s) during the treatment period
- achieving platelet count ≥ 100 x 10^9/L at any time after study day 1 to week 4 (ie, 7 days after the planned third dose of investigational product) in the absence of platelet transfusions during the preceding 7 days

Starting with the hypothesis of platelet count nadir, if any null hypothesis in the sequence is rejected at a 2-sided significance level of 0.05, then the subsequent hypothesis will be tested; if any null hypothesis is accepted, then the subsequent hypotheses will not be tested.

Summary statistics without formal testing will be provided for other endpoints.

9.2 Subject Accountability

The number and percent of subjects who were randomized, received investigational product, completed investigational product, discontinued investigational product and reasons for discontinuing, completed study, discontinued study and reasons for discontinuing will be summarized by treatment group. The number of subjects screened will also be reported.

The number and percentage of subjects randomized will be tabulated by the stratification factor and also by country and study site within country. Key study dates for the first subject randomized, last subject randomized, and data cut-off date for analysis will be presented.

The number and percentage of subjects included in each analysis set (described in Section 6) will be presented.

Follow-up time (time from study day 1 to EOS or last contact date) will be summarized by treatment group at each analysis using descriptive statistic.

9.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's initial visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used during the course of the study. Eligibility deviations are defined in the protocol. **IPDs due to COVID-19 will be summarized separately.**

9.4 Demographic and Baseline Characteristics

The following demographics and baseline characteristics will be summarized by treatment group and overall using descriptive statistics for the FAS.

- The stratification factor of tumor type (gastrointestinal, **pancreatic,** colorectal)
- The stratification factor of baseline platelet count ($< 50 \times 10^9$/L, $\geq 50 \times 10^9$/L)
- Age (continuous and categorized $\leq$ 65 years, $>$ 65 years)
- Sex (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Region (United States, Europe, Rest of World)
- Body mass index
- Weight
- Height
- ECOG (0-1, $\geq$ 2)
- Stage of disease (Stage 3, Stage 4 or recurrent disease)
- Line of chemotherapy treatment ($<$ 2, $\geq$ 2)
- **Type of chemotherapy regimen (FOLFOX, FOLFIRINOX, FOLFOXIRI, CAPEOX)**
- Number of previous chemotherapy cycles ($\leq$ 2, $>$ 2)
- Dose of previous chemotherapy cycle before entering the study (Modified dose, Full dose)
- Prior or Concurrent Bevacizumab use (Yes, No)
- Baseline platelet count (continuous and categorized by CTCAE version 5.0 thrombocytopenia grade)
- Prior bleeding events (Yes, No)

- Prior platelet transfusions (Yes, No)
- Prior use of erythropoiesis-stimulating agent (Yes, No)
- Prior use of granulocyte colony-stimulating factor (Yes, No)
- Prior use of programmed cell death 1 inhibitors or programmed cell death ligand 1 inhibitors (Yes, No)
- Concurrent use of programmed cell death 1 inhibitors or programmed cell death ligand 1 inhibitors (Yes, No)

9.5 Efficacy Analyses

The efficacy analyses below will be conducted.

9.5.1 Analyses of Primary Efficacy Endpoint(s)

The primary endpoint is the proportion of subjects with no thrombocytopenia induced dose modification. **The primary analysis will be based on the adjudication committee (AC) assessment of thrombocytopenia-induced dose modification. The proportion along with a 95% CI will be provided for each treatment group**. A 2-sided CMH test will be used to compare groups controlling for the stratification factors of tumor type and baseline platelet count. The Mantel-Haenszel estimate of common odds ratio for romiplostim vs placebo will be estimated along with a 95% CI for each treatment group and the difference in proportions between treatment groups will be provided with a 95% CI.

For primary analysis, subjects with missing observations for cycle 2 and/or cycle 3, or who discontinued any myelosuppressive agent early, are considered as not meeting the criteria of the primary endpoint. The following sensitivity analyses will be explored:

A sensitivity analysis using the investigator's assessment on thrombocytopenia -induced dose modification will be performed. The number and percentage of subjects with concordant and discordant assessments per investigator and AC will be summarized.

If more than 10% of subjects in the full analysis set have COVID-19 related IPDs with missing chemotherapy without platelet count assessment for cycle 2 or cycle 3, a sensitivity analyses may be explored by excluding those subjects with COVID-19 related IPDs.

For each specified covariate in Section 4.1, sensitivity analyses will be conducted to evaluate any potential confounding: (1) a 2-sided CMH test checking conditional independence between treatment groups and primary endpoint outcomes controlling for each individual covariate, (2) a logistic regression with primary endpoint outcome as the dependent variable and explanatory variables from treatment group, the specified covariate, and interaction of treatment by covariate.

Subgroup exploratory analyses will also be performed to explore the consistency of the treatment effect between subgroups described in Section 4.2. FAS will be used for the primary endpoint analysis.

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

9.5.2.1 Depth of Platelet Count Nadir From the Start of the First On-study Chemotherapy Cycle Through the EOTP (1)

The depth of platelet count nadir after the start of the 1st on-study chemotherapy cycle through the EOTP will be summarized and compared between romiplostim and placebo group. Summary statistics will include n, mean, standard deviation, standard error, median, Q1, Q3, minimum, and maximum. Linear regression models will be used to compare the mean nadir between the romiplostim and placebo groups. Dependent variables will include the treatment group, the stratification factors of tumor type and baseline platelet count, and the interactions between treatment group and the stratification factor. FAS will be used for the all the secondary endpoint analyses.

The following sensitivity analyses will be explored for the endpoint if subjects never started the first on-study chemotherapy cycle or never have platelet count measured after the first on-study chemotherapy cycle:

(1) Impute platelet nadir using the lowest nadir value for the remaining subjects in the treatment group

(2) Impute platelet nadir using the lowest platelet count from baseline to the last platelet count assessment

(3) Impute platelet nadir using the mean nadir value for the treatment group

(4) Sensitivity analysis excluding the missing subjects

The normality assumption for linear regression models will be checked using a normal probability plot of the residuals and the Shapiro-Wilk (SK) test (Shapiro and Wilk 1965).

The following steps will then take place:

If the normal probability plot and the SK test show strong evidence against the normality assumption, log-transformation will be conducted. After the transformation, the normality will be checked again using the normal probability plot of the residuals and the SK test:

a. If the normality assumption holds after the log-transformation, linear regression models will be used on log-transformed variables to compare the mean nadir.

b. If the normality assumption does not hold after the log-transformation, the nonparametric van Elteren test will be used to compare the mean nadir.

9.5.2.2 Time to First Platelet Response (2)

A 2-sided log-rank test stratified by tumor type and baseline platelet count will be performed to determine whether time to first platelet response is significantly different between treatment groups. The hazard ratio of achieving platelet response for romiplostim vs placebo and its corresponding 2-sided 95% CI will be provided using a stratified Cox regression model.

Kaplan-Meier curves for the time to achieving first platelet response will be presented along with Kaplan-Meier rates and 2-sided 95% CIs at specified time points (week 3, week 4, etc) for each treatment group. In addition, Kaplan-Meier quartiles (median, 25th, and 75th percentiles) will be estimated with 2-sided 95% CI, if estimable.

9.5.2.3 Duration-adjusted Event Rate of ≥ Grade 2 Bleeding Events (3)

Duration-adjusted event rate of grade ≥ 2 bleeding events will be calculated as described in Section 5. The number of grade ≥ 2 bleeding events will be summarized for each treatment group. An Andersen-Gill model (Andersen and Gill, 1982) with a robust variance estimator (Lin and Wei, 1989), stratified by tumor type and baseline platelet count, will be used to analyze recurrent bleeding events and will provide hazard ratio with 95% CI and p-value comparing treatment groups (see Appendix A. Code Fragment for Andersen-Gill Model for sample SAS code).

9.5.2.4 Overall Survival (4)

A 2-sided log rank test stratified by tumor type will test differences of survival rates between the two treatment groups. A hazard ratio with 95% CI from a stratified Cox regression model will describe the treatment effect. The cause of death will be summarized for each treatment group.

9.5.2.5 Platelet Transfusion(s) During the Treatment Period (5)

The proportion of subjects with at least 1 platelet transfusion during the treatment period will be provided with a 95% CI for each treatment group and the difference in proportions between treatment groups will be provided with a 95% CI. A 2-sided CMH test will be used to compare groups controlling for the stratification factors of tumor type and baseline platelet count. The Mantel-Haenszel estimate of common odds ratio for romiplostim vs placebo will be estimated along with a 95% CI.

9.5.2.6 Achieving a Platelet Count ≥ 100 x 10^9/L at any Time After Study Day 1 to Week 4 (6)

The proportion of subjects achieving platelet count ≥ 100 x 10^9/L at any time after study day 1 to week 4 (ie, 7 days after the third planned dose of investigational product) in the absence of platelet transfusions during the preceding 7 days, will be provided with a 95% CI for each treatment group and the difference in proportions between treatment groups will be provided with a 95% CI. A 2-sided CMH test will be used to compare groups controlling for the stratification factors of tumor type and baseline platelet count. The Mantel-Haenszel estimate of common odds ratio for romiplostim vs placebo will be estimated along with a 95% CI.

[redacted]

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoint(s)

The Medical Dictionary for Regulatory Activities (MedDRA) version 25.1 or later will be used to code adverse events. The adverse events will be summarized by treatment group using the safety analysis set.

The subject incidence will be summarized for all **TEAE**s, serious **TEAEs**, **TEAEs** leading to withdrawal of investigational product, **TEAEs** leading to withdrawal of chemotherapy agent,

treatment-related TEAEs, serious treatment-related TEAEs, grade ≥ 3 **TEAEs**, and fatal **TEAEs by system organ class and preferred term**.

In addition, subject incidence and duration-adjusted rates for events of interest will be summarized. **Subject listing of all adverse events occurred from the first dose of IP to 30(+5) days after last dose of the IP or last dose of on-study chemotherapy (up to 3 cycles), whichever occurs later, will be provided. A separate listing will be provided for all the AEs (including AEs starting in LTFU period).**

An Independent Biostatistics Group (IBG) will perform periodic safety analyses for review by an independent DMC. DMC will review all available safety data on a regular basis during the study and will make recommendations concerning the continuation or alteration of the study based on its data review. More details are included in the DMC charter.

9.6.2 Laboratory Test Results

The analyses of **key** safety laboratory endpoints will include summary statistics at selected time points by treatment group. Shifts in grades of safety laboratory parameters from baseline to worst post-baseline value for select blood chemistry analytes (albumin, creatinine**, total bilirubin) and hematology analytes (hemoglobin, white blood cells (WBC) count, platelet count, absolute neutrophil count) will be tabulated by treatment group.**

In addition, a summary of potential hepatoxicity by Hy's Law will also be tabulated (the criteria is defined as AST or ALT > 3 times upper limit of normal (ULN), total bilirubin > 2 times ULN, and alkaline phosphatase < 2 times ULN assessed within 7, 14 and 28 days).

9.6.3 Vital Signs

The analyses of vital signs **parameters of systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature** will include summary statistics at selected time points by treatment group.

Shifts in ECOG performance status scores between baseline and each post-baseline assessment will be tabulated by treatment group.

9.6.4 Electrocardiogram

The electrocardiogram (ECG) measurements from this clinical study were performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QT interval corrected (QTc) effect. Because these evaluations may not necessarily be performed under the rigorous conditions expected to lead to

meaningful evaluation of QTc data; neither summaries nor statistical analyses will be provided, and these data would not be expected to be useful for meta-analysis with data from other trials.

9.6.5 Antibody Formation

The number and percentage of subjects who develop anti- romiplostim and anti-TPO antibodies (binding and if positive, neutralizing) at any time will be tabulated by treatment group.

The week 1 baseline antibody sample will be obtained before the first administration of investigational product. Antibody samples will assess safety, development of binding and neutralizing antibodies to romiplostim and the potential to bind to endogenous TPO

9.6.6 Exposure to Investigational Product

The duration of investigational product exposure, cumulative dose, average weekly dose, most frequently received dose, minimum dose, and maximum dose will be summarized using descriptive statistics.

In addition, number and percentages of dose reduction, delays, and omission with reasons will be summarized by treatment group. **Missing visits due to COVID-19 will be summarized.**

9.6.7 Exposure to Other Protocol-required Therapy

The number and percentage of subjects receiving each chemotherapy agent, the number of chemotherapy cycles received, and the number and percentage of dose reductions, dose delays, and doses omitted (withheld) will be summarized by treatment group.

9.6.8 Exposure to Concomitant Medication

The number and proportion of subjects receiving concomitant medications will be summarized by preferred term for each treatment group as coded by the World Health Organization Drug (WHO DRUG) dictionary.

9.7 Other Analyses

The number and percentage of subjects who experience an event will be tabulated for each of the following endpoints: myelodysplastic syndromes and secondary malignancies (including progression from myelodysplastic syndrome to acute myeloid leukemia). In addition, Kaplan-Meier curves and hazard ratios between treatment group with 95% CIs will be calculated for myelodysplastic syndrome free time (censor at death), myelodysplastic syndrome free survival time (consider death an event), secondary malignancy free time (censor at death), and secondary malignancy free

survival time (consider death an event). These analyses will be summarized by treatment group using the safety analysis set.

9.7.1 Analyses of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoints

The Clinical Data Interchange Standards Consortium (CDISC) Analysis Data Model (ADaM) standard will be adopted to create the Analysis Dataset for Pharmacokinetics Concentrations (ADPC). The ADPC dataset includes the following variables: 1) subject level information (eg., subject ID, country, planned treatment, actual treatment received, population flags); 2) PK variables (eg., concentration, actual and scheduled PK sampling time); 3) Dosing variables (eg., planned and actual dose(s), start time, stop time and duration of drug infusion, time relative to first infusion start); 4) Physical measurement variables (eg., demographics, selected baseline characteristics and laboratory measurements) and 5) Miscellaneous variables (eg., study specific variables). The pharmacokinetic analysis will be carried out for PK analysis set.

[redacted]

10. Changes From Protocol-specified Analyses

There are no changes to the protocol-specified analyses.

11. Literature Citations / References

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Van Elteren PH. "On the Combination of Independent Two-Sample Tests of Wilcoxon." *Bulletin of the International Statistical Institute* 1960;37:351–361.

12. Data Not Covered by This Plan

Further analyses of pharmacokinetic or Pharmacokinetic/Pharmacodynamic endpoints, [redacted]

13. Appendices

Appendix A. Code Fragment for Andersen-Gill Model

Duration adjusted bleeding event (Andersen-Gill Approach):

- K is strata for tumor type
- J is strata for baseline platelet count
- Tstart is time of the (k-1) recurrence for visit = k, or the entry time 0 if visit = 1, or the follow-up time if the (k-1) recurrence time does not occur
- Tstop is time of the kth recurrent if visit = k or follow-up time if the kth recurrence does not occur
- Status is bleeding status of Tstop (1=recurrence and 0=censored)
- txgrp is the treatment group variable:
  - active
  - placebo

```
PROC PHREG covs(aggregate);

Class J K txgrp;

MODEL (Tstart,Tstop)*Status(0)=Txgrp / ties=efron;

Strata K J;

Id usubjid;

Run;
```

Appendix B. Handling of Dates, Incomplete Dates and Missing Dates

Imputation Rules for Partial or Missing Start Dates

The reference date for the following rules is the date of first dose[of study drug].

Start Date		Stop Date						
		Complete: *yyyymmdd*		Partial: *yyyymm*		Partial: *yyyy*		Missing
		< 1st dose	≥ 1st dose	< 1st dose *yyyymm*	≥ 1st dose *yyyymm*	< 1st dose *yyyy*	≥ 1st dose *yyyy*	
Partial: *yyyymm*	= 1st dose *yyyymm*	2	1	n/a	1	n/a	1	1
	≠ 1st dose *yyyymm*		2	2	2	2	2	2
Partial: *yyyy*	= 1st dose *yyyy*	3	1	3	1	n/a	1	1
	≠ 1st dose *yyyy*		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1=Impute the date of first dose; 2=Impute the first of the month; 3=Impute January 1 of the year; 4=Impute January 1 of the stop year

Note: Note: If the start date imputation leads to a start date that is after the stop date, then do not impute the start date.

Imputation Rules for Partial or Missing Stop Dates

Initial imputation

- **If the month and year are present, impute the last day of that month.**
- **If only the year is present, impute December 31 of that year.**
- **If the stop date is entirely missing, assume the event or medication is ongoing.**

If the imputed stop date is before the start date, set stop date to missing.

If the imputed stop date is after the death date, impute as death date.

Death Dates, Secondary Malignancy Onset Dates, and MDS Onset Dates

If death/malignancy/MDS year and month are available but day is missing:

- If mmyyyy for last contact date = mmyyyy for death/malignancy/MDS date, set death/malignancy/MDS date to the day after the last contact date or EOS date, whichever occurs first.
- If mmyyyy for last contact date < mmyyyy for death/malignancy/MDS date, set death/malignancy/MDS date to the first day of the death/malignancy/MDS month.

- If mmyyyy for last contact date > mmyyyy for death/malignancy/MDS date, data error and do not impute.

If both month and day are missing for death/malignancy/MDS date or a death / malignancy / MDS date is totally missing, do not impute.