**Title Page**

| | | |
|---|---|---|
| **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 |
| **Protocol Number:** | | 20140346 |
| **Investigational Product:** | | Romiplostim |
| **Trade Name:** | | Nplate® |
| **Sponsor** | **Name of Sponsor:** | Amgen Inc. |
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| | **Amendment 7** | **29 July 2021** |
|---|---|---|
| **Version/Date:** | **Data Element Standards Version** | **Date** |
| | 5.0 | Not applicable |

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**Investigator's Agreement:**

I have read the attached protocol entitled 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, dated **29 July 2021** agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), Declaration of Helsinki, and applicable national or regional regulations/guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by: me (including, if applicable, my spouse or legal partner and dependent children) and my sub investigators (including, if applicable, their spouses or legal partners and dependent children) at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

_____
Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

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## 1. Protocol Synopsis

**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

**Study Phase:** 3

**Indication:** Chemotherapy-induced thrombocytopenia

**Rationale**

This trial is designed to study romiplostim for the treatment of chemotherapy-induced thrombocytopenia (CIT) in patients receiving oxaliplatin-based chemotherapy regimen**s** for the treatment of gastrointestinal, pancreatic, or colorectal adenocarcinoma, which includes cancers of the esophagus, stomach, colon, pancreas, or rectum. This is a randomized, double-blind, placebo-controlled trial to study the safety and efficacy of romiplostim in this patient population. Current management of CIT includes platelet transfusions, chemotherapy dose delays and/or dose reductions, and in the United States (US), oprelvekin (Neumega®) (Neumega® Package Insert, 2011). However, due to its side effect profile, oprelvekin is rarely used in the clinical setting and it is no longer available from the manufacturer. Platelet transfusions are often reserved for patients with severe thrombocytopenia (platelet counts $< 10 \times 10^9$/L) (Kuter, 2015). Chemotherapy dose delays and dose reductions are the most commonly utilized measures for managing CIT; however, these measures lead to a reduction in chemotherapy relative dose intensity (Denduluri et al, 2015; Lyman et al, 2003). Therefore, an unmet need exists for alternative treatment options for CIT. A recent investigator-sponsored study, using a weekly romiplostim dosing schedule, provided evidence of efficacy in the treatment of CIT in patients with solid tumors (Soff et al, 2017). The dosage, administration, and schedule selected for study were derived from the results of Amgen's studies, as well as data reviewed from studies using romiplostim for the treatment of CIT (Al-Samkari et al, 2018, Soff et al, 2017). In these studies, weekly subcutaneous administration of romiplostim at a dose 2 µg/kg was identified as the dose level which not only enables the doubling of platelet count in healthy subjects, but could be an efficacious dose for patients with CIT (Wang, 2004).

## Objectives/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 ≥ 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 | • adverse events, including treatment-emergent adverse events, fatal adverse events, serious adverse events, and clinically significant changes in laboratory values.<br>• anti-romiplostim antibodies and antibodies to thrombopoietin (TPO)<br>• myelodysplastic syndromes and secondary malignancies |

**Hypotheses**

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.

**Overall Design**

This is a phase 3, randomized, placebo-controlled, multicenter, international study for the treatment of CIT in adult subjects receiving an oxaliplatin-based chemotherapy regimen for the treatment of gastrointestinal, pancreatic, or colorectal cancer. Subjects must have a platelet count **≤ 8**5 x $10^9$/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 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 x $10^9$/L, ≥ 50 x $10^9$/L). Baseline platelet count is defined as platelet count measured most 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 tumors 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. 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 **V**isit 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.

**Number of Subjects**

The study will enroll approximately 162 subjects with CIT and receiving an oxaliplatin-based chemotherapy regimen for the treatment of gastrointestinal, pancreatic, or colorectal cancer. Subjects will be stratified based on their tumor type and baseline platelet count into 1 of 2 arms (placebo or romiplostim).

**Summary of Subject Eligibility Criteria**

This study will enroll adults ≥ 18 years of age with histologically or cytologically confirmed diagnosis of gastrointestinal, pancreatic, or colorectal adenocarcinoma, defined as cancer of the esophagus, stomach, pancreas, colon, or rectum, who are currently receiving **(or plan to receive)** a chemotherapy regimen containing 5-FU or capecitabine and oxaliplatin (plus irinotecan in FOLFIRINOX or FOLFOXIRI). Use of an oxaliplatin-based combination regimen is permitted with (1) anti-angiogenic agents (such as bevacizumab) or (2) targeted therapy (such as anti-epidermal growth factor agents).

Tumor stage will not affect eligibility. Subjects must have at least 3 remaining planned cycles of chemotherapy at enrollment. Subjects must have a platelet count **≤ 8**5 x $10^9$/L on day 1 of the study.

For a full list of eligibility criteria, please refer to Section 6.1 to Section 6.2.

**Treatments**

Amgen investigational product (romiplostim or placebo) will be administered in the clinic by a qualified healthcare provider as a subcutaneous injection. The starting dose of investigational product will be 2 µg/kg based on the subject's recorded screening weight. Subjects will return to the clinic every 7 days (± 1 day) to provide platelet counts and undergo dose titrations under the supervision of the treating physician. 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. Weekly dose increases will continue in increments of 1 µg/kg up to a maximum dose of 10 µg/kg in an attempt to reach a target platelet count of ≥ 100 x $10^9$/L.

Non-Amgen, non-investigational chemotherapeutic agents should not be administered until platelet counts are ≥ 100 x $10^9$/L, or until **at least** week 4 **(see Section 7.4.1.2)**, whichever occurs first. **Do not start the first cycle of on-study chemotherapy before study week 2.** The start of the planned chemotherapy must be no more than 2 days after the local laboratory assessments have been taken **during the study visit.** Thereafter, chemotherapy agents will be administered for the treatment of gastrointestinal, pancreatic, or colorectal cancer according to chemotherapy dose modification guidelines outlined in Section 7.4.1.2.

**Procedures**

Written informed consent must be obtained from all subjects before any study-specific screening procedures are performed. At specified visits, outlined in the Schedule of Activities (Table 2-1), subjects will undergo physical exams with measurements of vital signs (including respiratory rate, heart rate, blood pressure, and temperature), height (screening only) and weight (screening only), Eastern Cooperative Oncology Group (ECOG) status, electrocardiogram (ECG), disease status assessment, recording of concomitant medications, chemotherapy administered, and incidence of platelet

transfusions, as well as review of adverse events and serious adverse events. Blood will be collected for laboratory testing including complete blood counts with differential, blood chemistry profiles, anti-TPO and anti-romiplostim antibodies. Platelet counts, prothrombin time (PT), partial thromboplastin time (PTT), and International Normalized Ratio (INR) will **also** be collected. 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. Local laboratory assessments taken during the study visit (± 1 day) and recorded in the case report form (CRF) must be the same values as used for investigational product dose calculations and chemotherapy dose modifications where applicable. Hemoglobin will be collected locally on day 1 only. Absolute neutrophil counts will be collected locally weekly through safety follow-up (SFU) 1. Additionally, in females of childbearing potential a urine or serum pregnancy test will be performed locally. [redacted]

For a full list of study procedures, including the timing of each procedure, please refer to Section 9.2 and the Schedule of Activities in Table 2-1.

**Statistical Considerations**

General Approach:

The study will have an overall alpha of 0.05 with 2-sided testing. To preserve the overall significance level, statistical testing of the primary and secondary efficacy endpoints will follow a hierarchical structure. If romiplostim demonstrates superiority to placebo for the primary endpoint, then the first secondary endpoint will be tested and so on until an endpoint is not significant or the last secondary efficacy endpoint has been tested.

Sample Size Considerations:

One-hundred and sixty-two subjects will be randomized in the study with 2:1 randomization ratio (108 subjects to romiplostim, 54 subjects to placebo). The study has 93% power for the primary endpoint (assuming subject incidence rates of the primary endpoint for placebo and romiplostim of 30% and 60%, respectively).

**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%.**

Analysis of Primary Endpoint:

The treatment effect with respect to the incidence of no thrombocytopenia-induced dose modification will be tested with a 2-sided Cochran-Mantel-Haenszel test that will adjust for the stratification factors at randomization. In addition, the percentage of subjects in each treatment group with no thrombocytopenia-induced chemotherapy dose modification will be summarized with an exact binomial 95% CI.

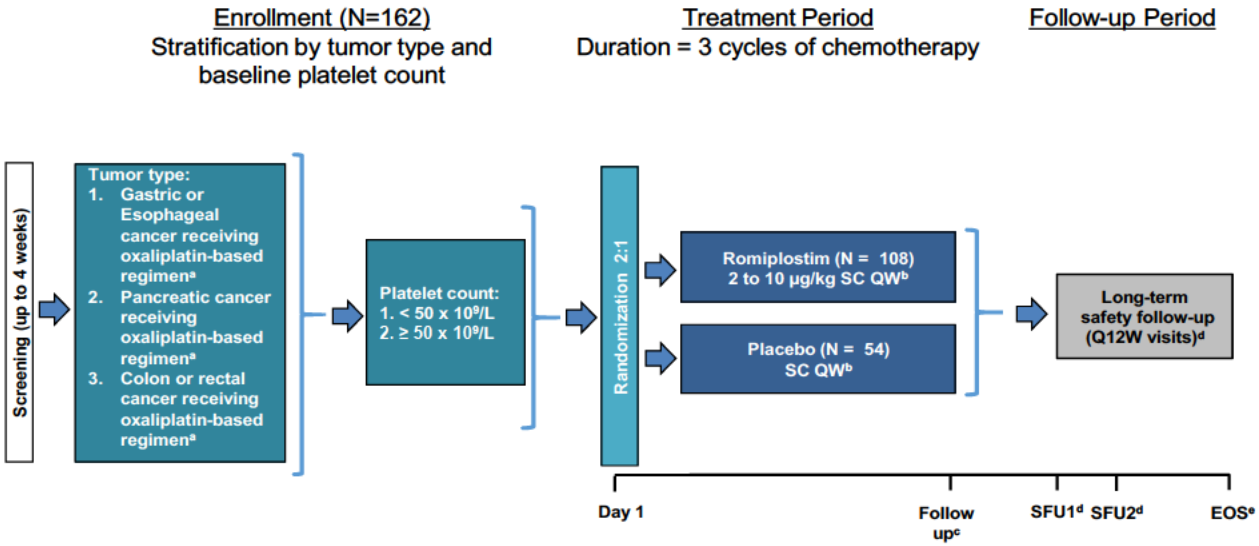
For a full description of statistical analysis methods, please refer to Section 10.

Sponsor Name: Amgen Inc.

# 2. Study Schema and Schedule of Activities

## 2.1 Study Schema

**Figure 2-1. Study Schema**




Footnotes defined on the next page

CRC = colorectal cancer; EOS = end of study; GI = gastrointestinal; IP = investigational product; LTFU = long-term follow-up; QW = once weekly; Q12W = every 12 weeks; SC = subcutaneous, SFU = safety follow-up.

[a] Subject randomization will be stratified by tumor type and baseline platelet count (< 50 x $10^9$/L, ≥ 50 x $10^9$/L) measured on study day 1. GI cancers, including tumors of the esophagus and stomach, will be included in one stratum, pancreatic cancers in a second stratum, and CRC, including tumors of the colon or rectum, will be included in a third stratum.

[b] Subjects will receive weekly IP dosing, 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. Non-Amgen, non-investigational chemotherapeutic agents will be administered for the treatment of primary malignancy according to chemotherapy dose modification guidelines outlined in Section 7.4.1.2.

[c] Treatment period will be long enough to allow for assessment of 3 planned cycles of chemotherapy. The follow-up visit will occur 1 week after the last scheduled dose of investigational product.

[d] Subjects will have their first **in-clinic** LTFU **V**isit at 30 (+5) days after the last dose of investigational product (SFU 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 (SFU 2). In addition, after the first LTFU **V**isit, all subjects will be followed by phone or in clinic every 12 weeks (± 2 weeks) **from the last dose of investigational product** until the EOS. 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. Note: 30 (+5) days after the last dose of IP (Safety Follow-up 1) may not necessarily coincide with 30 days after the last dose of on-study cycle of chemotherapy (Safety Follow-up 2).

[e] All subjects should complete EOS **V**isit up to 2 weeks after the last subject in the trial completes the LTFU Visit 1 year after their last dose of IP.

## 2.2 Schedule of Activities

**Table 2-1. Schedule of Activities**

| Procedures | Screening | Treatment Period[a] | | | | | | | | | | | | | | Follow up[b] | LTFU[c] | | | EOS[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| STUDY WEEK | Up to 28 days | 1[e] | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | QW[f] | Q4W[g] | 1 week after last dose of IP | SFU 1 (30 days after last dose of IP) | SFU 2 (30 days after last dose of on-study cycle of chemotherapy) | Q12W | |
| Window (days) | | | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | +5 | +5 | ±2 wks | +2 wks |
| **General assessments** | | | | | | | | | | | | | | | | | | | | |
| Informed consent | X | | | | | | | | | | | | | | | | | | | |
| Eligibility criteria | X | | | | | | | | | | | | | | | | | | | |
| Demographics, medical and surgical history, and prior therapies | X | | | | | | | | | | | | | | | | | | | |
| Physical exam and vital signs | X | X | X | X | X | | | | X | | | | X | | X | X | | | | |
| Height | X | | | | | | | | | | | | | | | | | | | |
| Body weight | X | | | | | | | | | | | | | | | | | | | |



Footnotes are defined on the last page of the table.

## Table 2-1. Schedule of Activities

| Procedures | Screening | Treatment Period[a] | | | | | | | | | | | | | | Follow up[b] | LTFU[c] | | | EOS[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| STUDY WEEK | Up to 28 days | 1[e] | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | QW[f] | Q4W[g] | 1 week after last dose of IP | SFU 1 (30 days after last dose of IP) | SFU 2 (30 days after last dose of on-study cycle of chemotherapy) | Q12W | |
| Window (days) | | | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | +5 | +5 | ±2 wks | +2 wks |
| ECOG performance status | X | X | | | X | | | | X | | | | X | | X | X | | | | |
| Electrocardiogram[h] | X | | | | | | | | | | | | | | | | | | | |
| Concomitant medications[i] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | X | X | X | X |
| Assessment/ collection/ recording/reporting of adverse events/serious adverse events | X[j] | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | X | X | X[k] | X[k] |
| Disease status assessment[l] | X | X | | | | | | | X[l] | | | | | | X[l] | X | | | X | X |



Footnotes are defined on the last page of the table

## Table 2-1. Schedule of Activities

| Procedures | Screening | Treatment Period[a] | | | | | | | | | | | | | | Follow up[b] | LTFU[c] | | | EOS[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| STUDY WEEK | Up to 28 days | 1[e] | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | QW[f] | Q4W[g] | 1 week after last dose of IP | SFU 1 (30 days after last dose of IP) | SFU 2 (30 days after last dose of on-study cycle of chemotherapy) | Q12W | |
| Window (days) | | | ± 1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | +5 | +5 | ±2 wks | +2 wks |
| Recording of chemotherapy administration[m] | Most recent cycle prior to study day 1 through 3 on-study cycles | | | | | | | | | | | | | | | X | X | X | | |
| Recording of platelet transfusions[n] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | X | | | |
| [redacted] | | | | | | | | | | | | | | | | | | | | |
| Local laboratory tests | | | | | | | | | | | | | | | | | | | | |
| Hemoglobin[p] | | X | | | | | | | | | | | | | | | | | | |
| ANC[p] | **X[z]** | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | X | | | |
| PT/INR and PTT | X | X | | | | | | | X | | | | | | | X | | | | |
| Local platelet counts[q] | **X[z]** | X[r] | X | X | X | X | X | X | X | X | X | X | X | X | | X | X | | | |



Footnotes are defined on the last page of the table

## Table 2-1. Schedule of Activities

| Procedures | Screening | Treatment Period[a] | | | | | | | | | | | | | | Follow up[b] | LTFU[c] | | | EOS[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| STUDY WEEK | Up to 28 days | 1[e] | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | QW[f] | Q4W[g] | 1 week after last dose of IP | SFU 1 (30 days after last dose of IP) | SFU 2 (30 days after last dose of on-study cycle of chemotherapy) | Q12W | |
| Window (days) | | | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | +5 | +5 | ±2 wks | +2 wks |
| Chemistry 1[s] | X | | | | | | | | | | | | | | | | | | | |
| Chemistry 2[s] | | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | X | | | |
| Hematology 1[aa] | X | | | | | | | | | | | | | | | | | | | |
| Hepatitis B, Hepatitis C and HIV tests, as required[x] | X | | | | | | | | | | | | | | | | | | | |
| Urine or serum pregnancy test[t] | X | | | | X | | | | X | | | | X | | X | | X | X | | |
| Central labs | | | | | | | | | | | | | | | | | | | | |
| Chemistry 3 | X | X | | | | | | | X | | | | | | | X | | | | |
| Hematology 2[aa] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | | | | |
| TPO | X | | | | | | | | | | | | | | | | | | | |
| Pharmacokinetic samples[u] | | X | | | X | | | | X | | | | | | | X | | | | |



Footnotes are defined on the last page of the table

## Table 2-1. Schedule of Activities

| Procedures | Screening | Treatment Period[a] | | | | | | | | | | | | | | Follow up[b] | LTFU[c] | | | EOS[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| STUDY WEEK | Up to 28 days | 1[e] | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | QW[f] | Q4 W[g] | 1 week after last dose of IP | SFU 1 (30 days after last dose of IP) | SFU 2 (30 days after last dose of on-study cycle of chemotherapy) | Q12 W | |
| **Window (days)** | | | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | +5 | +5 | ±2 wks | +2 wks |
| Antibody samples[v] | | X | | | | | | | X | | | | | | | X[w] | | | | |
| Hepatitis B, Hepatitis C and HIV tests, as required[x] | X | | | | | | | | | | | | | | | | | | | |
| **Treatment** | | | | | | | | | | | | | | | | | | | | |
| IP administration | | Weekly[y] | | | | | | | | | | | | | | | | | | |



Alk phos = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BUN = blood urea nitrogen; **CBC = complete blood count;** [redacted] CRF = case report form; ECOG = Eastern Cooperative Oncology Group; EOS = end of study; [redacted] GFR = glomerular filtration rate; HIV = human immunodeficiency virus; ICF = informed consent form; INR = international normalization; IP= investigational product; LTFU = long-term follow-up; PCR = polymerase chain reaction; [redacted] PT = prothrombin time; PTT = partial thromboplastin time; QW = every week; Q4W = every 4 weeks; Q12W = every 12 weeks; SFU = safety follow-up; TPO = thrombopoietin

**Note: Refer to Appendix 2 for definitions of Chemistry 1, 2, 3, as well as Hematology 1 and 2.**

[a] The treatment period will start on the first day of investigational product and will be long enough to allow for assessment of 3 planned cycles of chemotherapy (Please refer to Section 5.1). See Section 8.2 for instructions regarding subjects that choose to discontinue from the study.

[b] The follow-up visit will occur 1 week after the last scheduled dose of investigational product.

[c] Subjects will enter LTFU at 30 (+5) days after the last dose of IP (SFU 1). Subjects will be contacted 30 (+5**)** days after the last dose of the last 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 urine or serum pregnancy test (SFU 2). In addition, after the first LTFU **V**isit, all subjects will be followed by phone or in clinic every 12 weeks (± 2 weeks) **from the last dose of investigational product** until the EOS. Note: 30 (+5) days after the last dose of IP (SFU 1) may not necessarily coincide with 30 days after the last dose of on-study cycle of chemotherapy (SFU 2).

[d] All subjects should complete EOS **V**isit up to 2 weeks after the last subject in the trial completes LTFU at 1 year after the last dose of IP. EOS **V**isit can be done by phone.

[e] The date of the first dose of investigational product is defined as day 1, and will occur on the same day as randomization. **Subsequent study days will occur every 7 days (± 1 day).**

[f] After week 12, perform assessments weekly as indicated.

[g] After week 12, perform assessments every 4 weeks as indicated.

[h] Electrocardiogram will be obtained once during screening period per local institution standard of care.

[i] All concomitant therapies will be collected until completion of safety Visits 1 and 2 after which collected concomitant therapies will include the following: platelet related medications: commercial romiplostim, eltrombopag, avatrombopag, lusutrombopag, fostamatinib, and anticoagulants, only.

[j] Non-serious adverse events possibly related to any study procedures are reported after signing of the ICF. All other non-serious adverse events are reported after the first dose of protocol-required therapies. All serious adverse events are reported after signing of the ICF.

[k] Both non-serious adverse events and serious adverse events will be collected through 30 (+5) days after the last dose of protocol-required therapies (romiplostim/placebo [IP], chemotherapy [non-IP] up to 3 cycles). Note: For subjects who discontinue IP prior to completing 3 cycles of chemotherapy, non-serious adverse events should be collected through 3 on study chemotherapy cycles. Serious adverse events will be collected through the EOS. For the whole duration of the LTFU period, non-serious adverse events will be collected through EOS only if mandated by country-specific requirements.

[l] 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. During the treatment period, disease status assessment will be performed on day 1, week 8 (± 2 weeks), then every 8 (± 2) weeks thereafter, and at follow up. Radiographic assessment is not mandatory during these time intervals.

[m] Following enrollment and initiation of IP, the first cycle of chemotherapy during the treatment period should not be administered until platelet counts are ≥ 100 x $10^9$/L or until **at least** week 4, whichever comes first **(see Section 7.4.1.2)**. **Do not start the first cycle of on-study chemotherapy before study week 2.** Thereafter, non-Amgen, non-investigational chemotherapeutic agents will be administered for the treatment of primary malignancy according to chemotherapy dose modification guidelines outlined in Section 7.4.1.2. Chemotherapy administration, including information about planned and actual chemotherapy dose and schedule, should be recorded throughout 3 on study cycles, at the follow up at one week after the last dose of IP, SFU 1 and SFU 2. The start of the planned chemotherapy must be no more than 2 days after the local laboratory assessments have been taken **during the study visit**.

[n] For subjects who discontinue IP prior to completing 3 cycles of chemotherapy, platelet transfusions should be recorded through 3 on-study chemotherapy cycles.

[o] [redacted]

[p] ANC and hemoglobin will be assessed locally. ANC will be collected through 30 (+5) days after the last dose of IP. ANC values taken during the study visit (±1 day) and recorded in the CRF must be the same values as used for chemotherapy dose modifications where applicable. For subjects who discontinue IP prior to completing 3 cycles of chemotherapy, ANC should be recorded through 3 on-study chemotherapy cycles and the values recorded must be those taken prior to scheduled chemotherapy visits and used to inform decisions relating to chemotherapy dose modification. **Any ANCs performed outside of the study visits should be recorded if they are used to determine chemotherapy dose in study cycles 1, 2, and 3.**

[q] 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-IP 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. The platelet count taken during the study visit (± 1 day) and recorded in the CRF must be the same values as used for IP dose calculations and chemotherapy dose modifications where applicable. For subjects who discontinue IP prior to completing 3 cycles of chemotherapy, platelet counts should be measured through 3 on-study chemotherapy cycles to the end of the third on-study cycle and the values recorded must be those taken prior to scheduled chemotherapy visits and used to inform decisions relating to chemotherapy dose modification. **Any platelet counts performed in the cycle prior to enrollment should be recorded if they are used to determine chemotherapy dose in study cycle 1. Any platelet counts performed outside of the study visits should be recorded if they are used to determine chemotherapy dose in study cycles 1, 2, and 3.**

[r] Platelet count required prior to receiving the first dose of IP on day 1 – **see Section 6.1, inclusion criterion 110**.

[s] **At screening, full chemistry panel to be performed (at screening, both local and central chemistry and hematology labs are to be performed, however, local lab values may be used for eligibility). Thereafter, l**ocal lab values for BUN, creatinine, creatinine clearance, GFR, ALT, AST, Alk phos, and total bilirubin will be reported **at randomization and** when a subject is scheduled to receive chemotherapy through 3 on-study chemotherapy cycles. Local lab chemistries do not need to be reported if a subject is not scheduled to receive chemotherapy. Local lab chemistries taken during the study visit (± 1 day) and recorded in the CRF must be the same values as used for chemotherapy dose modifications where applicable. For subjects who discontinue IP prior to completing 3 cycles of chemotherapy, BUN, creatinine, creatinine clearance, GFR, ALT, AST, Alk phos, and total bilirubin should be recorded through 3 on-study chemotherapy cycles **for subjects** and the values recorded must be those taken prior to scheduled chemotherapy visits and used to inform decisions relating to chemotherapy dose modification. **Any of these local chemistries performed outside of the study visits should be recorded if they are used to determine chemotherapy dose in study cycles 1, 2, and 3.**

[t] A highly sensitive urine or serum pregnancy test must be performed **prior to enrollment** within 72 hours prior to the first dose of IP, monthly during the treatment period and then at 30 days after the last dose of investigational product and 30 (+5) days after the last dose of protocol-required therapies 30 **(+5)** days after the last dose of on-study cycle of chemotherapy non IP [up to 3 cycles]).

[u] Pharmacokinetic samples must be taken prior to administration of IP.

[v] Baseline antibody samples must be obtained on day 1 before the first administration of IP.

[w] Subjects who test positive for neutralizing antibodies to romiplostim or TPO at the follow up visit will be asked to return for additional follow up testing (see Section 9.2.6).

[x] Only for subjects without a diagnosis at screening. Subjects with a known diagnosis of active chronic Hepatitis B or C will require PCR for viral load assessment per eligibility criteria. If medical history confirms HIV infection, no need to repeat test during screening; subject will be ineligible. **Central test required only if cannot be performed locally.**

[y] **Investigational product should be administered every 7 days (± 1 day) starting from study day 1.** See Section 5.1 for details on when investigational product ends.

[z] **Collected as part of the local Hematology 1 analysis at screening.**

[aa] **At screening, both local and central chemistry and hematology labs are to be performed, however, local lab values may be used for eligibility.**

# 3. Introduction

## 3.1 Study Rationale

This trial is designed to study romiplostim for the treatment of chemotherapy-induced thrombocytopenia (CIT) in patients receiving oxaliplatin-based chemotherapy regimen for the treatment of gastrointestinal, pancreatic, or colorectal cancer, which includes cancers of the esophagus, stomach, colon, or rectum. This is a randomized, double-blind, placebo-controlled trial to study the safety and efficacy of romiplostim in this patient population. Current management of CIT includes platelet transfusions, chemotherapy dose delays and/or dose reductions, and in the United States (US), oprelvekin (Neumega®) (Neumega® Package Insert, 2011). However, due to its side effect profile, oprelvekin is rarely used in the clinical setting and it is no longer available from the manufacturer. Platelet transfusions are often reserved for patients with severe thrombocytopenia (platelet counts $< 10 \times 10^9$/L) due to transfusion-associated costs and the potential for transfusion-associated adverse events including, but not limited to, infections, allergic reactions, and alloimmunization leading to platelet transfusion refractoriness (Kuter, 2015). Chemotherapy dose delays and dose reductions are the most commonly utilized measures for managing CIT. These measures lead to a reduction in chemotherapy relative dose intensity, with literature noting the importance of receiving full-dose chemotherapy on schedule in the adjuvant setting (Denduluri et al, 2015; Lyman et al, 2003). Therefore, an unmet need exists for alternative treatment options for CIT. Two prior Amgen-sponsored studies, which used fixed doses of romiplostim at the beginning of each chemotherapy cycle, showed no new safety signals but did not demonstrate efficacy (Fanale et al, 2009; Natale et al, 2009). Several investigator-sponsored studies, which dosed romiplostim pre- and post-chemotherapy dose, also showed no new safety signals but did demonstrate moderate efficacy (Vadhan-Raj et al, 2010; Vadhan-Raj et al, 2009). A recent investigator-sponsored study, using a weekly romiplostim dosing schedule, provided evidence of efficacy in the treatment of CIT in patients with solid tumors (Soff et al, 2017).

### 3.1.1 Rationale for Study Population

The planned phase 3 study will enroll subjects with documented active gastrointestinal, pancreatic, or colorectal cancer who have CIT as a consequence of receiving an oxaliplatin-based chemotherapy regimen containing 5-fluorouracil 5-FU or capecitabine and oxaliplatin (plus irinotecan in FOLFIRINOX or FOLFOXIRI). In patients with metastatic colorectal cancer (CRC), a FOLFOX regimen has been demonstrated in

several studies to increase survival rate and decrease disease progression (Andre et al, 2004; Goldberg et al, 2004). Thrombocytopenia has been noted in more than 70% of patients receiving FOLFOX (Andre et al, 2004).

In the adjuvant setting, the importance of receiving full-dose chemotherapy on schedule (ie, high relative dose intensity) has been well established (Denduluri et al, 2015; Lyman et al, 2003). A retrospective study in patients with metastatic colorectal cancer noted that patients with a higher median chemotherapy dose intensity had a positive correlation with disease response rate, progression-free survival, and overall survival (Nakayama et al, 2014). Similarly, another retrospective multi-center cohort of patients with stage III colon cancer noted improved overall survival and disease-free survival in patients receiving a higher relative dose intensity (Aspinall et al, 2015). Therefore, given previous evidence from the literature to suggest the importance of maintaining chemotherapy dose intensity in colon and rectal cancers, these tumor types were chosen for this study to be able to demonstrate the ability to treat CIT and resume chemotherapy treatment.

### 3.1.2 Rationale for Study Duration

The planned phase 3 studies include a treatment period which will be long enough to allow for assessment of 3 planned cycles of chemotherapy. Subjects entering the study will have already received at least one cycle of chemotherapy and noted to have CIT. Subjects must have at least 3 remaining planned cycles of chemotherapy. Chemotherapy regimen for gastrointestinal, pancreatic, and colorectal cancer uses a combination of 5-FU or capecitabine and oxaliplatin (plus irinotecan in FOLFIRINOX or FOLFOXIRI). (NCCN Colon Cancer, 2017; NCCN Rectal Cancer, 2017).

## 3.2 Background

### 3.2.1 Disease

Chemotherapy used to treat cancer can suppress a patient's bone marrow, which can lead to a drop in platelets, neutrophils, and other blood counts. The occurrence of CIT varies with the type and schedule of chemotherapy used. A retrospective, observational cohort study using electronic medical records of over 47 000 adult cancer patients noted a prevalence of thrombocytopenia after initiation of chemotherapy ranging between 21.9% to 64.2% of patients, depending upon the specific chemotherapy regimen (Wu et al, 2009). A separate single-institution retrospective cohort study of 676 adult patients receiving chemotherapy noted the frequency of overall thrombocytopenia at 21.8% (Ten Berg et al, 2011).

Chemotherapy-induced thrombocytopenia is a commonly observed effect of myelosuppressive chemotherapy. Clinical symptoms of CIT can occur when platelet counts drop below 50 x $10^9$/L and include nosebleeds, bleeding from the gums, excessive bleeding from cuts, bruising, petechiae, and increased bleeding during surgical and invasive procedures. In addition, thrombocytopenia increases the risk of bleeding among cancer patients who need to be on anticoagulation due to history of thromboembolic events. Chemotherapy-induced thrombocytopenia with platelet counts below 100 x $10^9$/L may also lead to a delayed delivery of chemotherapy or a reduction in the chemotherapy dose, both of which adversely affects patients (Elting et al, 2001). It is difficult to predict which patients will develop prolonged CIT, and currently the only treatments for CIT are observation with chemotherapy dose delay or dose reduction, or supportive care with platelet transfusions. Platelet transfusions are usually reserved for patients who experience bleeding while thrombocytopenic or when platelet levels drop below 10 x $10^9$/L. Platelet transfusions often resolve the thrombocytopenia and are usually needed for only 3 to 4 days (Kuter, 2015). Although the benefits from platelet transfusions are short-lived, they have the potential to reduce hemorrhagic complications; however, repeated transfusions increase the risk of transfusion reactions, alloimmunization, and the transmission of infectious agents (Goodnough and DiPersio, 2002; Schiffer, 2001) and increase health care costs associated with the management of these side effects (Heyman and Schiffer, 1990). In the US, interleukin (IL)-11 (oprelvekin) has been approved for the prevention of severe thrombocytopenia and the reduction of the need for platelet transfusions in patients following myelosuppressive chemotherapy. However, it has been shown to have limited clinical efficacy (Gordon et al, 1996; Tepler et al, 1996; Vredenburgh et al, 1998). Clinical use of oprelvekin has been hindered by side effects, including fluid retention, arrhythmias, pulmonary edema, and a boxed warning for allergic reactions, including anaphylaxis (Neumega® United States Prescribing Information). Moreover, oprevelkin is no longer available from the manufacturer. Because of the lack of availability of safe and efficacious therapies, treatment for CIT is considered an unmet clinical need. This need for alternative treatment options for CIT is particularly important for patients receiving curative therapy, where dose reductions may lead to poorer disease-free and overall survival (Hassan and Waller, 2015; Kuter, 2015).

### 3.2.2 Amgen Investigational Product Background: Romiplostim

Romiplostim is a second-generation thrombopoietin (TPO) receptor agonist that resemble the function of TPO, but not the peptide structure (Kuter, 2010). Romiplostim

is a “peptibody” formed by the fusion of the Fc portion of an IgG1 monoclonal antibody with 4 TPO mimetic peptides. Romiplostim binds the distal cytokine homology region of the TPO receptor and activates the Janus kinase (JAK) and signal transducer and activator of transcription (STAT) pathways and the mitogen-activated protein (MAP) kinase pathways. This in turn boosts platelet production similar to endogenous TPO (Broudy and Lin, 2004; Kuter, 2010).

A detailed description of the chemistry, pharmacology, efficacy, and safety of romiplostim is provided in the Romiplostim Investigator’s Brochure.

### 3.2.3 Amgen-sponsored CIT Studies

Two studies have been conducted to evaluate romiplostim in subjects who are thrombocytopenic due to the effects of cancer chemotherapy: one study in adult subjects with lymphoma and the other study in adult subjects with non-small cell lung cancer (NSCLC). The primary objectives of each study were to evaluate safety and neither study demonstrated new safety signals.

Study 20050154 was a phase 2, randomized, double-blind, placebo-controlled, sequential dose-escalation cohort study designed to identify a well-tolerated, effective dose and schedule of romiplostim in subjects with NSCLC who had previously experienced thrombocytopenia during the chemotherapy cycle immediately preceding study entry. The primary objective was to evaluate safety, and the secondary objective was to evaluate efficacy.

Sixty-three subjects with stage IIIB or stage IV NSCLC who received 21-day cycles of gemcitabine/carboplatin or gemcitabine/cisplatin were enrolled in the study. Subjects were sequentially enrolled into 3 dosing cohorts (250, 500, or 750 μg) and received 1 subcutaneous administration of placebo or romiplostim on day 2 of each chemotherapy cycle. Within each cohort, subjects were allocated to romiplostim or placebo in a ratio of 4:1, respectively.

Two subjects (12.5%) in the 250 μg romiplostim cohort had treatment-related adverse events, and 1 subject in the 500 μg romiplostim cohort had treatment-related grade 2 platelet count increase, which resulted in discontinuation of romiplostim. Serious adverse events were reported in 8.3%, 43.8%, 27.8%, and 31.3% of subjects in the placebo, 250, 500, and 750 μg romiplostim cohorts, respectively; none were considered related to investigational product.

No statistically significant differences were observed between placebo and romiplostim for any of the secondary efficacy endpoints.

### 3.2.4 Investigator-sponsored CIT Studies

Phase 1/2 studies in solid tumors using pre- and post-chemotherapy dose schemas demonstrated the safety and efficacy of romiplostim in these settings. Current ongoing investigator-sponsored study, using a weekly dosing strategy titrated to a target platelet count, provided evidence of efficacy in this patient population.

#### 3.2.4.1 Phase 1/2 Study of Romiplostim in Solid Tumors

The safety and efficacy of romiplostim was evaluated in a phase 1/2 study in subjects with solid tumors. Twenty-four subjects who were receiving high-dose chemotherapy with carboplatin or doxorubicin and/or ifosfamide were administered romiplostim: cohorts 1 and 2 received chemotherapy alone in cycle 1 and with romiplostim in cycle 2. Cohort 1 was dosed at 1, 3, or 10 µg/kg subcutaneously for 2 doses, 2 days apart starting the day after chemotherapy (post-chemo dosing schedule) (Vadhan-Raj et al, 2009). Cohort 2 was dosed at 10 µg/kg 5 days prior to chemotherapy and again following chemotherapy (pre- and post-chemo dosing schedule).

Twenty-four subjects who received chemotherapy with romiplostim (compared to chemotherapy without romiplostim) had a reduction in the duration of thrombocytopenia and the platelet nadir counts were either stable or increased. The number of days with platelet counts $< 100 \times 10^9$/L was 7 days in the chemotherapy with romiplostim group compared to 10 days in the chemotherapy without romiplostim group ($p = 0.023$), and the days with platelet counts $< 50 \times 10^9$/L was 2 days vs 6 days ($p = 0.001$), respectively. In the ifosfamide group ($n = 20$), platelet nadir decreased in 7 patients, increased in 5 patients, and was stable in 8 patients. The study showed that romiplostim was safe in combination with high-dose chemotherapy regimen and reduced severe thrombocytopenia and platelet transfusions.

This study demonstrated efficacy and safety in a combination therapy setting. However, this study enrolled a small number of subjects and did not include efficacy endpoints that definitively show clinical benefit of romiplostim in CIT.

#### 3.2.4.2 Retrospective Reviews of Romiplostim Use for CIT

Parameswaran et al (2014), performed a retrospective review of the use of romiplostim for dose-limiting CIT in 20 patients at Memorial Sloan-Kettering Cancer Center from 2010 to 2012. Romiplostim was initiated at 1 to 2 µg/kg weekly, with dose

escalation by 1 μg/kg per week until platelet counts responded to ≥ 100 x $10^9$/L. If patients resumed chemotherapy, weekly romiplostim was continued.

Romiplostim improved platelet counts in all 20 patients. In 19 of 20 patients, platelet counts of ≥ 100 x $10^9$/L were achieved. The mean dose of romiplostim to achieve adequate platelet response was 2.9 μg/kg (range 1.0 to 5.1 μg/kg). Sixteen patients achieved platelet response by 2 weeks. Fifteen patients resumed cytotoxic chemotherapy with continued romiplostim support, and 14 tolerated at least 2 subsequent cycles of chemotherapy, on schedule, without recurrence of dose-limiting CIT.

Review of safety data showed 3 events of deep-vein thrombosis, which would not be unexpected in this patient population. Overall, the immune thrombocytopenia weekly dose strategy demonstrated efficacy and safety in this solid tumors retrospective study.

Al-Samkari et al (2018) performed a retrospective review of the concurrent use of romiplostim with cancer chemotherapy in 42 patients at Massachusetts General Hospital from 2010 to 2017, of which 22 patients met all inclusion criteria and had an underlying solid tumor diagnosis. The median platelet count nadir prior to romiplostim use was 74 x $10^9$/L (range 21 – 145 x $10^9$/L). Romiplostim was administered weekly with a median starting dose of 3 μg/kg (range 1 - 10 μg/kg). Ten of 17 (59%) patients with baseline platelet counts < 100 x $10^9$/L achieved platelet counts ≥ 100 x $10^9$/L one week after a single dose of romiplostim, with 76% (13 of 17) achieving platelet counts ≥ 100 x $10^9$/L after 2 to 3 weekly doses.

All 22 patients were able to receive two or more chemotherapy cycles while on romiplostim, with 18 patients receiving chemotherapy at or above the dose intensity of the chemotherapy cycle prior to starting romiplostim.

Review of safety data was notable for no patients having had a thrombotic event while receiving romiplostim. Three (14%) patients had bleeding events but did not require platelet transfusions. Four (18%) patients received platelet transfusions with 2 in preparation for a procedure, 1 for anemia and thrombocytopenia, and 1 for treatment of CIT.

#### 3.2.4.3 Ongoing Investigator-sponsored Study

In a randomized, controlled study with a cross-over design, subjects with CIT (platelets < 100 x $10^9$/L) for at least 4 weeks despite chemotherapy delay or dose

reduction were randomized 2:1 romiplostim (2 μg/kg) to control (observation) (Soff et al, 2017).

The primary endpoint was the proportion of patients achieving a platelet count $> 100 \times 10^9$/L by the end of a 3-week treatment period. Secondary endpoints included ability to tolerate resumption of chemotherapy for at least 2 cycles without recurrence of CIT.

An interim analysis was conducted with 23 subjects (n = 15 romiplostim arm, 8 observation arm). Platelet counts for 14 subjects (93%) in the romiplostim arm corrected within 3 weeks. In the observation arm, the platelet levels in 1 subject (12.5%) spontaneously corrected in 3 weeks, representing a statistically significant difference ($p = 0.001$). The observational arm was discontinued and all subsequent subjects were enrolled in the treatment arm.

Of the 32 subjects who received up front romiplostim, 27 subjects (84%) were able to achieve platelet counts ≥ $100 \times 10^9$/L by the third week, and 25 subjects (78%) in the romiplostim group were able to resume chemotherapy after correction of their CIT.

There was no evidence of bone marrow side effects from romiplostim treatment. Four (12.5%) of 32 subjects experienced a thromboembolic event (Soff et al, 2017).

### 3.3 Benefit/Risk Assessment

The following benefit risk assessment supports the conduct of this clinical trial. Reference should be made to the Investigator's Brochure for further data on romiplostim.

#### 3.3.1 Therapeutic Context

Therapeutic options for CIT are limited. Current management of CIT includes platelet transfusions, chemotherapy dose delays and/or dose reductions.

Platelet transfusions are often reserved for patients with severe thrombocytopenia (platelet counts < $10 \times 10^9$/L) due to transient benefit and the potential for transfusion-associated adverse events including, but not limited to, infections, allergic reactions, and alloimmunization leading to platelet transfusion refractoriness (Hod and Schwartz, 2008; Kuter, 2015; Slichter et al, 2005). Chemotherapy dose delays and dose reductions are the most commonly utilized measures for managing CIT. Multiple studies across different malignancies have shown that these measures lead to a reduction in chemotherapy relative dose intensity (RDI), which may decrease the therapeutic effect

of treatment and diminished overall survival of patients (Denduluri et al, 2015; Loibl et al, 2011; Vadhan-Raj et al, 2009; Lyman et al, 2003).

Treatment for CIT is considered an unmet medical need because of the lack of safe and efficacious therapies in this setting (Kuter, 2015). This need for alternative treatment options for CIT is particularly important for patients receiving curative therapy, where dose reductions may lead to poorer disease-free and overall survival (Hassan and Waller, 2015; Kuter, 2015).

### 3.3.2 Key Benefits

#### 3.3.2.1 Ability to Administer On-time, Full Dose Chemotherapy

Dose reduction or delays in chemotherapy caused by thrombocytopenia can lead to a reduction in relative dose intensity, which can decrease the efficacy of chemotherapy and lead to diminished overall survival and health outcomes in patients (Denduluri et al, 2015; Loibl et al, 2011; Vadhan-Raj et al, 2009; Lyman et al, 2003), therefore the ability to administer on-time, full-dose chemotherapy is considered to be a key favorable effect.

In the retrospective review of romiplostim use for dose-limiting CIT in subjects with a wide range of cancer types, 15 of 20 subjects were able to resume cytotoxic chemotherapy with continued romiplostim support and 14 tolerated at least 2 subsequent cycles of chemotherapy, on schedule, without recurrence of dose-limiting CIT (Parameswaran et al, 2014). Analysis of the ongoing, randomized, controlled phase 2 crossover investigator-initiated studies (IISs) (Soff et al, 2017) of weekly romiplostim dosing versus observation for CIT, showed that 84% (27 of 32) of subjects who received up front romiplostim were able to achieve platelet counts ≥ 100 x $10^9$/L by the third week, and 78% (25 of 32) of subjects in the romiplostim group were able to resume chemotherapy after correction of their CIT.

#### 3.3.2.2 Reduction in Incidence of ≥ Grade 2 Bleeding Events

Another key favorable effect is related to the reduction in bleeding events (≥ grade 2) in subjects with CIT, which can occur as a consequence of CIT when platelet counts fall below 50 x $10^9$/L and can have severe outcome, including death (Elting et al, 2001).

#### 3.3.2.3 Reduction in Incidence of Platelet Transfusions

Platelet transfusions are usually reserved for severe thrombocytopenia following chemotherapy due to the potential for transfusion associated side-effects and high healthcare costs associated with management of these effects (Kuter, 2015; Heyman

and Schiffer, 1990). It is anticipated that romiplostim will raise platelet counts faster than placebo, resulting in the decreased incidence of platelet transfusions.

#### 3.3.2.4 Platelet Nadir

A clinically important effect of nadir platelet counts caused by chemotherapy includes bleeding, which can necessitate the need for transfusions and may potentially have a severe outcome, including death (Elting et al, 2001).

#### 3.3.2.5 Time to First Platelet Response

A faster platelet response can prevent the need for chemotherapy dose delays, leading to improved overall survival in patients. In the retrospective review of patients with CIT, 19 of 20 subjects achieved platelet counts ≥100 x $10^9$/L by 3 weeks (Parameswaran et al, 2014). Analysis of the ongoing, randomized, controlled phase 2 crossover investigator-initiated studies (Soff et al, 2017) of weekly romiplostim dosing versus observation for CIT, showed that 84% (27 of 32) of subjects who received up front romiplostim were able to achieve platelet counts ≥ 100 x $10^9$/L by the third week. In the observation group, only 1 of 8 subjects (13%) achieved platelet counts ≥ 100 x $10^9$/L by the third week ($p < 0.001$).

### 3.3.3 Key Risks

#### 3.3.3.1 Medication Errors

Romiplostim is administered in small volumes via subcutaneous injection, and small differences in dose may have large effects on platelet counts. Overdose may result in an excessive increase in platelet counts associated with thrombotic/thromboembolic complications; underdose may result in low platelet counts that can lead to an increased risk of bleeding events. No medication errors were reported in the Study 20050154, an Amgen CIT study. See Section 7.1.1.2 for information on dosage, administration, and schedule of investigational product.

#### 3.3.3.2 Thrombotic/Thromboembolic Complications

Thrombotic complications, which can represent one of the earliest signs of cancer, occur at a higher rate in cancer patients than in the general population and have important implications for treatment and quality of life (Clagett et al, 1988; Cronin-Fenton et al, 2010; Prandoni et al, 2002; Shen et al, 1980; White et al, 2005). Most commonly, these events are deep vein thrombosis (DVT) or pulmonary embolism, which are both forms of venous thromboembolism (VTE). Arterial events, such as stroke and myocardial infarction occur less commonly (Falanga, 2005). Venous thromboembolism is also associated with increased mortality in cancer patients (Khorana et al, 2006; Lyman,

2011). Chemotherapy agents most strongly correlated with thrombotic complications are platinum (8% to 18%), such as cisplatin or carboplatin, asparaginase (4% to 14%), fluorouracil (15% to 17%), and antiangiogenic agents, such as thalidomide and lenalidomide (Kroger et al, 2006). Cisplatin, in particular, is correlated with a 12% to 18% risk of strokes, recurrent peripheral arterial events, and aortic thrombosis (Numico et al, 2005). Research has consistently shown that chemotherapy treatment significantly increases the risk of thromboembolic events (Haddad and Greeno, 2006; Kyriazi and Theodoulu, 2013; Lyman, 2011).

In addition to the increased risk of VTE in this patient population, romiplostim treatment is expected to increase the number of circulating platelets and platelet counts above the normal range and thus carries a theoretical risk for thrombotic/thromboembolic complications. These complications have a high patient impact and any clinical sequelae (eg, stroke) may not be reversible. In this study, subjects with platelet counts > 450 x $10^9$/L will have investigational product withheld, with treatment re-initiated when platelet counts are ≤ 450 x $10^9$/L (refer to Section 7.4.1.1 for dosage adjustments).

In the retrospective review of romiplostim for use for dose-limiting CIT (Parameswaran et al, 2014), the safety data showed 3 of 20 subjects experienced DVT, which would not be unexpected in this patient population. Three of 51 subjects in the phase 1/2 IIS (NCT00147225 Vadhan-Raj et al, 2009), in subjects with solid tumors treated with romiplostim, experienced a thromboembolic event (2 subjects with pulmonary embolism and 1 subject with DVT).

In the Amgen-sponsored Study 20050154, none of the subjects in the placebo group and 1 subject in each romiplostim-treatment dosage groups experienced a thrombotic/thromboembolic event (thrombophlebitis, retinal artery occlusion, and pulmonary embolism, respectively).

#### 3.3.3.3 Reoccurrence of Thrombocytopenia After Cessation of Romiplostim

For many patients receiving romiplostim, it is likely that treatment may eventually need to be stopped. There is a clear potential mechanism for increased risk of bleeding if treatment is discontinued in the presence of anticoagulants or anti-platelet agents. Withdrawal of romiplostim results in decreased TPO receptor stimulation, resulting in a decrease in platelet production. Cases can potentially be very serious and severe (including life-threatening cases); however, the risk of recurrence of thrombocytopenia can be monitored. There is currently no subject incidence data available for the adult CIT patient population. In Amgen Study 20050154, although platelet counts were

monitored at 1 week after the end of the last chemotherapy cycle (approximately 4 weeks after the last dose of investigational product), the lack of treatment efficacy limited assessment for re-occurrence of thrombocytopenia after cessation of romiplostim.

#### 3.3.3.4 Increased Bone Marrow Reticulin

The risk of increased bone marrow reticulin or bone marrow fibrosis is not well documented in patients with solid tumors. Bone marrow changes are more commonly studied and frequently occur in patients with hematologic malignancies. Reticulin fibrosis is associated with many benign and malignant conditions (Kuter et al, 2007b). A few studies have sought to elucidate the relationship between increases in bone marrow fibrosis and disease pathology (Kuter et al, 2007b).

Increased bone marrow reticulin may be due to the increased number of megakaryocytes in the bone marrow and their subsequent release of cytokines as a result of TPO receptor stimulation, consistent with findings associated with other TPOs (Kuter, 2007a; Tefferi, 2005). Increases in bone marrow reticulin have not been associated with adverse clinical sequelae, and the reticulin grade are reversible after romiplostim is discontinued (Kuter et al, 2009; Study 20080009).

As with bone marrow fibrosis, romiplostim is not intended to be used chronically in subjects with CIT, therefore the risk of increased bone marrow reticulin in subjects with CIT is reduced. Bone marrow evaluations were not part of Study 20050154. One of 20 subjects in the retrospective review of romiplostim use in CIT had a repeat bone marrow aspirate and biopsy performed after completion of approximately 1 year of romiplostim, with no evidence of increased reticulin deposit.

#### 3.3.3.5 Bone Marrow Fibrosis

Bone marrow fibrosis may be potentially very serious and severe, and can cause progressive anemia, leukopenia or leukocytosis, thrombocytopenia or thrombocytosis, and multi-organ extramedullary hematopoiesis, most commonly causing hepatomegaly and symptomatic splenomegaly (Kuter et al, 2007b). In idiopathic thrombocytopenic purpura subjects, increases in bone marrow reticulin have not been associated with adverse clinical sequelae, and the reticulin grade are reversible after romiplostim is discontinued (Kuter et al, 2009; Study 20080009). However, in the CIT population the risk of bone marrow fibrosis is reduced as romiplostim is not intended to be used chronically.

#### 3.3.3.6 Progression of Existing Myelodysplastic Syndrome

Myelodysplastic syndromes are a group of bone marrow disorders characterized by the failure to produce enough healthy blood cells, most commonly in the elderly (Bonadies et al, 2017). Myelodysplastic syndrome is associated with cytopenias and increased risk of bleeding and infection (Sekeres and List, 2006). Cancer patients treated with chemotherapy are at elevated risk of developing myelodysplastic syndrome (MDS). Myelodysplastic syndrome that occurs after chemotherapy or radiation treatment is known as secondary MDS and can often develop into acute myeloid leukemia (AML) (Bonadies et al, 2017).

Conventional chemotherapy-related leukemia (ie, myelodysplasia and AML) has a median time to development of 3 to 5 years, with the risk decreasing markedly after the first decade (Bhatia, 2013). Secondary MDS accounts for about 10% of MDS cases and the typical latency period after exposure is 5 to 7 years (Sekeres, 2010). For TPO receptor agonists, there is a theoretical concern that they may stimulate the progression of existing myeloid malignancies or MDS.

In addition, there is concern that romiplostim may change the natural rate of progression of MDS to AML. The evaluation of this risk is confounded by the difficulty of distinguishing leukemic blasts from normal early hematopoietic blasts. In subjects with MDS, the natural history of the disease is worsening of the condition, ultimately leading to the development of AML. This is an expected consequence of the disease (Germing et al, 2008; Shi et al, 2004).

In an MDS placebo controlled study (Study 20060198), during the 58-week study period in the safety analysis set (168 Nplate and 82 placebo), progression to AML occurred in 10 (6.0%) subjects in the Nplate arm and 4 (4.9%) subjects in the placebo arm (hazard ratio [95% CI] = 1.20 [0.38, 3.84]). Of the 250 subjects, 210 (84.0%) entered the long-term follow-up phase of this study. With 5-years of follow-up, 29 (11.6%) subjects showed progression to AML, including 20/168 (11.9%) subjects in the Nplate arm versus 9/82 (11.0%) subjects in the placebo arm (hazard ratio [95% CI] = 1.06 [0.48, 2.33]).

Subjects were excluded from clinical studies (and will also be excluded from this study - see exclusion criteria #204) if they had a history of myelodysplastic syndrome. No hematological malignancy events were reported in Study 20050154.

### 3.3.4 Conclusion

Currently, there is no standard approach to the management of CIT beyond delay or reduction of chemotherapy doses and platelet transfusion support. The benefits and risks of romiplostim for the treatment of CIT in the adult population with solid tumors have been characterized thus far with 3 IISs, a retrospective review of romiplostim use, and the Amgen-sponsored Study 20050154. These clinical studies investigating the use of romiplostim for CIT have demonstrated a favorable benefit-risk balance. Specifically, results provide supportive evidence that the use of romiplostim allows patients with CIT to receive chemotherapy treatment cycles as prescribed with no need to delay or reduce doses, and reduces severe thrombocytopenia, risk of bleeding, and platelet transfusions. These studies also provide evidence that romiplostim also has an acceptable safety profile when used in patients receiving high-dose chemotherapy regimens for different solid tumor types. Based upon these studies the benefit-risk balance for romiplostim in the phase 3 studies in CIT is also anticipated to be favorable.

## 4. Objectives, Endpoints and Hypotheses

### 4.1 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.<br>• anti-romiplostim antibodies and antibodies to thrombopoietin (TPO)<br>• myelodysplastic syndromes and secondary malignancies |

| **Exploratory** | |
|---|---|
| [redacted] | |

## 4.2 Hypotheses

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.

# 5. Study Design

## 5.1 Overall 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 $10^9$/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 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 baseline platelet count (< 50 x $10^9$/L, ≥ 50 x $10^9$/L). Baseline platelet count is defined as platelet count measured most prior to the time of the planned investigational product administration. Gastrointestinal adenocarcinomas, including tumors of the esophagus and 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 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-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 **V**isit up to 2 weeks after the last subject in the trial completes their LTFU **Visit** at 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.

The overall study design is described by a study schema in Section 2.1. The endpoints are defined in Section 4.1.

### 5.2 Number of Subjects

The study will enroll approximately 162 subjects with CIT and receiving an oxaliplatin-based chemotherapy regimen for the treatment of documented active gastrointestinal, pancreatic, or colorectal cancer. Subjects will be stratified based on their tumor type and baseline platelet count (< 50 x $10^9$/L, ≥ 50 x $10^9$/L) into 1 of 2 arms (placebo or romiplostim).

Subjects in this clinical investigation shall be referred to as “subjects.” For the sample size justification, see Section 10.1.

#### 5.2.1 Replacement of Subjects

Subjects who are withdrawn or removed from treatment or the study will not be replaced.

### 5.2.2 Number of Sites

Approximately 100 investigative sites in multiple countries, including United States, European Union, and countries in South America, will be included in the study. Sites that do not enroll subjects within 1 year of site initiation may be closed.

## 5.3 End of Study

### 5.3.1 End of Study Definition

**Primary Completion**: 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(s).

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.

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).

**End of Study**: The end of study date is 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, LTFU), as applicable.

Based on the definition above, the EOS date is the date when the last subject in the trial has completed his/her EOS **V**isit.

### 5.3.2 Study Duration for Subjects

The study will consist of a screening period of up to 4 weeks, a treatment period which will be of sufficient duration to allow assessment of 3 planned cycles of chemotherapy, a follow-up visit one week following last dose of investigational product, and a LTFU period, which will begin 30 (+5) days after the last dose of investigational product. The LTFU period for all subjects will continue until death or until the last subject in the trial completes their LTFU Visit 1 year after the last dose of investigational product. Therefore, duration of the study for each subject will be from approximately 1**4** to **50** months, depending on the length of their LTFU period.

### 5.4 Justification for Investigational Product Dose

The doses selected for study were derived from the results of Amgen's studies in healthy subjects and studies in immune thrombocytopenia subjects.

The initial planned starting dose for this study is consistent with the starting dose from Soff et al, 2016. Notably, the median dose of romiplostim to achieve platelet counts ≥ 100 x $10^9$/L was similar from two separate retrospective reviews, with Parameswaran et al showing 2.9 µg/kg (range 1.0 to 5.1 µg/kg) and Al-Samkari et al showing 3 µg/kg (range 1 to 10 µg/kg) (Al-Samkari et al, 2018; Parameswaran et al, 2014). The starting dose of 2 µg/kg was chosen to limit thrombocytosis which could contribute to a pro-thrombotic state in patients with cancer who are potentially more prone to thrombotic complications.

### 5.5 Patient Input on Study Design

Not applicable.

## 6. Study Population

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening). This log may be completed and updated via an Interactive Voice Response System (IVRS)/Interactive Web Response System (IXRS).

Eligibility criteria will be evaluated during screening and on day 1 of the study for platelet count **per Section 6.1, inclusion criterion 110**.

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Appendix 3).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, will not be provided.

### 6.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

101 Subject has provided informed consent prior to initiation of any study specific activities/procedures or subject's legally acceptable representative has provided informed consent prior to any study-specific activities/procedures being initiated when the subject has any kind of condition that, in the opinion of the investigator, may compromise the ability of the subject to give written informed consent.

102 Males or females ≥ 18 years of age at signing of the informed consent.

103 Histologically or cytologically confirmed diagnosis of gastrointestinal, pancreatic, or colorectal adenocarcinoma, defined as cancers of the esophagus **(including**

**esophagogastric junction [EGJ] cancer)**, stomach, pancreas, colon, or rectum. Tumor stage will not affect eligibility.

**109** Subjects must be receiving one of the following regimens:

- An oxaliplatin-based chemotherapy regimen, containing 5 FU or capecitabine plus oxaliplatin (irinotecan may be added for FOLFIRINOX or FOLFOXIRI) on a 14- or 21-day schedule, respectively.

  **OR**

- **Subjects must have CIT from a non-protocol chemotherapy regimen, planning to start treatment with 1 of the above protocol chemotherapy regimens which has been delayed ≥ 1 week due to CIT.**

Note: Use of these regimens are permitted with (1) anti angiogenic agents (such as bevacizumab) or (2) targeted therapy (such as anti epidermal growth factor receptor agents).

**110** Subjects must have a **local** platelet count **≤ 85** x $10^9$/L on study day 1.

106 Subjects must be at least 14 days removed from the start of the chemotherapy cycle immediately prior to study day 1 if they received FOLFOX, FOLFIRINOX or FOLFOXIRI, and 21 days removed if they received CAPEOX.

107 Subjects must have at least 3 remaining planned cycles of chemotherapy at study enrollment.

108 Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.

### 6.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply.

Previous or Current Medical Conditions

201 Acute lymphoblastic leukemia.

202 Acute myeloid leukemia.

203 Any myeloid malignancy.

204 Myelodysplastic syndrome. Baseline bone marrow biopsy is not required to rule out MDS. However, if a bone marrow biopsy and cytogenetics were performed as part of diagnostic or staging work-up, these results will be collected to confirm.

205 Myeloproliferative disease.

206 Multiple myeloma.

207 Within 4 months prior to enrollment, any history of active congestive heart failure (New York Heart Association [NYHA] Class III to IV), symptomatic ischemia, uncontrolled arrhythmias, clinically significant electrocardiogram (ECG) abnormalities, screening ECG with corrected QT (QTc) interval of > 470 msec, pericardial disease, or myocardial infarction.

208 Major surgery ≤ 28 days or minor surgery ≤ 3 days prior to enrollment.

209 New or uncontrolled venous thromboembolism or thrombotic events within 3 months prior to screening. To be eligible, subjects must have received at least

14 days of anticoagulation for a new thrombotic event and considered to be both stable and suitable for continued therapeutic anticoagulation during trial participation.

210 History of arterial thrombosis (eg, stroke or transient ischemic attack) within 6 months of screening.

211 Evidence of active infection within 2 weeks prior to first dose of study treatment.

**230** Known human immunodeficiency virus infection. Subjects without a documented diagnosis in their medical history will require a **local** laboratory assessment at screening. **If local laboratory results are not available, use central laboratory results.**

**231** Known active chronic hepatitis B or C infection. Subjects without a documented diagnosis in their medical history will require a **local** laboratory assessment at screening. **If local laboratory results are not available, use central laboratory results.** Hepatitis B and C infection is based on the following results:

- Positive for hepatitis B surface antigen (HBsAg) (indicative of chronic hepatitis B or recent acute hepatitis B).
- Negative HBsAg and positive for hepatitis B core antibody: hepatitis B virus DNA by polymerase chain reaction (PCR) is necessary. Detectable hepatitis B virus DNA suggests occult hepatitis B.

214 Positive Hepatitis C virus antibody (HCVAb): hepatitis C virus RNA by PCR is necessary. Detectable hepatitis C virus RNA suggests chronic hepatitis C.
In addition to the conditions listed in exclusion criteria 201 through 206, secondary malignancy within the past 5 years except:

- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
- Adequately treated cervical carcinoma in situ without evidence of disease.
- Adequately treated breast ductal carcinoma in situ without evidence of disease.
- Prostatic intraepithelial neoplasia without evidence of prostate cancer.
- Adequately treated urothelial papillary noninvasive carcinoma or carcinoma in situ.
- Malignancy treated with curative intent and with no known active disease present for $\geq$ 3 years before enrollment and felt to be at low risk for recurrence by the treating physician (excluding malignancies listed in exclusion criteria 201 – 206).

215 Thrombocytopenia due to another etiology other than CIT (eg, chronic liver disease, prior history of immune thrombocytopenia purpura).

**Prior/Concomitant Therapy**

216 Previous use of romiplostim, pegylated recombinant human megakaryocyte growth and development factor, eltrombopag, recombinant human TPO, any other TPO receptor agonist, or any investigational platelet producing agent.

**Prior/Concurrent Clinical Study Experience**

217 Currently receiving treatment in another investigational device or drug study, or less than 28 days since ending treatment on another investigational device or

drug study(ies). Other investigational procedures while participating in this study are excluded.

**Diagnostic Assessments**

218 Anemia (hemoglobin < **80 g/L [**8 g/dL**]**) on the day of initiation of investigational product as assessed by local labs. Use of red cell transfusions and erythropoietic stimulating agents is permitted throughout the study as per institutional guidelines.

219 Neutropenia (absolute neutrophil count < 1 x $10^9$/L) on the day of initiation of investigational product as assessed by local labs. Use of granulocyte-colony stimulating factor is permitted throughout the study as per institutional guidelines.

**232** Abnormal renal function with creatinine clearance < 30 mL/min using the Cockcroft-Gault estimated creatinine clearance as assessed by **local** laboratory during screening. **If local laboratory results are not available, use central laboratory results.**

**233** Abnormal liver function (total bilirubin > 3 X ULN; alanine aminotransferase [ALT] or aspartate aminotransferase [AST] > 3 X ULN for subjects without liver metastases or ≥ 5 X ULN for subjects with liver metastases) as assessed by **local** laboratory during screening. **If local laboratory results are not available, use central laboratory results.**

**Other Exclusions**

222 Females who are pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment and for an additional 6 months after treatment (and chemotherapy) discontinuation (females of childbearing potential should only be included after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test.)

223 Females of childbearing potential unwilling to use a highly effective method of contraception during treatment and for an additional 6 months after treatment (and chemotherapy) discontinuation. Refer to **Appendix 5** for additional contraceptive information.

224 Males unwilling to use contraception* (male condom or sexual abstinence) or their female partner(s) of childbearing potential who are unwilling to use a highly effective method of contraception during treatment (and chemotherapy) and for an additional 6 months after treatment (and chemotherapy) discontinuation.
*If the male's sole partner is of non-childbearing potential, he is not required to use additional forms of contraception during the study.

225 Subject has known sensitivity to any of the products to be administered during dosing.

226 Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures (eg, [redacted] to the best of the subject and investigator's knowledge.

227 History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.

228 Male subjects with a pregnant partner who are unwilling to practice abstinence or use a condom during treatment (and chemotherapy) and for an additional period of 6 months after treatment (and chemotherapy) discontinuation.

229 Male subjects unwilling to abstain from donating sperm during treatment (and chemotherapy) and for an additional 6 months after treatment (and chemotherapy) discontinuation.

## 6.3 Subject Enrollment

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see **Section** 12.3).

The subject or the subject's legally acceptable representative must personally sign and date the IRB/IEC and Amgen approved informed consent before commencement of study-specific procedures.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. Subjects may be randomized into this study only once. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment case report form (CRF).

Each subject who enters into the screening period for the study (defined as the point when the subject signs the informed consent) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by the IVRS/IXRS. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened. Also, in case of re-consent due to expiring window for consent during screening, the subject number will remain the same. This number will not necessarily be the same as the randomization number assigned for the study.

## 6.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study.

**If a subject is a screen failure, the following electronic case report forms (eCRFs) are required: Demographics, Was Subject Enrolled?, and Investigator Signature (electronic signature).**

**If a Serious Adverse Event is observed from the time Informed Consent is signed up to the point of screen failure, the following eCRFs are also required: Events, Medical History and Concomitant Medications. The pages only need to be updated for information relating to the Serious Adverse Event. For interventional trials, certain events are to be reported/transmitted to Amgen Safety within 24 hours of awareness.** Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened up to 3 times at the discretion of the investigator. Further rescreening requires approval from Amgen Medical Monitors.

If a subject is being rescreened, he or she may need to reconsent to the study to ensure that the IRB/IEC approved main informed consent form is signed within 28 days of enrollment or randomization. Subjects who are determined not eligible after rescreening must be screen-failed in the IVRS/IXRS and the reason for the screen-failure provided.

## 7. Treatments

Study treatment is defined as any investigational product(s), non-investigational product(s), placebo, or medical device(s) intended to be administered to a study subject according to the study protocol.

Note that in several countries, investigational product and non-investigational product are referred to as investigational medicinal product and non-investigational medicinal product, respectively.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of each treatment described in Section 7.1 below.

### 7.1 Treatment Procedures

#### 7.1.1 Investigational Products: Romiplostim and Placebo

##### 7.1.1.1 Dose formulation

Romiplostim will be manufactured and packaged by Amgen Inc., and distributed using Amgen's clinical study investigational product distribution procedures.

Romiplostim is supplied in a 5 mL single-use vial as a sterile, white, preservative-free, lyophilized powder containing histidine, mannitol, sucrose, and polysorbate 20, and has a pH 5.0 when reconstituted with sterile water for injection.

Placebo will be provided in identical 5 mL single-use vials as a sterile, white, preservative-free, lyophilized powder containing histidine, mannitol, sucrose, and polysorbate 20 and has a pH 5.0 when reconstituted with sterile water for injection.

#### 7.1.1.2 Dosage, Administration, and Schedule

Investigational product will be administered in the clinic by a qualified healthcare provider as a subcutaneous injection. The starting dose of investigational product will be 2 µg/kg based on the subject's recorded screening weight. Subjects will return to the clinic every 7 days (± 1 day) to provide platelet counts and undergo dose titrations under the supervision of the treating physician. Local laboratory assessments taken during the study visit (± 1 day) and recorded in the CRF must be the same values as used for investigational product dose calculations and chemotherapy dose modifications where applicable. **The study visits will start on study day 1 and continue every 7 days (± 1 day) measured relative to study day 1.** 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. **Any platelet counts performed in the cycle prior to enrollment should be recorded if they are used to determine chemotherapy dose in study cycle 1. Any platelet counts performed outside of the study visits should be recorded if they are used to determine chemotherapy dose in study cycles 1, 2, and 3.**

**Investigational product d**ose adjustments are based on changes in platelet counts only. Weekly dose increases will continue in increments of 1 µg/kg up to a maximum dose of 10 µg/kg in an attempt to reach a target platelet count of ≥ 100 x $10^9$/L (see Section 7.4.1.1 for more detail). 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-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. The total volume of preparation, planned dose, quantity administered, start date/time, and box number of investigational product are to be recorded on each subject's CRF(s).

**If the subject misses the visit window (7 days ± 1 day), the investigational product (IP) dose should be considered missed for that week and given at the next weekly study visit.**

**All study visit procedures, including IP administration, must be completed within the study visit window (± 1 day).**

### 7.1.2 Non-investigational Products

In this study, the non-Amgen, non-investigational planned chemotherapeutic agents will be administered according to chemotherapy dose modification guidelines outlined in Section 7.4.1.2. These guidelines will only apply to the 3 on-study cycles of this protocol and while recommended it will not be necessary for the investigators to follow them outside of the 3 study cycles.

Chemotherapeutic agents are commercially available and will not be provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies. Guidance on dose modification of chemotherapeutic agents can be found in Section 7.4.1.2.

The dose of non-investigational product used, start date, stop date, and reasons for chemotherapy dose reduction are to be recorded on each subject's CRF(s). **The chemotherapy doses are to be recorded using the same units for all 3 on-study cycles and the cycle prior to enrollment.**

**The start of the planned chemotherapy must be no more than 2 days after the local laboratory assessments have been taken during the study visit.**

### 7.1.3 Medical Devices

No investigational devices will be used in this study.

Other non-investigational medical devices may be used in the conduct of this study as part of standard care.

Non-investigational medical devices (eg, syringes, sterile needles), that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

### 7.1.4 Other Protocol-required Therapies

No additional therapies are required by the protocol.

### 7.1.5 Other Treatment Procedures

Other than Amgen investigational product (romiplostim and placebo) and non-Amgen, non-investigational standard of care chemotherapeutic agents, no other treatment procedures are required by the protocol.

### 7.1.6 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug**, combination product,** or device after it is released for distribution to market or clinic by either **(1)** Amgen or **(2)** distributors and partners for whom Amgen manufactures the material. **This includes all components distributed with the drug, such as packaging drug containers, delivery systems, labeling, and inserts.**

This includes any drug(s), device(s) or combination product(s) provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) includes investigational product.

Product complaints will be collected for: romiplostim and placebo.

Any product complaint(s) associated with an investigational product(s), non-investigational product(s), device(s), or combination product(s) supplied by Amgen are to be reported according to the instructions provided in the IPIM.

### 7.1.7 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

The following medications are not permitted throughout the 3 on-study cycles:

- Commercially available romiplostim (Nplate®)
- Other thrombopoietic receptor agonists (eg, eltrombopag [Promacta® or Revolade®], avatrombopag [Doptelet®])
- Recombinant human TPO
- Oprelvekin (Neumega®)
- Herbal supplements that are associated with bleeding side effects including, but not limited to, gingko biloba, garlic, ginseng, fish oil, dong quai, feverfew. Garlic and ginseng taken through a normal diet would not be excluded.
- Any other investigational agents that are not approved
- Subjects must not schedule any elective surgeries during the treatment period and for at least 28 days after the last administration of investigational product. If a subject undergoes any urgent surgery during the course of the study, investigational product must be withheld and the investigator or designee should notify the sponsor's medical monitor as soon as possible. A subject may be allowed to resume investigational product if both the investigator and sponsor's medical monitor agree to restart study therapy.

### 7.2 Method of Treatment Assignment

Subjects will be randomized in 2:1 allocation ratio, to romiplostim or placebo, respectively, in double-blind manner.

The randomization number will be provided by the IVRS/IXRS system.

The randomization will be stratified by tumor type and baseline platelet count ($< 50 \times 10^9$/L, $\geq 50 \times 10^9$/L). Gastrointestinal tract cancers, including tumors of the esophagus or stomach, will be included in one stratum, pancreatic cancers will be included in a second stratum, and colorectal cancers, including tumors of the colon or rectum, will be included in a third stratum.

The randomization date is to be documented in the subject's medical record and on the enrollment CRF.

### 7.3 Blinding

This is a double-blind study. Treatment assignment will be blinded to all subjects, site personnel, and Amgen as described below.

#### 7.3.1 Site Personnel Access to Individual Treatment Assignments

A subject's treatment assignment is to only be unblinded when knowledge of the treatment is essential for further clinical management of the subject on this study. Unblinding at the study site for any other reason will be considered a protocol deviation. Unblinding is done via IVRS. The Amgen Trial Manager must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the subject's condition. In this case, the Amgen Trial Manager must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF, as applicable.

#### 7.3.2 Access to Individual Subject Treatment Assignments by Amgen or Designees

Blinded individuals will not have access to unblinded information until the study is formally unblinded. Unblinding and potentially unblinding information is not to be distributed to the study team, investigators or subjects prior to the study being formally unblinded except as specified (eg, Section 7.3.1).

## 7.4 Dose Modification

### 7.4.1 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

#### 7.4.1.1 Amgen Investigational Product: Romiplostim and Placebo

Each subject's dose of investigational product (romiplostim or placebo) will be adjusted based on weekly platelet counts (see Table 7-1). **The target platelet count at initiation of the first on-study cycle of chemotherapy is ≥ 100 x $10^9$/L. Starting from week 4, subjects may start the first cycle of chemotherapy with dose adjustments according to the dose modification guidelines listed below.**

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 discontinuation. Local laboratory assessments taken during the study visit (± 1 day) and recorded in the CRF must be the same values as used for investigational product dose calculations and chemotherapy dose modifications where applicable. **Any platelet counts performed in the cycle prior to enrollment should be recorded if they are used to determine chemotherapy dose in study cycle 1. Any platelet counts performed outside of the study visits should be recorded if they are used to determine chemotherapy dose in study cycles 1, 2, and 3**.

**Table 7-1. Investigational Product Dose Adjustment Rules**

| Platelet count (x $10^9$/L) | Investigational Product Dose Adjustment Rule[a] |
|---|---|
| < 100 | Increase dose by 1 µg/kg each week (to a maximum of 10 µg/kg) |
| 100 - 250 | Dose remains constant |
| 251 - 450 | Dose reduced by 1 ug/kg. Do not withhold dose[b, c] |
| > 450 | Withhold dose[d] |

IP = investigational product
[a] The starting dose of investigational product will be 2 µg/kg based on the subject's recorded screening weight. See Section 7.1.1.2 for full details.
[b] If the current dose is 1 µg/kg and a dose reduction is required, the dose will be withheld until the platelet count falls to < 100 x $10^9$/L. Once the platelet count is < 100 x $10^9$/L, dosing will resume at a dose of 1 µg/kg using the dose adjustment rules above.
[c] If platelet count > 250 x $10^9$/L is due to a platelet transfusion in the preceding 7 days, the subject will continue to receive investigational product at the previous dose level.
[d] For patients who previously had their dose withheld because their platelet count was > 450 x $10^9$/L, restart IP based on dose withheld and according to adjustment rules above.

Subjects who have a platelet count < 100 x $10^9$/L for 4 consecutive weeks at the maximum investigational product dose of 10 µg/kg should be discontinued from investigational product**, allowing for up to 12 weeks of dosing before a subject is declared a non-responder. To assess if a subject has responded to the 12th dose given at the beginning on the 12th week of the study, the platelets would be drawn a week later at the week 13 visit when a subject has completed 12 weeks of dosing.**

Dosing will be discontinued at any time during the study if neutralizing antibodies to romiplostim or to endogenous TPO are detected.

The reason for dose change of investigational product is to be recorded on each subject's CRF(s).

#### 7.4.1.2 Non-Amgen Non-investigational Product: Standard-of-care Chemotherapy

The following will be specified prior to the first administration of investigational product: chemotherapy agents in the planned treatment regimen, planned total dose and unit of each agent, number of days per cycle, and planned dosing schedule. The planned chemotherapy regimen reflects what the investigator considers standard dose and schedule for that regimen. The following will be captured during the treatment period: the actual chemotherapy dose and unit administered; date of administration; whether the subject experienced a dose reduction, delay, or omission due to thrombocytopenia; whether the subject experienced chemotherapy treatment discontinuation due to thrombocytopenia; and whether there was a reason other than thrombocytopenia for dose reduction, delay, omission, or discontinuation. An independent adjudicator will periodically verify the reason for chemotherapy dose modification in the study. Chemotherapy dose modifications include dose reductions, dose delays, dose omissions, and treatment discontinuations. During the 3 on study cycles, a chemotherapy delay must be increments of 1 week to align with the weekly study visits if applicable.

Following enrollment and initiation of investigational product, the first cycle of chemotherapy during the treatment period should not be administered until platelet counts are ≥ 100 x $10^9$/L or until **at least** week 4, whichever occurs first. **If platelet counts at the start of chemotherapy cycle 1 are < 100 x $10^9$/L, recheck platelet count 1 week later and continue to hold until platelet count ≥ 100 x $10^9$/L. Starting from week 4, subjects may start the first cycle of chemotherapy with dose**

**adjustments according to the dose modification guidelines listed below. If the platelets remain < 100 x $10^9$/L, the investigator has the discretion to continue IP for dose escalation up to 12 weeks before beginning the first on-study chemotherapy cycle. After 12 weeks without starting study cycle 1 on IP, the subject is considered a non-responder.**

**Do not start the first cycle of on-study chemotherapy before study week 2.** The start of the planned chemotherapy must be no more than 2 days after the local laboratory assessments have been taken **during the study visit**. The reason for dose change of non-Amgen non-investigational products is to be recorded on each subject's CRF(s). Any chemotherapy dose modifications made for reasons other than thrombocytopenia will be captured in the CRF.

**The investigator should not perform any dose modifications due to CIT if the subject's platelet count is above the levels listed in the dose modification guidelines. Do not dose modify for cycle 1 unless the platelets are < 100 x $10^9$/L on or after week 4. Use dose modification guidelines for cycles 2 and 3.**

Chemotherapy dose modifications for thrombocytopenia for patients with gastric, esophageal, pancreatic, colon, or rectal adenocarcinoma receiving an oxaliplatin-based regimen should be conducted as follows.

**Table 7-2. Dose Modification Based on Platelet Counts– mFOLFOX6**

| Blood Counts | Delay Cycle | Oxaliplatin | 5-FU |
|---|---|---|---|
| **Platelets < 75 x $10^9$/L day 1 (at the beginning of a chemotherapy cycle)** | **Delay by 1 week and until platelets have recovered ≥ 75 x$10^9$/L.** | | |
| | **1st occurrence of a 2 week delay or delay for 1 week on 2 separate occasions** | | **Eliminate 5-FU bolus**<br>**If no bolus was given reduce cIV 5-FU by 20%** |
| | **2nd Occurrence of a 2 week delay or delay for 1 week on 2 separate occasions** | **Reduce oxaliplatin dose from 85 to 65 mg/m$^2$** | **Reduce cIV 5-FU by 20%** |
| **Platelets < 50 x $10^9$/L during treatment** | **Delay next dose until platelets recover to ≥ 75 x$10^9$/L.** | **Reduce oxaliplatin dose to 75 mg/m$^2$ (adjuvant therapy) or to 65 mg/m$^2$ (metastatic CRC)** | |

**5-FU = 5-fluorouracil; cIV = continuous intravenous; CRC = colorectal cancer**
**Source: Oxaliplatin USPI; Cheeseman et al, 2002; Hochster et al, 2008.**

**Delay treatment cycle by one week for platelets < 75 x $10^9$/L on the day 1 of treatment. If treatment is delayed for 2 weeks or delayed for one week on 2 separate occasions, eliminate 5-FU bolus. If no bolus was given reduce cIV 5-FU by 20%. With the second occurrence, reduce cIV 5-FU by 20% and reduce oxaliplatin dose from 85 to 65 mg/$m^2$. For platelets <50 x $10^9$/L** during **treatment delay next dose until platelets recover to ≥ 75 x$10^9$/L then reduce oxaliplatin dose to 75 mg/$m^2$ (adjuvant therapy) or to 65 mg/$m^2$ (metastatic CRC).**

**Table 7-3. Dose Modification Based on Platelet Counts - FOLFIRINOX**

| Blood Counts | Delay Cycle | Oxaliplatin | 5-FU | Irinotecan |
|---|---|---|---|---|
| Platelets < 75 x $10^9$/L day 1 (at the beginning of a chemotherapy cycle) | Delay by 1 week and until platelets have recovered ≥ 75 x$10^9$/L. | Reduce oxaliplatin dose from 85 to 60 mg/$m^2$ | Reduce bolus and cIV 5-FU to 75% of original dose | |
| | | | | 2nd Occurrence: reduce dose to 150 mg/$m^2$ |
| Platelets < 50 x $10^9$/L during treatment | | Reduce oxaliplatin dose from 85 to 60 mg/$m^2$ | Reduce bolus and cIV 5-FU to 75% of original dose | |
| | | | 2nd Occurrence: reduce cIV 5-FU an additional 25% | 2nd Occurrence: reduce dose to 150 mg/$m^2$ |

**5-FU = 5-fluorouracil; cIV = continuous intravenous**
**Source: Conroy et al, 2011.**

**If day 1 treatment delayed by 1 week for platelet count < 75 x $10^9$/L, reduce oxaliplatin dose from 85 to 60 mg/$m^2$ and reduce both the bolus and cIV 5-FU to 75% of original doses. For second occurrence, reduce irinotecan dose to 150 mg/$m^2$. Beginning in on-study chemotherapy cycle 2 if nonrecovery after 2-week delay, or third occurrence of platelets < 75 x $10^9$/L, discontinue treatment. For platelet count < 50 x $10^9$/L** during **treatment, reduce oxaliplatin dose from 85 to 60 mg/$m^2$ and the cIV 5-FU dose to 75% of the original dose. For the second occurrence, reduce dose of irinotecan to 150 mg/$m^2$ and the dose of cIV 5-FU an additional 25%. Discontinue treatment for third occurrence.**

**Table 7-4. Dose Modification Based on Platelet Counts - mFOLFIRINOX**

| Blood Counts | Delay Cycle | Oxaliplatin | 5-FU | Irinotecan |
|---|---|---|---|---|
| **Platelets < 75 x $10^9$/L day 1 (at the beginning of a chemotherapy cycle)** | **Delay by 1 week and until platelets have recovered ≥ 75 x$10^9$/L.** | **Reduce oxaliplatin dose from 85 to 60 mg/$m^2$** | **Reduce cIV 5-FU to 75% of original dose** | |
| | | | | **2nd Occurrence: reduce dose to 120 mg/$m^2$** |
| **Platelets < 50 x $10^9$/L during treatment** | | **Reduce oxaliplatin dose from 85 to 60 mg/$m^2$** | **Reduce cIV 5-FU to 75% of original dose** | |
| | | | **2nd Occurrence: reduce cIV 5-FU an additional 25%** | **2nd Occurrence: reduce dose to 120 mg/$m^2$** |

**5-FU = 5-fluorouracil; cIV = continuous intravenous**
**Source: Conroy et al, 2018**

**If day 1 treatment delayed by 1 week for platelet count <75 x $10^9$/L, reduce oxaliplatin dose from 85 to 60 mg/$m^2$ and reduce the cIV 5-FU to 75% of original doses. For second occurrence, reduce irinotecan dose to 120 mg/$m^2$. Beginning in on-study chemotherapy cycle 2 if nonrecovery after a 2-week delay, or if there is a third occurrence of platelets <75 x $10^9$/L, discontinue treatment. For platelets < 50 x $10^9$/L** during **treatment, reduce oxaliplatin dose from 85 to 60 mg/$m^2$ and the infusional FU dose to 75% of the original dose. For the second occurrence, reduce dose of irinotecan to 120 mg/$m^2$ and the dose of infusional FU an additional 25%. Discontinue treatment for third occurrence.**

**The dose modifications for the FOLFOXIRI regimen in colorectal cancer patients were not published in the original phase III trial** (**Falcone et al, 2007). Use the** dose modifications above based on those in a trial using a comparable regimen (FOLFIRINOX) for advanced pancreatic cancer (**Conroy et al, 2011).**

**For CAPEOX (Nehls et al, 2008; Capecitabine USPI), delay the treatment cycle for one week if the platelet count is < 100 x $10^9$/L on day 1. If treatment is delayed for 2 weeks or delayed for 1 week on 2 separate occasions, reduce the doses of oxaliplatin and capecitabine by 10% to 20%. Subsequent treatment cycles should be delayed until the platelets are ≥ 75 x $10^9$/L.**

Renal insufficiency requiring dose modification

- For patients with severe renal impairment (creatinine clearance < 30 mL/min), the starting dose of oxaliplatin should be reduced to 65 mg/m$^2$ (Oxaliplatin prescribing information, 2017).
- Decrease the dose of capecitabine by 25% in patients with CrCl 30-50 mL/min and hold for more severe kidney disease. (Xeloda USPI 2019)
- For irinotecan there is no specific dose reduction recommendation for renal insufficiency. (Irinotecan USPI)

Hepatic insufficiency requiring dose modification

- For patients with hepatic impairment with total bilirubin > 5 mg/dL, 5-fluorouracil should not be administered (Floyd et al, 2006). Decrease the dose of capecitabine by 25% in subsequent cycles for bilirubin > 1.5-3 x ULN. (Blum, 1999)
- The dose of irinotecan should be reduced by 25% in patients with bilirubin > 1.5-3 x ULN. (Floyd 2006).

Where there are multiple toxicities including thrombocytopenia, renal, and hepatic toxicities dose modification should be made after reviewing all applicable dose modification guidelines provided and choosing the lowest recommended dose for the most severe grade of toxicity.

### 7.5 Preparation/Handling/Storage/Accountability

Guidance and information on preparation, handling, storage, accountability, destruction, or return of the investigational product during the study are provided in the IPIM.

### 7.6 Treatment Compliance

Investigational product will be administered in the clinic by a qualified healthcare provider as a subcutaneous injection. Study clinic staff will note the dose and time of dosing on the CRF.

### 7.7 Treatment of Overdose

In high-dose preclinical studies, the noted effects were related to the pharmacological action of romiplostim. Overdose may result in an excessive increase in platelet counts associated with thrombotic/thromboembolic complications. In the event of an investigational product overdose, platelet counts should be monitored frequently and investigational product dose withheld if platelet counts are > 450 x $10^9$/L. Reinitiate treatment with investigational product when platelet counts are ≤ 450 x $10^9$/L and refer to Section 7.4.1.1 for dosage adjustments.

## 7.8 Prior and Concomitant Treatment

### 7.8.1 Prior Treatment

Prior anti-cancer therapies that were being taken/used from 3 years prior to enrollment through the informed consent will be collected.

For prior therapies being taken for treatment of gastrointestinal, pancreatic, or colorectal cancer, collect therapy name, indication, dose, unit, start date and stop date.

For all other prior therapies, such as radiotherapy, collect therapy name, indication, site (radiotherapy only), dose, unit, frequency route, start date and stop date.

### 7.8.2 Concomitant Treatment

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 7.1.7.

All concomitant therapies will be collected until completion of **safety follow-up (SFU) 1 and SFU 2** after which collected concomitant therapies will include the following: platelet related medications: commercial romiplostim, eltrombopag, avatrombopag, lusutrombopag, fostamatinib, and anticoagulants, only.

For platelet transfusions, collect reason, dose, volume, unit, and start date. For all other concomitant therapies, collect therapy name, indication, dose, unit, frequency, start date and stop date.

## 8. Discontinuation Criteria

Subjects have the right to withdraw from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Sections 8.1, 8.2.1, and 8.2.2.

## 8.1 Discontinuation of Study Treatment

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the

investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see Table 2-1) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data. In particular, the recording of planned chemotherapy administration, which is vital in determining the primary endpoint, can be obtained through medical records if the subject agrees to remain on study despite choosing to discontinue investigational product and other study-related procedures.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with 12.3.

Reasons for removal from protocol-required investigational product(s) or procedural assessments include any of the following:

- Decision by Sponsor
- Lost to follow-up
- Death
- Ineligibility determined
- Protocol deviation
- Non-compliance
- Adverse event
- Subject request
- Requirement for alternative therapy
- Disease progression or relapse per investigator
- Protocol-specified criteria; see Section 7.4:
    - Subjects who have a platelet count < 100 x $10^9$/L for 4 consecutive weeks at the maximum investigational product dose of 10 µg/kg should be discontinued from investigational product.
    - Administration of investigational product should be discontinued at any time during the study if neutralizing antibodies to romiplostim or to endogenous TPO are detected.

- Pregnancy

### 8.2 Discontinuation From the Study

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study, and must document the subject's decision to withdraw in the subject's medical records.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see Appendix 6 for further details).

All subjects who discontinue taking protocol-required therapies, should be encouraged where possible to remain on study to complete the rest of their study visit(s) as would be required by the study protocol. If a subject makes the decision to fully terminate their participation whilst in the trial, the subject should continue to complete the following visits if not already completed:

- the follow-up visit (1 week after the last dose of IP) and
- the first safety follow up visit (SFU 1) (30 days after the last dose of IP)
- the second SFU 2 (30 days after the last dose of on-study cycle of chemotherapy)
- the EOS **V**isit (if the subject is in LTFU and has completed all the above follow up visits, then the EOS **V**isit can be completed at the time of terminating their participation from the study)
- If the subject has yet to complete the above follow-up visits, then the EOS **V**isit should be performed at the same time as the final follow up visit eg, SFU 2.

If the subject does not wish to complete any further visits, then the EOS procedures should be completed (if the subject consents to this) and listed as the subjects last visit on the date the subject decides to terminate early.

#### 8.2.1 Reasons for Removal From Washout, Run-in or Invasive Procedures

Not applicable for this study.

#### 8.2.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- Decision by sponsor

- Withdrawal of consent from study
- Death
- Lost to follow-up

### 8.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or is able to continue in the study.
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts are to be documented in the subject's medical record.
- If the subject continues to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.
- For subjects who are lost to follow-up, the investigator can search publicly available records (where permitted) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

## 9. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (see Table 2-1).

As protocol waivers or exemptions are not allowed if an enrolled subject is subsequently determined to be ineligible for the study, this must be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject is to continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

### 9.1 General Study Periods

#### 9.1.1 Screening, Enrollment and/or Randomization

Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy for any disallowed therapy. After the subject has

signed the informed consent form, the site will register the subject in the IVRS/IXRS and screen the subject in order to assess eligibility for participation. The screening window is up to 4 weeks.

**At screening, both local and central chemistry and hematology labs are to be performed, however, local lab values may be used for eligibility.**

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Screen fail subjects may be rescreened up to 3 times at the discretion of the investigator. Further rescreening requires approval from Amgen Medical Monitors.

Rescreen subjects must first be registered as screen failures in IVRS/IXRS and subsequently registered as rescreens. Once the subject is registered as rescreen, a new 4-week screening window will begin. Subjects will retain the same subject identification number assigned at the original screening. If the rescreening period begins more than 28 days after the original signing of the informed consent form, all screening procedures, including informed consent, must be repeated. If the rescreening **and randomization** occurs within 28 days after the original signing of the informed consent, only those criteria that were originally not met would be required to be repeated.

### 9.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Table 2-1). On-study visits may be completed within ± 1 day. The date of the first dose of investigational product is defined as day 1, and will occur on the same day as randomization. All subsequent doses and study visits will be scheduled based on the day 1 date and will occur weekly throughout the treatment period. Investigational product is to be administered only after all other study visit procedures have been completed during each visit that it is required. 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-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. 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 for a range of between 7-**21** weeks.

### 9.1.3 End of Treatment

The treatment period will be long enough to allow for assessment of 3 planned cycles of chemotherapy **(see Section 5.1 for details).**

The follow-up visit will occur 1 week (± 1 day) after the last scheduled dose of investigational product.

### 9.1.4 End of Treatment Period

The follow-up visit is scheduled to be 7 days (± 1 day) after the last dose of investigational product. End of treatment period (EOTP) is defined as the latest assessment date of that visit. If a subject does not complete a follow-up visit, then EOTP will be 7 days after the last dose of investigational product or the EOS date, whichever is earlier.

### 9.1.5 Long-term Follow-up

Subjects will have an in-clinic LTFU Visit 30 **(+5)** days after the last dose of investigational product. (Safety Follow-up 1). Subjects will be contacted 30 days (+1 week) 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). In addition, after the first LTFU **V**isit, all subjects will be followed by phone or in clinic every 12 weeks (± 2 weeks) **from the last dose of investigational product** until the EOS. 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.

### 9.1.6 End of Study Visit

Excluding early termination of the study, the EOS **V**isit 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. EOS **V**isit can be done by phone.

## 9.2 Description of General Study Assessments and Procedures

The sections below provide a description of the individual study procedures for required time points.

### 9.2.1 General Assessments

#### 9.2.1.1 Informed Consent

All subjects or their legally authorized representative must sign and personally date the IRB/IEC approved informed consent before any study-specific procedures are performed.

#### 9.2.1.2 Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness.

#### 9.2.1.3 Medical History

The investigator or designee will collect a complete medical and surgical history that started 3 years prior to screening through the time of signing of informed consent. Medical history will include information on the subject's concurrent medical conditions. A history of prior and/or concurrent use of alcohol and tobacco will be obtained. Record all findings on the medical history CRF.

#### 9.2.1.4 Physical Examination

Physical examination will be performed as per standard of care. Physical examination findings should be recorded on the appropriate CRF (eg, medical history, event).

#### 9.2.1.5 Physical Measurements

Height in centimeters and weight in kilograms should be measured without shoes.

#### 9.2.1.6 Performance Status

The performance status will be assessed using the ECOG performance status scale.

### 9.2.2 Efficacy Assessments

#### 9.2.2.1 Platelet Counts

Platelet counts will be measured at each visit (on a weekly basis) during the treatment period and throughout the 3 on-study cycles to the end of the third study cycle for patients receiving investigational product and non-investigational product. Platelet counts will be assessed locally. 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. Note: For subjects who discontinue investigational product prior to completing 3 cycles of chemotherapy, platelet counts should be measured through 3 on-study chemotherapy cycles to the end of the third on-study cycle, and the values recorded must be those taken prior to scheduled chemotherapy visits and used to inform decisions relating to chemotherapy dose modification.

#### 9.2.2.2 Bleeding Scale

Subjects must be assessed for signs and symptoms of bleeding at every weekly visit. These findings must be reported as per CTCAE grading criteria (Miller et al, 1981). Grading is based on physical examination at the time of the visit by the investigator or on patient's history supplemented by available medical reports. Bleeding manifestations reported by the patient but not visible at the time of data collection are graded 1.

#### 9.2.2.3 Chemotherapy Dose

The planned and delivered chemotherapy dose will be recorded as area under the curve, milligram per kilogram, or milligram per square meter.

Chemotherapy administration, including information about planned and actual chemotherapy dose and schedule, should be recorded throughout 3 on study cycles, at the follow up at one week after the last dose of IP, SFU1 and SFU2. For the purposes of determining dose reductions, **for those subjects continuing protocol-required chemotherapy regimens**, the 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 subjects beginning a protocol-required chemotherapy regimen, the planned dose for cycle 1 will be the standard dose determined by the Investigator.** Chemotherapy dose modifications occurring during on-study cycle 1 will not count 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**, even if not attributable to CIT**. This will also apply to dose modifications occurring during on study cycle 2. 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. During the 3 on study cycles, a chemotherapy delay must be increments of 1 week to align with the weekly study visits if

applicable. 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. In this situation the local laboratory assessments recorded must be those taken prior to scheduled chemotherapy visits and used to inform decisions relating to chemotherapy dose modification. **Any local laboratory tests performed in the cycle prior to enrollment should be recorded if they are used to determine chemotherapy dose in study cycle 1. Any local laboratory tests performed outside of the study visits should be recorded if they are used to determine chemotherapy dose in study cycles 1, 2, and 3 (see Schedule of Activities [Section 2.2] for further information).**

For the primary endpoint, we will capture information at each weekly study visit on the actual chemotherapy dose and unit, start/stop dates, whether the subject experienced a dose reduction, delay, or omission due to thrombocytopenia with platelet counts below 100 x $10^9$/L, whether the subject experienced chemotherapy treatment discontinuation due to thrombocytopenia with platelet counts below 100 x $10^9$/L or per the guidelines provided when there is thrombocytopenia for the specific tumor types and regimens (Section 7.4.1.2), and whether there was a reason other than thrombocytopenia for dose reduction, delay, omission, or discontinuation. Chemotherapy dose delays, dose reductions, and dose omissions will be permitted according to chemotherapy dose modification guidelines outlined in Section 7.4.1.2. For each planned chemotherapy agent, any thrombocytopenia related modifications which include dose reduction, dose delays, dose omission, and treatment discontinuation, at any time during on-study cycle 2 or 3 will be counted as failure in the primary endpoint analysis. An independent adjudicator will periodically verify the reason for chemotherapy dose modifications during on-study cycles 1-3.

### 9.2.3 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities (Table 2-1).

#### 9.2.3.1 Adverse Events

##### 9.2.3.1.1 Time Period and Frequency for Collecting and Reporting Safety Event Information

###### 9.2.3.1.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the CTCAE version 5.0 and is described in Appendix 4.

Adverse events possibly related to any study procedures are reported after signing of the ICF. All other adverse events are reported after the first dose of protocol-required therapies (romiplostim/placebo [investigational product], chemotherapy [non-investigational product] up to 3 cycles). The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after signing of the ICF or from the first dose of protocol-required therapies, as specified above, through the 30 (+5) days after the last dose of protocol-required therapies (last dose of investigational product and last dose of last cycle [up to 3 cycles] of chemotherapy non-investigational product) are reported using the Event CRF. If mandated by country-specific requirements, non-serious adverse events will be collected through the whole duration of the LTFU period until EOS.

Note: For subjects who discontinue investigational product prior to completing 3 cycles of chemotherapy, non-serious adverse events should be collected through 3 on-study chemotherapy cycles.

###### 9.2.3.1.1.2 Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through the end of study are reported using the Event CRF.

All serious adverse events will be collected, recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 4. The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available.

The criteria for grade 4 in the CTCAE version 5.0 grading scale differs from the regulatory criteria for serious adverse events. It is left to the investigator's judgment to report these grade 4 abnormalities as serious adverse events. **For any adverse event that applies to this situation, comprehensive documentation of the event's severity must be recorded in the subject medical records.**

#### 9.2.3.1.1.3 Serious Adverse Events After the Protocol-required Reporting Period

**If the investigator becomes aware of** serious adverse events **after** the protocol-required reporting period **(as defined in Section 9.2.3.1.1.2) is complete**, these serious adverse events **will** be reported to Amgen **(regardless of causality)**. **The** investigator **will** report serious adverse events to Amgen within 24 hours following the investigator's knowledge of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases and handled accordingly based on relationship to investigational product.

**If further safety related data is needed to fulfill any regulatory reporting requirements for a reportable event, then additional information may need to be collected from the subject's records after the subject ends the study.**

#### 9.2.3.1.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

#### 9.2.3.1.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

All new information for previously reported serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Event CRF.

#### 9.2.3.1.4 Regulatory Reporting Requirements for Serious Adverse Events

If subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

Prompt notification by the investigator to the sponsor of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

Individual safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

To comply with worldwide reporting regulations for serious adverse events, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded by Amgen before submission to regulatory authorities. Aggregate analyses may also be unblinded by the Safety Assessment Team (SAT) as appropriate. Investigators will receive notification of related serious adverse events reports sent to regulatory authorities in accordance with local requirements.

#### 9.2.3.1.5 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and female partners of male subjects will be collected after the start of study treatment and until 30 days after the last dose of protocol-required therapies.

If a pregnancy is reported, the investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in **Appendix 5**. Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

Further details regarding pregnancy and lactation are provided in **Appendix 5**.

#### 9.2.3.2 Vital Signs

Vital signs will be monitored throughout the duration of the study as indicated in the Schedule of Assessments (Table 2-1).

The following measurements must be performed: systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature. Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in the most recumbent position possible. The position selected for a subject should be the same throughout the study and documented on the vital signs CRF. The temperature location selected for a subject should be the same throughout the study and documented on the vital signs CRF. If abnormalities are found and they are considered an adverse event, record on the Event CRF.

#### 9.2.3.3 Electrocardiograms (ECGs)

Electrocardiograms will be performed at screening per local institution standard of care. Subject must be in supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position possible.

The ECG must include the following measurements: heart rate, QRS, QT, QTc, and PR interval.

The investigator will review all ECGs. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen.

#### 9.2.3.4 Vital Status

Vital status must be obtained for all subjects within the limits of local law. This includes subjects who may have discontinued study visits with or without withdrawing consent and should include interrogation of public databases, if necessary. If deceased, the date and reported cause(s) of death should be obtained.

### 9.2.4 Clinical Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities for the timing and frequency.

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the Event CRF. The investigator must determine whether an abnormal value in an individual study subject represents a

clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the Schedule of Activities. Local laboratory assessments taken during the study visit (± 1 day) and recorded in the CRF must be the same values as used for investigational product dose calculations and chemotherapy dose modifications where applicable. The start of the planned chemotherapy must be no more than 2 days after the local laboratory assessments have been taken **during the study visit**. **Any local laboratory tests performed in the cycle prior to enrollment should be recorded if they are used to determine chemotherapy dose in study cycle 1. Any local laboratory tests performed outside of the study visits should be recorded if they are used to determine chemotherapy dose in study cycles 1, 2, and 3.**

Except at screening, laboratory/analyte results that could unblind the study (pharmacokinetic and antibodies samples) will not be reported to investigative sites or other blinded personnel until the study has been unblinded. However, if the value for any laboratory analyte is significantly outside of the reference range by a predefined value, the local and central laboratory will notify the investigative site of the absolute value of the analytes to ensure adequate safety oversight of the enrolled subject. Also, if positive neutralizing antibodies to romiplostim or TPO are detected, the central laboratory will notify the investigative site to ensure adequate safety oversight of the enrolled subject.

#### 9.2.4.1 Pregnancy Testing

For females of childbearing potential, a highly sensitive urine or serum pregnancy test should be completed **prior to enrollment** within 72 hours prior to the first dose of investigational product, monthly during the treatment period**,** and then at 30 days after the last dose of investigational product and 30 (+5) days after the last dose of protocol-required therapies 30 **(**+5**)** days after the last dose of on-study cycle of chemotherapy non-investigational product [up to 3 cycles]).

Note: Females who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements. (If a female subject, or the partner of a male subject, becomes pregnant it must be reported on the Pregnancy Notification Worksheet, see Figure 12-2). Refer to **Appendix 5** for contraceptive requirements.

Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as required per local laws and regulations.

### 9.2.6 Antibody Testing Procedures

Refer to the central laboratory manual for instructions on collection, preparation, storage, and shipment of antibody samples. The week 1 baseline antibody sample must 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. While the subject is receiving investigational product, blood samples will be collected for anti-romiplostim antibodies at predose (day 1), week 8, and at the follow-up visit.

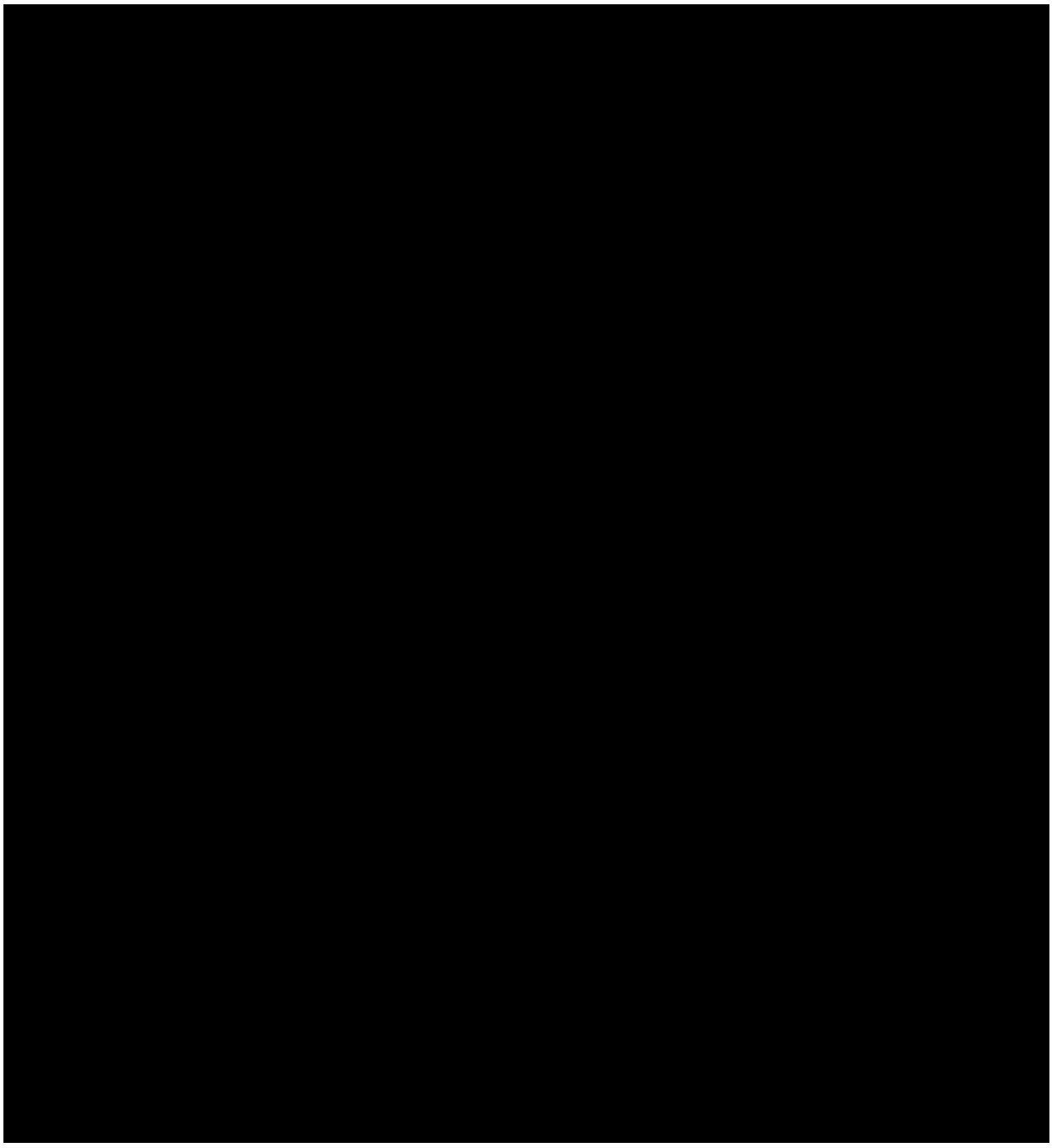
Blood samples will be collected from all subjects for the measurement of anti-romiplostim binding antibodies. Samples testing positive for binding antibodies will also be tested for neutralizing antibodies. Additional blood samples may be obtained to rule out anti-romiplostim antibodies during the study.

Subjects who test positive for neutralizing antibodies to romiplostim at the final scheduled study visit will be asked to return for additional follow-up testing. This testing should occur every 3 months starting from when the site has been notified of the positive result, until: (1) neutralizing antibodies are no longer detectable or (2) the subject has been followed for a period of at least 1 year (± 4 weeks). More frequent testing (eg, every month) or testing for a longer period of time may be requested in the event of

safety-related concerns. Follow-up testing will not be required where it is established that the subject did not receive romiplostim.

Subjects who test positive for binding, non-neutralizing antibodies and have clinical sequelae that are considered potentially related to an anti-romiplostim antibody response may also be asked to return for additional follow-up testing.

Should a subject have a loss of response or fail to maintain a response to investigational product, sites should contact the Clinical Research Associate to inform Amgen that an unscheduled serum sample will be required to rule out anti-romiplostim antibodies.



[redacted]

### 9.2.8 Health Economics OR Medical Resource Utilization and Health Economics

Medical resource utilization and health economics data, associated with medical encounters, will be collected in the CRF by the investigator and study-site personnel for all subjects throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- Duration of hospitalization (total days or length of stay, including duration by wards)
- Number and type of diagnostic and therapeutic tests and procedures

- Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications)
- Quality of life measures

## 10. Statistical Considerations

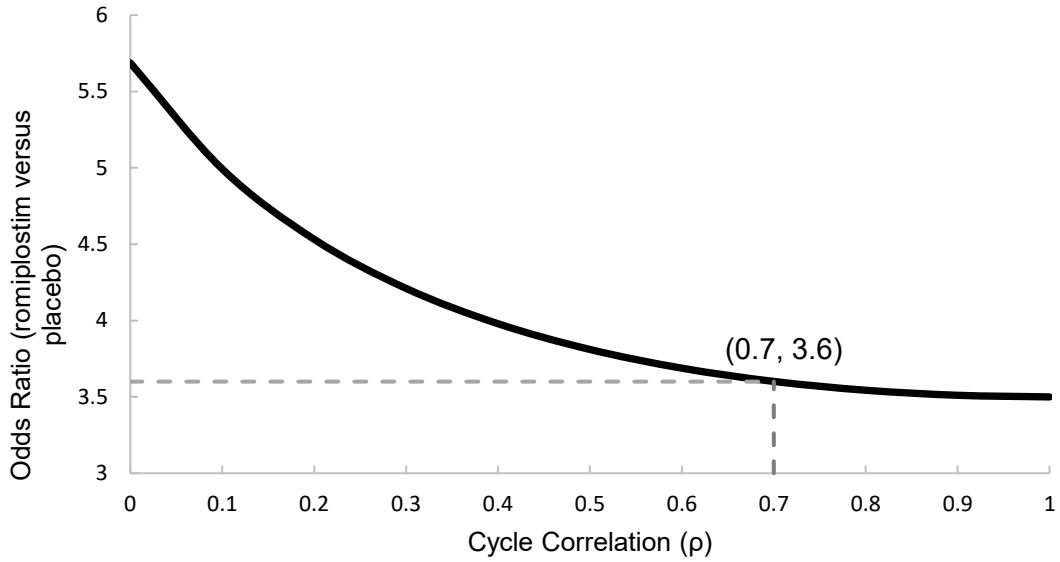
### 10.1 Sample Size Determination

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, $\rho$ 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 10-1).

**Figure 10-1. 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 10-1).

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 ($< 50 \times 10^9$/L, $\geq 50 \times 10^9$/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%.**

## 10.2 Analysis Sets, Subgroups, and Covariates

### 10.2.1 Analysis Sets

#### 10.2.1.1 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.

#### 10.2.1.2 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. **Subjects who receive at least one dose of romiplostim will be included in the romiplostim treatment group.**

[redacted]

### 10.2.2 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 ($< 50 \times 10^9$/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, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Region (United States, Europe, Rest of World)
- Body mass index
- ECOG ($0-1$, $\geq 2$)
- Stage of disease (Stage 1 to 3, Stage 4 or recurrent disease)
- Line of chemotherapy treatment ($1$, $\geq 2$)
- Type of chemotherapy regimen (FOLFOX, FOLFIRINOX, FOLFOXIRI, CAPEOX)
- Number of previous chemotherapy cycles ($\leq 2$, $> 2$)

- 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)

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

Descriptive analyses will be provided including summary statistics for continuous covariates and percentage of subjects by each level of categorical covariates.

For each above specified covariate, sensitivity analyses will be explored 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 dependent variable and explanatory variables from treatment group, the specified covariate, interaction of treatment by covariate.

### 10.2.3 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 in the primary endpoint for the below subgroups:

- 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 ($\leq 2$, $> 2$)
- 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)

### 10.2.4 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. **Subjects with** missing **chemotherapy but having** platelet count assessment **within 2 days of the planned chemotherapy start or chemotherapy discontinuation** will be **determined by the adjudication committee**.

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

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

### 10.3 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses. To preserve study integrity, the final analysis will be conducted and reported following the end of study, as defined in Section 5.3.1.

#### 10.3.1 Planned Analyses

##### 10.3.1.1 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.**

#### 10.3.1.2 Primary Analysis

The primary analysis will be performed at the primary completion date. 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).

#### 10.3.1.3 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.

### 10.3.2 Methods of Analyses

#### 10.3.2.1 General Considerations

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. Subjects who did not achieve a response event during the treatment period are censored at their last

platelet count assessment date up to the EOTP or study day 1 if they did not have any platelet assessment

- 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.

#### 10.3.2.2 Efficacy Analyses

##### 10.3.2.2.1 Primary Endpoint

Primary endpoint is no thrombocytopenia-induced modification of any myelosuppressive treatment agent in the second and third cycles of the planned on-study chemotherapy regimen. Chemotherapy dose modification in the first cycle of the planned on study chemotherapy regimen will not be counted toward the primary endpoint. Chemotherapy dose modification includes dose reduction, delay, omission, and discontinuation. The proportion of subjects with no thrombocytopenia-induced modification will be provided with a 95% CI **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 common odds ratio for romiplostim vs placebo will be estimated along with a 95% CI**. T**he difference in proportions between treatment groups will be provided with a 95% CI. Additional sensitivity analysis will be described in the Statistical Analysis Plan.

##### 10.3.2.2.2 Secondary Endpoints

###### 10.3.2.2.2.1 Depth of Platelet Nadir

The first secondary endpoint is the depth of platelet nadir from the start of the first on-study chemotherapy cycle through the EOTP. 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 factor of tumor type and baseline platelet count, and the interactions between treatment group and the stratification factors. The normality assumption for linear regression models will be

checked using a normal probability plot of the residuals and the Shapiro-Wilk test (Shapiro and Wilk, 1965). If the data fail to meet the normality assumption, data transformation or a non-parametric method may be considered. The detailed analysis plan will be described in the Statistical Analysis Plan.

#### 10.3.2.2.2.2 Time to Platelet Response

The time to first platelet response is defined by platelet count ≥ 100 x $10^9$/L in the absence of platelet transfusions during the preceding 7 days. Time to first platelet response will be calculated from the study day 1 to the date of achieving first platelet count ≥ 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 the EOTP or study day 1 if they did not have any platelet assessment.

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 **estimates** and 2-sided 95% CIs at specified time points (week 3, week 4, etc) for each treatment group. In addition, Kaplan-Meier quartiles (median, $25^{th}$, and $75^{th}$ percentiles) will be estimated with 2-sided 95% CI, if estimable.

#### 10.3.2.2.2.3 Duration-adjusted Event Rate of ≥ Grade 2 Bleeding Events

Duration-adjusted event rate of grade ≥ 2 bleeding events are calculated as total number of events divided by the total duration (per 100-subject-years) from study day 1 until the date of last dose of investigational product plus 30 days. 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.

#### 10.3.2.2.2.4 Overall Survival

Overall survival time is calculated from study day 1 to death. Subjects who have not died will be censored at their last contact date. A 2-sided stratified log rank 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.

#### 10.3.2.2.2.5 Platelet Transfusion

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 common odds ratio for romiplostim vs placebo will be estimated along with a 95% CI.

#### 10.3.2.2.2.6 Achieving a Platelet Count ≥ 100 x $10^9$/L

The proportion of patients 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 common odds ratio for romiplostim vs placebo will be estimated along with a 95% CI.

### 10.3.2.2.3 Exploratory Endpoints

Analyses for exploratory endpoints will be described in the statistical analysis plan.

## 10.3.2.3 Safety Analyses

### 10.3.2.3.1 Adverse Events

The subject incidence of treatment-emergent adverse events will be summarized by system organ class, by preferred term according to Medical Dictionary for Regulatory Activities (MedDRA) for each treatment group. This summary for treatment-emergent adverse events will include the following categories:

- all adverse events
- fatal adverse events
- serious adverse events
- treatment-related adverse events
- adverse events of interest, such as hemorrhage and thrombotic/thromboembolic events
- adverse events leading to investigational product discontinuation

#### 10.3.2.3.2 Laboratory Test Results

The analyses of 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 pre-specified laboratory parameters will be tabulated by treatment group.

#### 10.3.2.3.3 Vital Signs

The analyses of vital signs will include summary statistics at selected time points by treatment group.

#### 10.3.2.3.4 Physical Measurements

The analysis of weight will include summary statistics by treatment group.

#### 10.3.2.3.5 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.

#### 10.3.2.3.6 Exposure to Investigational Product

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

#### 10.3.2.3.7 Exposure to Non-investigational Products

Descriptive statistics of chemotherapy agents and the percentage of dose reduction will be summarized by treatment group.

#### 10.3.2.3.8 Exposure to Concomitant Medication

Number and proportion of subjects receiving therapies of interest will be summarized by preferred term for each treatment group as coded by the World Health Organization Drug (WHODRUG) dictionary.

### 10.3.2.4 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 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.

## 11. References

Adrucil (fluorouracil injection) [prescribing information]. North Wales, PA: Teva Pharmaceuticals Inc; October 2017.

Andersen PK, Gill RD. Cox's Regression Model For Counting Processes: A Large Sample Study. *The Annals of Statistics*. 1982;10.4:1100–1120.

Andre T, Boni C, Mounedj-Boudiaf L, et al, Oxaliplatin, Fluorouracil, and Leucovorin as Adjuvant Treatment for Colon Cancer. *N Engl J Med*. 2004;350:2343-2351.

Al-Samkari H, Marshal AL, Goodarzi K, Kuter DJ. The use of romiplostim in treating chemotherapy-induced thrombocytopenia in patients with solid tumors. *Haematologica*. 2018;103(4):e169-172.

Aspinall SL, Good CB, Zhao X, et al, Adjuvant chemotherapy for stage III colon cancer: relative dose intensity and survival among veterans. *BMC* Cancer. 2015;15:62. pii: haematol.2017.180166. doi: 10.3324/haematol.2017.180166. [Epub ahead of print]

Bhatia S. Therapy-related myelodysplasia and acute myeloid leukemia. *Semin Oncol*. 2013;40(6):666-675.

Blum JL, Jones SE, Buzdar AU, et al: Multicenter phase **II** study of capecitabine in paclitaxel-refractory metastatic breast cancer. J Clin Oncol 17:485, 1999-493.)

Bonadies N, Feller A, Rovo A, et al, Trends of classification, incidence, mortality, and survival of MDS patients in Switzerland between 2001 and 2012. *Cancer Epidemiol*. 2017;46:87–92.

Broudy VC, Lin NL. AMG531 stimulates megakaryopoiesis in vitro by binding to Mpl. *Cytokine.* 2004;25:52-60.

**Camptosar (Irinotecan) USPI. New York, NY: Pharmacia & Upjohn Co; 2020.**

Cella D, Beaumont JL, Webster KA, Lai J-S, Elting L. Measuring the concerns of cancer patients with low platelet counts: the Functional Assessment of Cancer Therapy-Thrombocytopenia (FACT-Th) questionnaire. *Supportive Care in Cancer.* 2006;14:1220-1231.

Cella DF, Tulsky DS, Gray G, et al, The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol.* 1993;11:570-579.

**Cheeseman SL, Joel SP, Chester JD, et al. A 'modified de Gramont' regimen of fluorouracil, alone and with oxaliplatin, for advanced colorectal cancer. *Br J Cancer*. 2002; 87:393.**

Clagett GP, Reisch JS. Prevention of venous thromboembolism in general surgical patients. Results of meta-analysis. *Ann Surg*. 1988;208:227–240.

**Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer. *N Engl J Med.* 2011; 364:1817.**

**Conroy T, Hammel P, Hebbar M, et al. FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer. *N Engl J Med* 2018; 379:2395.**

Cronin-Fenton DP, Sondergaard F, Pederson LA, et al, Hospitalisation for venous thromboembolism in cancer patients and the general population: a population-based cohort study in Denmark, 1997 – 2006. *Br J Cancer*. 2010;103(7):947-953

Denduluri N, Patt DA, Wang Y, et al, Dose Delays, Dose Reductions, and Relative Dose Intensity in Patients With Cancer Who Received Adjuvant or Neoadjuvant Chemotherapy in Community Oncology Practices. *J Natl Compr Canc Netw.* 2015;13:1383-1393.

Elting LS, Rubenstein EB, Martin CG, et al, Incidence, cost, and outcomes of bleeding and chemotherapy dose modification among solid tumor patients with chemotherapy-induced thrombocytopenia. *J Clin Oncol*. 2001;19(4):1137-1146.

EuroQoL Group. EuroQoL: a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16:199–208.

Falanga A. Thrombophilia in cancer. *Semin Thromb Hemost*. 2005;32(1):104–110.

**Falcone A, Ricci S, Brunetti I, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol*. 2007;25:1670-1676.**

Fanale M, Stiff P, Noonan K, et al, Safety of romiplostim for treatment of severe chemotherapy induced thrombocytopenia (CIT) in patients with lymphoma receiving multi-cycle chemotherapy: results from an open-label dose- and schedule-finding study. *Eur J Cancer Suppl.* 2009;7:563. Abstract 9209.

Fischer D, Stewart AL, Bloch DA, Lorig K, Laurent D, Holman H. Capturing the Patient's View of Change as a Clinical Outcome Measure. *JAMA.* 1999;282:1157-1162.

Floyd J, Mirza, I, Sachs B, et al, Hepatoxicity of Chemotherapy. *Semin Oncol*. 2006;33(1):50-67.

Germing U, Aul C, Niemeyer CM, Haas R, Bennett JM. Epidemiology, classification and prognosis of adults and children with myelodysplastic syndromes. *Ann Hematol*. 2008;87(9):691-699.

Goodnough LT, DiPersio JF. Issues in the management of cancer-related thrombocytopenia. *Oncology (Williston Park)*. 2002;16(11):1558-1574.

Goldberg RM, Sargent DJ, Morton RF, et al, A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxiplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol*. 2004;22(1):23-30.

Gordon MS, McCaskill-Stevens WJ, Battiato LA, et al, A phase I trial of recombinant human interleukin-eleven (NEUMEGA@ rhIL-11 growthfactor) in women with breast cancer receiving chemotherapy. *Blood.* 1996;87:3615-3624.

Haddad TC, Greeno EW. Chemotherapy-induced thrombosis. *Thrombosis Research*. 2006;118(5):555 - 568.

**Haller DG, Tabernero J, Maroun J, et al. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. *J Clin Oncol*. 2011;29:1465.**

Hassan MN, Waller EK. Treating chemotherapy-induced thrombocytopenia: is it time for oncologists to use thrombopoietin agonists? *Oncology*. 2015;29(4):295-296.

Heyman MR, Schiffer CA. Platelet transfusion therapy for the cancer patient. *Semin Oncol.* 1990;17:198-209.

**Hochster HS, Hart LL, Ramanathan RK, et al. Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: results of the TREE Study. J Clin Oncol 2008; 26:3523.**

Hod E, Schwartz J. Platelet transfusion refractoriness. *Br J Haematol*. 2008;142(3):348-360.

Khorana AA, Francis CW, Culakova E, Fisher RI, Kuderer NM, Lyman GH. Thromboembolism in hospitalized neutropenic cancer patients. *J Clin Oncol*. 2006;24:484–490.

Kroger K, Weiland D, Ose C, et al, Risk factors for venous thromboembolic events in cancer patients. *Ann Oncol*. 2006;17(2):297–303.

Kuter DJ. Managing thrombocytopenia associated with cancer chemotherapy. *Oncology* (Williston Park). 2015;29:282-294.

Kuter DJ. Biology and chemistry of thrombopoietic agents. *Semin Hematol.* 2010;47(3):243-248.

Kuter DJ, Mufti GJ, Bain BJ, et al, Evaluation of bone marrow reticulin formation in chronic immune thrombocytopenia patients treated with romiplostim. *Blood*. 2009;114(18):3748-3756.

Kuter DJ. New thrombopoietic growth factors. *Blood*. 2007a;109:4607-4616.

Kuter DJ, Bain B, Mufti G, et al, Bone marrow fibrosis: pathophysiology and clinical significance of increased bone marrow stromal fibres. *Br J Haemotol*. 2007b;139(3):351-362.

Kyriazi V and Theodoulou E. Assessing the risk and prognosis of thrombotic complications in cancer patients. *Arch Pathol Lab Med*. 2013;137: 1286-1295.

Lin DY, Wei LJ. The Robust Inference For the Cox Proportional Hazard Model. *Journal of American Statistical Association.* 1989;84:1074–1078.

Loibl S, Skacel T, Nekljudova V, et al, Evaluating the impact of Relative Total Dose Intensity (RTDI) on patients' short and long-term outcome in taxane- and anthracycline-based chemotherapy of metastatic breast cancer- a pooled analysis. *BMC Cancer*. 2011; 11:131

Lyman GH, Dale DC, Crawford J. Incidence and predictors of low dose-intensity in adjuvant breast cancer chemotherapy: a nationwide study of community practices. *J Clin Oncol.* 2003;21:4524-4531.

Lyman GH. Venous thromboembolism in the patient with cancer: focus on burden of disease and benefits of thromboprophylaxis. *Cancer*. 2011;117(7): 1334-1349.

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

Nakayama G, Tanaka C, Uehara K, et al, The impact of dose/time modification in irinotecan and oxaliplatin-based chemotherapies on outcomes in metastatic colorectal cancer. *Cance Chemother Pharmacol*. 2014;73:847-855.

Natale R, Charu V, Schütte W, et al, D. 9248 Safety of romiplostim for treatment of chemotherapy-induced thrombocytopenia (CIT) in patients with advanced non-small cell lung cancer (NSCLC). *Eur J Cancer Suppl*. 2009;7:574. Abstract 9248.

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Colon Cancer, Version 2.2017. J Natl Compr Canc Netw. 2017.

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Rectal Cancer, Version 3.2017. *J Natl Compr Canc Netw.* 2017. https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf

Neumega® [Package Insert]. Wyeth BioPharma Division of Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc, 2011.

Neumega® [United States Prescribing Information]. Wyeth BioPharma Division of Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc, 2012.

Numico G, Garrone O, Dongiovanni V, et al, Prospective evaluation of major vascular events in patients with nonsmall cell lung carcinoma treated with cisplatin and gemcitabine. *Cancer*. 2005;103:994-999.

Oxaliplatin [prescribing information]. Pine Brook, PA: Alvogen Inc; April 2017.

Parameswaran R, Lunning M, Mantha S, et al, Romiplostim for management of chemotherapy-induced thrombocytopenia. *Support Care Cancer*. 2014;22:1217-1222.

Prandoni P, Lensing AW, Piccioli A, et al, Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood*. 2002;100:3484–3488.

Romiplostim Investigator's Brochure. Thousand Oaks, CA. Amgen Inc.

Schiffer CA. Diagnosis and management of refractoriness to platelet transfusion. *Blood Rev.* 2001;15:175-180.

Schwenkglenks M, Matter-Walstra K. Is the EQ-5D suitable for use in oncology? An overview of the literature and recent developments. *Expert Rev Pharmacoecon Outcomes Res.* 2016;16:207-219.

Sekeres M. Epidemiology, natural history, and practice patterns of patients with myelodysplastic syndromes in 2010. J Natl Compr Canc Netw. 2011;9:57–63.

Sekeres MA, List A. Immunomodulation in myelodysplastic syndromes. *Best Practice & Research Clinical Haematology*. 2006;19(4):757–767.

Shapiro SS and Wilk MB. An analysis of variance test for normality (complete samples). *Biometrika*. 1965;52:591–611.

Shen VS, Pollak EW. Fatal pulmonary embolism in cancer patients: is heparin prophylaxis justified? *South Med J*. 1980;73:841–843.

Shi J, Shao ZH, Liu H, et al, Transformation of myelodysplastic syndromes into acute myeloid leukemias. *Chin Med J (Engl).* 2004;117(7):963-967.

Slichter SJ, Davis K, Enright H, et al, Factors affecting posttransfusion platelet increments, platelet refractoriness, and platelet transfusion intervals in thrombocytopenic patients. *Blood*. 2005;105(10):4106-4114.

Soff GA, Miao Y, Devlin SM, et al, Romiplostim for chemotherapy-induced thrombocytopenia (CIT). Results of a Phase 2 Trial. *Blood*. 2017;130:289.

Soff GA, Parameswaran R, Mantha S, Miao Y, Mones JV. Romiplostim management of chemotherapy-induced thrombocytopenia. J Clin Oncol. 2016. Abstract 10134.

Ten Berg MJ, van den Bemt PM, Shantakumar S, et al, Thrombocytopenia in adult cancer patients receiving cytotoxic chemotherapy: results from a retrospective hospital-based cohort study. Drug Saf. 2011;34:1151-1160.

Tefferi A. Experimental myelofibrosis in mice and the implications to human disease. *Leukemia Res*. 2005;29:723-726.

Tepler I, Elias L, Smith JW et al, A randomized placebo-controlled trial of recombinant human interleukin-11 in cancer patients with severe thrombocytopenia due to chemotherapy. *Blood.* 1996;87:3607-3614.

Vadhan-Raj S, Trent J, Araujo DM, et al, Evaluation of AMG 531 in chemotherapy-induced thrombocytopenia (CIT): Results of a phase 1/II study. J Clin Oncol. 2009;27:20616. Abstract e20616.

Vadhan-Raj S, Hagemeister F, Fayad LE, et al, Randomized, Double-Blind, Placebo-Controlled, Dose and Schedule-Finding Study of AMG 531 In Chemotherapy-Induced Thrombocytopenia (CIT): Results of a Phase I/II Study. Blood. 2010;116:1544. Abstract 1544.

Vredenburgh JJ, Hussein A, Fisher D, et al, A randomized trial of recombinant human interleukin-11 following autologous bone marrow transplantation with peripheral blood progenitor cell support in patients with breast cancer. *Biol Blood Marrow Transplant*. 1998;4(3):134-141.

Wang B, Nichol JL, Sullivan JT. Pharmacodynamics and pharmacokinetics of AMG 531, a novel thrombopoietin receptor ligand. Clin Pharmacol Ther. 2004;76:628-638.

White RH, Zhou H, Murin S, Harvey D. Effect of ethnicity and gender on the incidence of venous thromboembolism in a diverse population in California in 1996. *Thromb Haemost*. 2005;93(2):298–305.

Wu Y, Aravind S, Ranganathan G, Martin A, Nalysnyk L, MD, Anemia and thrombocytopenia in patients undergoing chemotherapy for solid tumors: A descriptive study of a large outpatient oncology practice database, 2000–2007. Clin Ther. 2009;31:2416–2432.

**Xeloda (capecitabine) USPI. South San Francisco, CA: Genentech USA, Inc; February 2019.**

# 12. Appendices

## 12.1 Appendix 1. List of Abbreviations and Definitions of Terms

| Abbreviation or Term | Definition/Explanation |
|---|---|
| 5-FU | 5-fluorouracil |
| ALT | alanine aminotransferase |
| AML | acute myeloid leukemia |
| AST | aspartate aminotransferase |
| CAPEOX | capecitabine and oxaliplatin |
| CIT | chemotherapy-induced thrombocytopenia |
| CMH | Cochran-Mantel-Haenszel |
| [redacted] | [redacted] |
| COVID-19 | Coronavirus disease 2019 |
| CRC | colorectal cancer |
| CRF | case report form |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DMC | data monitoring committee |
| DVT | deep vein thrombosis |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| **eCRF** | **electronic case report form(s)** |
| 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 **V**isit 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 [± 1 day] after the last dose of investigational product). If a subject does not complete a follow up visit, then EOTP will be 7 days after the last dose of investigational product or the EOS date, whichever is earlier |
| [redacted] | [redacted] |

| Abbreviation or Term | Definition/Explanation |
|---|---|
| [redacted] | [redacted] |
| FOLFOX | Oxaliplatin, 5-FU, leucovorin |
| FOLFOXIRI | fluorouracil, leucovorin, oxaliplatin, and irinotecan |
| FOLFIRINOX | fluorouracil, leucovorin, oxaliplatin, and irinotecan |
| GCP | Good Clinical Practices |
| GI | gastrointestinal |
| [redacted] | [redacted] |
| ICF | informed consent form |
| ICH | International Council for Harmonisation |
| IEC | Independent Ethics Committee |
| IIS | investigator-initiated study |
| INR | International Normalized Ratio |
| IP | investigational product |
| IPIM | Investigational Product Instruction Manual |
| IRB | Institutional Review Board |
| Interactive Voice Response System (IVRS) | telecommunication technology that is linked to a central computer in real time as an interface to collect and process information |
| Interactive Web Response System (IXRS) | web based technology that is linked to a central computer in real time as an interface to collect and process information |
| LTFU | long-term follow-up |
| MDS | myelodysplastic syndrome |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NCCN | National Comprehensive Cancer Network |
| NSCLC | non-small cell lung cancer |
| [redacted] | [redacted] |
| PCR | polymerase chain reaction |
| PT | prothrombin time |
| PTT | partial thromboplastin time |
| RDI | relative dose intensity |
| **SFU** | **safety follow-up** |

| Abbreviation or Term | Definition/Explanation |
|---|---|
| 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. |
| Study day 1 | defined as the first day that protocol-specified investigational product(s)/protocol-required therapies is/are administered to the subject, which should also be the randomization date |
| TBL | total bilirubin |
| TPO | thrombopoietin |
| ULN | upper limit of normal |
| VTE | venous thromboembolism |

## 12.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 12-1 will be performed by the central and local laboratories. **Additional analyte test results may be reported by the local or central laboratories in accordance with standard laboratory procedures (eg, components of a hematology panel).** Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Sections 6.1 to **6.2** of the protocol. Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

**Table 12-1. Analyte Listing**

| Chemistry 1 (local) | Chemistry 2 (local) | Chemistry 3 (central) | Hematology 1 (local) | Hematology 2 (central) | Other Labs |
|---|---|---|---|---|---|
| Sodium | AST[b] | Sodium | RBC | RBC | Central Laboratory: |
| Potassium | ALT[b] | Potassium | Hemoglobin | Hemoglobin | Romiplostim pharmacokinetic samples[a] |
| Chloride | Alk phos[b] | Chloride | Hematocrit | Hematocrit | |
| Bicarbonate | Total bilirubin[b] | Bicarbonate | MCV | MCV | Antibodies[a]: |
| Total protein | Creatinine[b] | Total protein | MCH | MCH | • To romiplostim |
| Albumin | BUN[b] | Albumin | MCHC | MCHC | • Cross-reacting to endogenous TPO |
| Calcium | GFR[b] | Calcium | RDW | RDW | |
| Adjusted calcium | CrCl[b] | Adjusted calcium | Reticulocytes | Reticulocytes | TPO |
| Magnesium | | Magnesium | WBC | WBC | Local Laboratory: |
| Phosphorus | | Phosphorus | ANC | ANC | Platelet count |
| Glucose | | Glucose | Platelet count | Differential | Hemoglobin |
| BUN or urea | | BUN or urea | Differential | • Bands/stabs | ANC |
| Creatinine | | Creatinine | • Bands/stabs | • Eosinophils | Urine or serum pregnancy[c] |
| Total bilirubin | | Uric acid | • Eosinophils | • Basophils | PT/INR |
| Direct bilirubin | | Total bilirubin | • Basophils | • Lymphocytes | PTT |
| Alk phos | | Direct bilirubin | • Lymphocytes | • Monocytes | Hepatitis B surface antigen[d] |
| AST (SGOT) | | Alk phos | • Monocytes | • Atypical lymphocytes | Hepatitis B core antibody[d] |
| ALT (SGPT) | | LDH | • Atypical lymphocytes | | Hepatitis C antibody[d] |
| **Amylase** | | AST (SGOT) | | | HIV[d] |
| **Lipase** | | ALT (SGPT) | | | |
| | | Amylase | | | |
| | | Lipase | | | |

Alk phos = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CrCl = creatinine clearance; GFR = glomerular filtration rate; HIV = human immunodeficiency virus; INR = international normalization ratio; LDH = lactase dehydrogenase; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PTT = partial thromboplastin time; PT = prothrombin time; RBC = red blood cell count; RDW = red cell distribution width; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; TPO = thrombopoietin; WBC = white blood cells

[a] These lab parameters should be blinded.

[b] Local lab values for BUN, creatinine, creatinine clearance, GFR, ALT, AST, Alk phos, and total bilirubin will be reported when a subject is scheduled to receive chemotherapy through 3 on-study chemotherapy cycles. Local lab chemistries do not need to be reported if a subject is not scheduled to receive chemotherapy.

[c] A highly sensitive urine or serum pregnancy test must be performed.

**[d] Only performed using central laboratories if unable to perform using local laboratories.**

## 12.3 Appendix 3. Study Governance Considerations

### Data Monitoring Committee

An Independent Biostatistics Group (IBG) will perform periodic safety analyses for review by an independent Data Monitoring Committee (DMC), which will include at least **2** clinicians and at least 1 biostatistician who are external to Amgen. The IBG and DMC will have access to subjects' individual treatment assignments. To minimize the potential introduction of bias to the conduct of the study, members of the DMC and Data Monitoring Group will not have any direct contact with study site personnel or subjects. The DMC will communicate major safety concerns and recommendations regarding study modification or termination based on the safety parameters to Amgen in accordance with the DMC charter. **T**he DMC **will** also review **the interim futility analysis results** to assess if the study should stop for futility.

Records of all meetings will be maintained by the DMC for the duration of the study. Records of all meetings will be transferred and stored in the trial master folder at the conclusion of the study. Further details are provided in the DMC charter.

### Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, informed consent form, Investigator's Brochure, and other relevant documents (eg, subject recruitment advertisements) must be submitted to an Institutional Review Board/Independent Ethics Committee (IRB/IEC) by the investigator and reviewed and approved by the IRB/IEC. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

Amgen may amend the protocol at any time. The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document **that Amgen distributes to the site**. The investigator must send a copy of the approval letter from the IRB/IEC and amended

protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen
- Notifying the IRB/IEC of serious adverse events occurring at the site, deviations from the protocol or other adverse event reports received from Amgen, in accordance with local procedures
- Overall conduct of the study at the site and adherence to requirements of Title 21 of the U.S. Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

**Informed Consent Process**

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the sample informed consent form are to be communicated formally in writing from the Amgen Trial Manager to the investigator. The written informed consent form is to be prepared in the language(s) of the potential patient population.

The investigator or his/her delegated representative will explain to the subject, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific screening procedures or any investigational product(s) is/are administered, and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative defined as an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study site.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was

obtained. The authorized person obtaining the informed consent must also sign the informed consent form.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study unless it is a local requirement. The investigator shall then inform the primary care physician. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records; refer to Section 8.

Subjects must be re-consented to the most current version of the informed consent form(s) during their participation in the study.

The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the informed consent form(s) must be provided to the subject or the subject's legally authorized representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood. (Refer to ICH GCP guideline, Section 4.8.9.)

A subject who is rescreened is not required to sign another informed consent form if the rescreening **and randomization** occurs within 28 days from the previous informed consent form signature date.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each subject the objectives of the exploratory research. Subjects will be told

that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for exploratory research. Subjects who decline to participate will not provide this separate signature.

**Data Protection/Subject Confidentiality**

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

Subject will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the case report form (CRF) demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

For Serious Adverse Events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

In compliance with governmental regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

**Publication Policy**

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to

collaborate with authors and Amgen staff, as appropriate, as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states:

Authorship credit is to be based on: (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above.

Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.

All persons designated as authors must qualify for authorship, and all those who qualify are to be listed.

Each author must have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

**Investigator Signatory Obligations**

Each clinical study report is to be signed by the investigator or, in the case of multicenter studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will be any or all of the following:

- A recognized expert in the therapeutic area
- An Investigator who provided significant contributions to either the design or interpretation of the study
- An Investigator contributing a high number of eligible subjects

**Data Quality Assurance**

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, centrally or adjudicated data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Clinical monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements per the sponsor's monitoring plan.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Research & Development Compliance and Audit function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study-related

records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Retention of study documents will be governed by the Clinical Trial Agreement.

CRFs must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language. Consult the country-specific language requirements.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

**Source Documents**

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Source documents may also include data captured in the Interactive Voice Response System (IVRS)/Interactive Web Response System (IXRS) system (if used, such as subject ID and randomization number) and CRF entries if the CRF is the site of the original recording (ie, there is no other written or electronic record of data, such as [redacted]

Data reported on the CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements to include:

- Subject files containing completed CRFs, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen
- Investigational product-related correspondence including Proof of Receipts (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable
- Non-investigational product(s), and/or medical device(s) or combination product(s) documentation, as applicable

Retention of study documents will be governed by the Clinical Trial Agreement.

**Study and Site Closure**

Amgen or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the Clinical Trial Agreement. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen investigational product(s) by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product(s) and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

**Compensation**

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

## 12.4 Appendix 4. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

**Definition of Adverse Event**

| **Adverse Event Definition** |
|---|
| • An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment.<br>• Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device or procedure.<br>• **Note: Treatment-emergent adverse events will be defined in the Statistical Analysis Plan (SAP).** |
| **Events Meeting the Adverse Event Definition** |
| • Any abnormal laboratory test results (hematology, clinical chemistry) or other safety assessments (eg, electrocardiogram [ECG], radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).<br>• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.<br>• New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.<br>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.<br>• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae.<br>• For situations when an adverse event or serious adverse event is due to primary tumor type being studied report all known signs and symptoms. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (eg, metastatic pancreatic cancer). Note: The term “disease progression” should not be used to describe the adverse event.<br>• The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event. Also, “lack of efficacy” or “failure of expected pharmacological action” also constitutes an adverse event or serious adverse event. |
| **Events NOT Meeting the Adverse Event Definition** |
| • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event.<br>• Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).<br>• Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. |

**Definition of Serious Adverse Event**

| **A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:** |
|---|
| **Results in death (fatal)** |
| **Immediately life-threatening**<br>The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. |
| **Requires in-patient hospitalization or prolongation of existing hospitalization**<br>In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event is to be considered serious.<br>Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event. |
| **Results in persistent or significant disability/incapacity**<br>The term disability means a substantial disruption of a person's ability to conduct normal life functions.<br>This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption. |
| **Is a congenital anomaly/birth defect** |
| **Other medically important serious event**<br>Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious.<br>Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. |

**Recording Adverse Events and Serious Adverse Events**

| **Adverse Event and Serious Adverse Event Recording** |
|---|
| • When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.<br>• The investigator will then record all relevant adverse event/serious adverse event information in the Event case report form (CRF). |

- The investigator must assign the following adverse event attributes:
  - Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms);
  - Dates of onset and resolution (if resolved);
  - **Did the event start prior to the first dose of investigational product;**
  - **Assessment of seriousness;**
  - Severity (or toxicity defined below);
  - Assessment of relatedness to Amgen investigational product (romiplostim or placebo) or other protocol-required therapies; mandated study activity/procedure;
  - Action taken**; and**
  - **Outcome of event**.
- If the severity of an adverse event changes from the date of onset to the date of resolution, record as a single event with the worst severity on the Event CRF.
- It is not acceptable for the investigator to send photocopies of the subject's medical records to Amgen in lieu of completion of the Event CRF page.
- If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to Amgen.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

**Evaluating Adverse Events and Serious Adverse Events**

| **Assessment of Severity** |
|---|
| The investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on:<br>The Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 which is available at the following location:<br>http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. |
| **Assessment of Causality** |
| • The investigator is obligated to assess the relationship between investigational product and/or study-mandated procedures and each occurrence of each adverse event/serious adverse event.<br>• Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.<br>• The investigator will use clinical judgment to determine the relationship.<br>• Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. |

- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each adverse event/serious adverse event, the investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality.
- There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data.
- The investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

**Follow-up of Adverse Event and Serious Adverse Event**

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Amgen to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide Amgen with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed Event CRF.
- The investigator will submit any updated serious adverse event data to Amgen within 24 hours of receipt of the information.

**Reporting of Serious Adverse Event**

| **Serious Adverse Event Reporting via Electronic Data Collection Tool** |
|---|
| • The primary mechanism for reporting serious adverse event will be the electronic data capture (EDC) system.<br>• If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using an Electronic Serious Adverse Event (eSAE) Contingency Report Form (paper form; see Figure 12-1) within 24 hours of the investigator's knowledge of the event.<br>• The site will enter the serious adverse event data into the electronic system as soon as it becomes available.<br>• After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data.<br>• If a site receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC has been taken off-line, then the site can report this information on an Electronic Serious Adverse Event Contingency Form (paper form; see Figure 12-1).<br>• **Once the study has ended, serious adverse event(s) should be reported to Amgen (regardless of causality) if the investigator becomes aware of a serious adverse event. The investigator should use the paper-based Serious Adverse Event Contingency Report Form to report the event.** |

## Figure 12-1. Sample Electronic Serious Adverse Event Contingency Report Form

Completion Instructions - Electronic Adverse Event Contingency Report Form
(For use for clinical trial studies using Electronic Data Capture [EDC])

NOTE: This form is to be used under restricted conditions outlined on page 1 below. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

General Instructions

**The protocol will provide instruction on what types of events to report for the study. This form is to be used ONLY to report events that must be captured in the Amgen safety database. *Indicates a mandatory field.**

**Types of Events to be reported on this form**

- **Serious Adverse Events (regardless of causal relationship to IP)**

1. **Site Information**

   **Site Number*** – Enter your assigned site number for this study

   **Investigator*, Country*, Reporter*, Phone No., and Fax No.** – Enter information requested

2. **Subject Information**

   **Subject ID Number*** – Enter the entire number assigned to the subject

   **Age at event onset, Sex, and Race** – Enter the subject's demographic information

   **End of Study date** – If the subject has already completed the study or terminated the study early, enter the End of Study date

***If you are submitting follow-up information to a previous report, provide the serious adverse event term for the previous report as well as the start date for the initial event.***

3. **Serious Adverse Event**

   **Provide the date the Investigator became aware of this Information**

   **Serious Adverse Event Diagnosis or Syndrome*** –
   - If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
   - If a diagnosis is not known, the relevant signs/symptoms should be entered.
   - If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

   **Date Started*** – Enter date the adverse event first started (not the date on which the event met serious criteria )rather than the date of diagnosis or hospitalizion. . **This is a mandatory field.**

   **Date Ended** – Enter date the adverse event ended and not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

   **If event occurred before the first dose of Investigational Product (IP)/drug under study**, add a check mark in the corresponding box.

   **Is event serious?* – Indicate Yes or No. This is a mandatory field.**

   **Serious Criteria Code* – This is a mandatory field for serious events.** Enter all reasons why the reported event has met serious criteria:
   - Immediately life-threatening – Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
   - If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

   **Relationship to IP** – The Investigator must determine and enter the relationship of the event to the IP at the time the event is initially reported. **This is a mandatory field.**

   **Relationship to Amgen device*** – The Investigator must determine and enter the relationship of the event to the Amgen device (e.g. prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field. This question does not apply to non-Amgen devices used in the study (e.g. heating pads, infusion pumps)**

   **Outcome of Event*** – Enter the code for the outcome of the event at the time the form is completed. **This is a mandatory field.**
   - Resolved – End date is known
   - Not resolved / Unknown – End date is unknown
   - Fatal – Event led to death

   **If event is related to a study procedure**, such as a biopsy, radiotherapy or withdrawal of a current drug treatment during a wash-out period, add a check mark to the corresponding box. This does not include relationship to IP or concomitant medication – only diagnostic tests or activities mandated by the protocol.

4. **Hospitalization**

   If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did

   not worsen while on study which involved a hospitalization for an elective treatment, is not considered an adverse event.

*FORM-056006* *Instructions Page 1 of 2* *Version 7.0 Effective Date: 1 February 2016*

## Completion Instructions - Electronic Adverse Event Contingency Report Form (for use for Studies using Electronic Data Capture [EDC])

**Note, this form is to be used under restricted conditions outlined on page 1 of the form. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.**

Protocol specified hospitalizations are exempt.

5. **IP/Drug Under Study Administration including Lot # and Serial # when known / available.**
   **Blinded or open-label –** If applicable, indicate whether the investigational product is blinded or open-label
   **Initial Start Date –** Enter date the product was first administered, regardless of dose.
   **Date of Dose Prior to or at the time of the Event –** Enter date the product was last administered prior to, or at the time of, the onset of the event.
   **Dose, Route, and Frequency at or prior to the event –** Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.
   **Action Taken with Product –** Enter the status of the product administration.

***At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.***

6. **Concomitant Medications**
   **Indicate if there are any medications.**
   **Medication Name, Start Date, Stop Date, Dose, Route, and Frequency –** Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.
   **Co-suspect –** Indicate if the medication is co-suspect in the event
   **Continuing –** Indicate if the subject is still taking the medication
   **Event Treatment –** Indicate if the medication was used to treat the event
7. **Relevant Medical History**
   Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.
8. **Relevant Laboratory Tests**
   **Indicate if there are any relevant laboratory values.**
   **For each test type,** enter the test name, units, date the test was run and the results.
9. **Other Relevant Tests**
   **Indicate if there are any tests, including any diagnostics or procedures.**
   **For each test type,** enter the date, name, results and units (if applicable).

***At the top of Page 3, provide your Site Number and the Subject ID Number in the designated section.***

10. **Case Description**
    **Describe Event –** Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6). If necessary, provide additional pages to Amgen.

**Complete the signature section at the bottom of page 3 and fax the form to Amgen.** *If the reporter is not the investigator, designee must be identified on the Delegation of Authority form.*

| AMGEN<br>Study # 20140346<br>Romiplostim (Nplate®) | **Electronic Serious Adverse Event Contingency Report Form**<br>For Restricted Use |
|---|---|

**Reason for reporting this event via fax**

**The Clinical Trial Database (eg. Rave):**

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

***SELECT OR TYPE IN A FAX#***

**1. SITE INFORMATION**

| Site Number | Investigator | Country |
|---|---|---|
| | | |

| Reporter | Phone Number | Fax Number |
|---|---|---|
| | ( ) | ( ) |

**2. SUBJECT INFORMATION**

| Subject ID Number | Age at event onset | Sex | Race | If applicable, provide End of Study date |
|---|---|---|---|---|
| | | ☐F ☐M | | |

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term: _____ and start date: Day ____ Month ____ Year _____

**3. SERIOUS ADVERSE EVENT**

Provide the date the investigator became aware of this information: Day Month Year

| Serious Adverse Event diagnosis or syndrome<br>If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report<br>*List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.* | Date Started<br>Day Month Year | Date Ended<br>Day Month Year | Check only if event occurred before first dose of IP | Is event serious? | If serious, enter Serious Criteria code (see codes below) | Relationship: Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP? Romiplostim No✓ | Romiplostim Yes✓ | Outcome of Event<br>Resolved<br>Not resolved<br>Fatal<br>Unknown | Check only if event is related to study procedure<br>eg, biopsy |
|---|---|---|---|---|---|---|---|---|---|
| | | | | ☐Yes ☐No | | | | | |
| | | | | ☐Yes ☐No | | | | | |
| | | | | ☐Yes ☐No | | | | | |

| Serious Criteria: | 01 Fatal<br>02 Immediately life-threatening | 03 Required/prolonged hospitalization<br>04 Persistent or significant disability /incapacity | 05 Congenital anomaly / birth defect<br>06 Other medically important serious event |
|---|---|---|---|

**4. Was subject hospitalized or was a hospitalization prolonged due this event?** ☐No ☐Yes If yes, please complete all of Section 4

| Date Admitted<br>Day Month Year | Date Discharged<br>Day Month Year |
|---|---|
| | |
| | |

**5. Was IP/drug under study administered/taken prior to this event?** ☐No ☐Yes If yes, please complete all of Section 5

| | Prior to, or at time of Event | | | | | | |
|---|---|---|---|---|---|---|---|
| | Date of Initial Dose | Date of Dose | Dose | Route | Frequency | Action Taken with Product<br>01 Still being Administered<br>02 Permanently discontinued<br>03 Withheld | Lot # and Serial # |
| IP/Amgen Device: | Day Month Year | Day Month Year | | | | | |

AMGEN
Study # 20140346
Romiplostim (Nplate®)

## Electronic Serious Adverse Event Contingency Report Form

For Restricted Use

| Romiplostim | ☐ Blinded ☐ Open Label | | | | | | | Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown |
|---|---|---|---|---|---|---|---|---|

| Site Number | Subject ID Number |
|---|---|
| | |

**6. CONCOMITANT MEDICATIONS (eg, chemotherapy)** Any Medications? ☐ No ☐ Yes If yes, please complete:

| Medication Name(s) | Start Date (Day Month Year) | Stop Date (Day Month Year) | Co-suspect No✓ | Co-suspect Yes✓ | Continuing No✓ | Continuing Yes✓ | Dose | Route | Freq. | Treatment Med No✓ | Treatment Med Yes✓ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |

**7. RELEVANT MEDICAL HISTORY** ***(include dates, allergies and any relevant prior therapy)***

**8. RELEVANT LABORATORY VALUES** ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

| Date (Day Month Year) | Test | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Unit | | | | | | | | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |

**9. OTHER RELEVANT TESTS** ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

| Date (Day Month Year) | Additional Tests | Results | Units |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |

| AMGEN<br>Study # 20140346<br>Romiplostim (Nplate®) | Electronic Serious Adverse Event Contingency Report Form<br>For Restricted Use |
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| AMGEN<br>Study # 20140346<br>Romiplostim (Nplate®) | Electronic Serious Adverse Event Contingency Report Form<br>For Restricted Use |
|---|---|

| | Site Number | Subject ID Number | |
|---|---|---|---|
| | | | |

**10. CASE DESCRIPTION** ***(Provide narrative details of events listed in section 3)*** Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

| | | |
|---|---|---|
| Signature of Investigator or Designee –<br><br>_____<br>*I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.* | Title | Date |

## 12.5 Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information

Study-specific contraception requirements for male and female of childbearing potential are outlined in Section 6.

Male and female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant or father a child during treatment and for 6 months after the last dose of protocol-required therapies.

Additional medications given during the study may alter the contraceptive requirements. The investigator must discuss these contraceptive changes with the subject.

**Definition of Females of Childbearing Potential**

A female is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Females in the following categories are not considered female of childbearing potential:

- Premenopausal female with 1 of the following:
  - Documented hysterectomy;
  - Documented bilateral salpingectomy; or
  - Documented bilateral oophorectomy.

  Note: Site personnel documentation from the following sources is acceptable: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.
- Premenarchal female
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal acceptable contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment

**Contraception Methods for Female Subjects**

Highly Effective Contraceptive Methods

Note: Failure rate of < 1% per year when used consistently and correctly.

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- Intrauterine device
- Intrauterine hormonal-releasing system
- Bilateral tubal ligation/occlusion
- Vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)

**Contraception Methods for Male Subjects**

- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with protocol-required therapies; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)
- Use a condom during treatment and for an additional 6 months after the last dose of protocol-required therapies
- The female partner should consider using a highly effective method contraception.

Note: If the male's sole female partner is of non-childbearing potential he is not required to use additional forms of contraception during the study.

**Unacceptable Methods of Birth Control for Male and Female Subjects**

Birth control methods that are considered unacceptable in clinical trials include:

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhea method

**Collection of Pregnancy Information**

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 30 days after treatment discontinuation.

- Information will be recorded on the Pregnancy Notification Worksheet (see Figure 12-2). The worksheet must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws.)
- After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 30 days after discontinuation of protocol-required therapies. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.
- If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.
- Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in Section 12.4. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment (see Section 8.1 for details).

Male Subjects With Partners Who Become Pregnant or Were Pregnant at the Time of Enrollment

- In the event a male subject fathers a child during treatment, and for an additional 30 days after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Worksheet. The worksheet (see Figure 12-2) must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws.)
- The investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.

- After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

**Collection of Lactation Information**

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 30 days after the last dose of protocol-required therapies.
- Information will be recorded on the Lactation Notification Worksheet (see below) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion **222**.
- With the female subjects signed authorization for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 30 days after the last dose of protocol-required therapies.

## Figure 12-2. Pregnancy and Lactation Notification Worksheet

**AMGEN® Pregnancy Notification Worksheet**

*Fax Completed Form to the Country-respective Safety Fax Line*

SELECT OR TYPE IN A FAX#

**1. Case Administrative Information**

**Protocol/Study Number:** 20140346

**Study Design:** ■ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

**2. Contact Information**

**Investigator Name** _____ **Site #** _____

**Phone** (____) _____ **Fax** (____) _____ **Email** _____

**Institution** _____

**Address** _____

**3. Subject Information**

**Subject ID #** _____ **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm____ / dd____ / yyyy____

**4. Amgen Product Exposure**

| Amgen Product | Dose at time of conception | Frequency | Route | Start Date |
|---|---|---|---|---|
| | | | | mm____/dd____/yyyy____ |

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

**5. Pregnancy Information**

Pregnant female's LMP mm____ / dd____ / yyyy____ ☐ Unknown

Estimated date of delivery mm____ / dd____ / yyyy____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm____ / dd____ / yyyy____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm____ / dd____ / yyyy____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details: _____

**Form Completed by:**

**Print Name:** _____ **Title:** _____

**Signature:** _____ **Date:** _____

Effective Date: March 27, 2011 Page 1 of 1

## AMGEN® Lactation Notification Worksheet

*Fax Completed Form to the Country-respective Safety Fax Line*

SELECT OR TYPE IN A FAX# enter fax number

### 1. Case Administrative Information

**Protocol/Study Number:** 20140346

**Study Design:** ☑ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

### 2. Contact Information

**Investigator Name** _____ **Site #** _____

**Phone** (____)_____ **Fax** (____)_____ **Email** _____

**Institution** _____

**Address** _____

### 3. Subject Information

**Subject ID #** _____ **Subject Date of Birth:** mm____ / dd____/ yyyy____

### 4. Amgen Product Exposure

| Amgen Product | Dose at time of breast feeding | Frequency | Route | Start Date |
|---|---|---|---|---|
| | | | | mm____/dd____/yyyy____ |

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm ____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

### 5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

**Form Completed by:**

**Print Name:** _____ **Title:** _____

**Signature:** _____ **Date:** _____

Effective Date: 03 April 2012, version 2. Page 1 of 1

## 12.6 Appendix 6. Sample Storage and Destruction

Any blood sample collected according to the Schedule of Activities can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand gastrointestinal**,** pancreatic**,** or colorectal cancer, the dose response and/or prediction of response to romiplostim, characterize antibody response, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of pharmacogenetic, biomarker development, or other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining sample types (eg, blood, tumor) samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as

appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Section 12.3 for subject confidentiality.

## 12.7 Appendix 7. Use of Home Healthcare and Telemedicine During the COVID-19 Pandemic

**Appendix 7 is not applicable for participating sites in Bulgaria.**

Home Healthcare Visits

In an effort to ensure continuity and oversight of medical care when there are site/travel restrictions and/or safety concerns resulting from the COVID-19 pandemic, the investigator may use home healthcare services, if approved by the sponsor, in accordance with local regulatory guidance. The investigator may provide home healthcare services approved by the site's institution and performed by site staff or alternatively use a home healthcare service **if** provided by the sponsor to conduct study procedures as required according to the Schedule Activities (Table 2-1), subject to the investigator's discretion.

For example, home visit procedures may include:

- Preparation and administration of investigational product
- Collection of vital sign data
- Assessments of adverse events and concomitant medications
- [redacted]
- Laboratory blood sample collection and processing (including urine/ blood pregnancy test as appropriate)

Home healthcare provider staff must be included on the study delegation log (authorized by the investigator) before any study-related tasks to be conducted by each home healthcare provider are started. In addition, study-specific training including requirements for preparation and administration of investigational product and recording source documentation for the home healthcare provider, must be completed before they conduct any study-related tasks. Following home healthcare visits, all the information collected will be documented on the home health care services visit worksheet and forwarded to the investigator. A comprehensive list of all home healthcare services, as well as mandatory procedural and data collection requirements, will be separately provided in a home healthcare manual.

Telemedicine

In an effort to ensure continuity and oversight of medical care and oversight when there are site/travel restrictions and/or safety concerns resulting from the COVID-19 pandemic, the investigator may use telemedicine, if approved by the sponsor, in accordance with local regulatory guidance. The investigator may use locally approved

telemedicine services or an appropriate platform **if** supplied by the sponsor to conduct study procedures as required according to the Schedule Activities (Table 2-1), subject to the investigator's discretion.

For example, procedures performed using telemedicine may include:

- Physical examination (limited to procedures that can be performed visually)
- Assessments of adverse events and concomitant medications
- ECOG performance status

**Amendment 7**

**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**

Amgen Protocol Number Romiplostim 20140346

Amendment Date: 29 July 2021

**Rationale:**

The rationale for this protocol amendment is to include the following updates:

Changes to inclusion criteria: Due to the low accrual to study 20140346 and the high number of screen failures the following changes are being made to the inclusion criteria:

- Change Day 1 platelet count from < 75 x $10^9$/L to ≤ 85 x $10^9$/L
- Allow subjects to be registered if a protocol allowed chemotherapy regimen is planned and has been delayed due to CIT for at least a week.

Expand chemotherapy dose modification guidelines to minimize variation among sites in dosing chemotherapy for CIT. The current guidelines are primarily from the individual drug's label. Only the FOLFOX regimen is in the oxaliplatin label. The other protocol approved regimens are not in the oxaliplatin label. The dose modification guidelines that were used in the phase 3 clinical trials that demonstrated their efficacy and safety were added to the protocol to reduce variation in dosing among sites.

Allow screening laboratory studies to be done locally to determine patient eligibility and minimize the time before registration.

One interim futility analysis will be performed when approximately 81 subjects complete 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.

Administration, typographical and formatting changes were made throughout the protocol. Updates have been implemented to align with the current template.

**Superseding Amendment # 6**

**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**

Amgen Protocol Number Romiplostim 20140346

| | |
|---|---|
| Amendment Date: | 02 September 2020 |
| Superseding Amendment Date | 02 November 2020 |

**Rationale:**

The following changes were made to the protocol dated 02 September 2020.

- Clarify the dosing schedule of investigational product when it is given on those weeks with concomitant chemotherapy.
- Clarifies that investigational product is given on chemotherapy day 1 of each chemotherapy cycle during the 3 on study cycles.
- Text was added that the relevant laboratory tests are checked one time weekly and that the start of the planned chemotherapy must be no more than 2 days after the local laboratory assessments have been taken**.**
- An administrative change provides guidance to use the chemotherapy dose modification guidelines outlined in Section 7.4.1.2.
- Another administrative change provides laboratory guidance to be consistent with the Schedule of Activities.
- Text was added to Appendix 7, Use of Home Healthcare and Telemedicine During the COVID-19 Pandemic, that it is not applicable for participating sites in Bulgaria per local regulations.

On 02 November 2020, the protocol amendment 6 was superseded to fix the following:

- To fix the formatting/Numbering of the section headings from Inclusion criteria 6.1 onwards.
- To fix the other historical formatting issues or editorial changes (including typographical, grammatical, and formatting).

**Amendment # 6**

**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**

Amgen Protocol Number Romiplostim 20140346

Amendment Date: 02 September 2020

**Rationale:**

- Clarify the dosing schedule of investigational product when it is given on those weeks with concomitant chemotherapy.
- Clarifies that investigational product is given on chemotherapy day 1 of each chemotherapy cycle during the 3 on study cycles.
- Text was added that the relevant laboratory tests are checked one time weekly and that the start of the planned chemotherapy must be no more than 2 days after the local laboratory assessments have been taken**.**
- An administrative change provides guidance to use the chemotherapy dose modification guidelines outlined in Section 7.4.1.2.
- Another administrative change provides laboratory guidance to be consistent with the Schedule of Activities.
- Text was added to Appendix 7, Use of Home Healthcare and Telemedicine During the COVID-19 Pandemic, that it is not applicable for participating sites in Bulgaria per local regulations.

**Amendment 5**

**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**

Amgen Protocol Number *Romiplostim 20140346*

Amendment Date: *08 June 2020*

**Rationale:**

This protocol is being amended to:

- Update inclusion criteria to:
    - Allow new chemotherapy regimens
    - Add pancreatic cancer
- Allow three rescreening attempts
- Allow Home Health Care and Telemedicine when on-site study visits are impacted by the Coronavirus disease 2019 (COVID-19) pandemic
- Provide administrative and editorial updates throughout

**Amendment 4**

**Protocol Title: RECITE: A Phase 3 Randomized Placebo-controlled Double-blind Study of Romiplostim for the Treatment of Chemotherapy-induced Thrombocytopenia in Patients Receiving FOLFOX-based Chemotherapy for Treatment of Gastrointestinal or Colorectal Cancer**

Amgen Protocol Number (Romiplostim) 20140346

EudraCT Number: 2017-002992-25

NCT Number: NCT03362177



Amendment Date: 19 August 2019

**Rationale:**

This protocol is being amended to:

- add text to clarify that platelet counts, platelet transfusions, adverse events, chemotherapy dose and chemistry analytes should be recorded for 3 on-study chemotherapy cycles if the subject discontinues investigational product prior to completing 3 cycles of chemotherapy
- Change Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 to version 5.0
- Add thrombotic/thromboembolic events to treatment-emergent adverse events of interest
- Modify criteria to exclude females who are pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment and for an additional 6 months after after the last dose of protocol-required therapies
- Amend protocol exclusion criteria 223 and 224 to reflect that unwillingness to use a highly effective method of contraception by female participants or female partner(s) of a male participant will meet the respective exclusion criterion
- Specify that contraception methods must be used for an additional 6 months after the last dose of protocol-required therapies
- Add criteria to exclude male subjects who are unwilling to use contraception or unwilling to abstain from donating sperm during treatment (and chemotherapy) and for an additional 6 months after treatment
- Change contraception requirements for female subjects from acceptable to highly effective contraceptive methods

- Update analyte table to include local blood urea nitrogen (BUN) collection
- Specify that for urine pregnancy testing a highly sensitive urine pregnancy test must be performed.
- Add text to perform monthly pregnancy test during the treatment period and one further pregnancy test at 30 days after the last dose of protocol-required therapies.

**Amendment 3**

**Protocol Title: A Phase 3 Randomized Placebo-controlled Double-blind Study of Romiplostim for the Treatment of Chemotherapy-induced Thrombocytopenia in Patients Receiving FOLFOX-based Chemotherapy for Treatment of Gastrointestinal or Colorectal Cancer**

Amgen Protocol Number Nplate 20140346

EudraCT number 2017-002992-25

NCT number NCT03362177

Amendment Date: 27 February 2019

**Rationale:**

This protocol is being amended to:

- Update the order of secondary endpoints. This is to address FDA request received for 20170770 SPA No Ageement letter that the rank of the duration adjusted event rate of ≥ Grade 2 bleeding events and platelet transfusions endpoints should be higher than achieving a platelet count of ≥100 x $10^9$/L endpoint in the testing strategy for the secondary endpoints.
- Add language to clarify definition of dose modifications, which already included chemotherapy dose reductions and delays, to also include dose omissions and treatment discontinuations. Any of the above reasons for dose modifications will be counted as failures in the primary endpoint analysis.
- Add a stratification factor of baseline platelet count (< 50 x $10^9$/L, ≥ 50 x $10^9$/L) at randomization. Study schema updated to show additional stratification.
- Add guidance on chemotherapy dose modifications due to renal and hepatic toxicity.
- Add an evaluation of the normality assumption strategy for the first secondary endpoint and propose possible alternate methods.
- Add additional potential confounding covariate programmed cell death 1 inhibitor use and programmed cell death ligand 1 inhibitor use per FDA request.
- Add missing data assessment with possible reasons.
- Make editorial and administrative changes for grammatical reasons as well as for internal consistency within the protocol.

Amendment 2

Protocol Title: A Phase 3 Randomized Placebo-controlled Double-blind Study of Romiplostim for the Treatment of Chemotherapy-induced Thrombocytopenia in Patients Receiving FOLFOX-based Chemotherapy for Treatment of Gastrointestinal or Colorectal Cancer

Amgen Protocol Number Romiplostim 20140346

EudraCT number 2017-002992-25

NCT number NCT03362177

Amendment Date: 14 November 2018

**Rationale:**

This protocol is being amended to:

- Clarify local laboratory collection of hemoglobin and absolute neutrophil counts on day 1
- Include hepatitis and HIV tests at screening in Schedule of Activities for consistency within protocol
- Update End of Study Definitions for clarity and consistency
- Clarify hepatitis and HIV testing requirement for subjects without a documented diagnosis in medical history
- Clarify concomitant medication timing when a subject is receiving a concomitant chemotherapy on a study visit date
- Update study schema by moving number of subjects (N=162) from screening to enrollment phase and in alignment with the rest of the protocol
- Update the schedule of assessment to be consistent with updates to the protocol
- Update primary endpoint definition to include any dose delay or dose reduction in second and third cycle. This is to address FDA request that the primary analyses of the efficacy endpoints should be based on intent to treat population
- Update the primary analyses of the efficacy endpoints such that subject will meet the criteria of the primary endpoint if they have no thrombocytopenia-induced modification of any myelosuppressive agent in the second and third cycles of the planned on study chemotherapy regimen
- Change the hierarchical order of secondary endpoints with platelet nadir as first secondary endpoint, and bleeding events and overall survival moved higher in the order
- Clarify the reference time point for monitoring overall survival as 1 year after the last dose of investigational product
- Add vital status as part of assessments during long term follow up
- Add instruction on how to handle discordant platelet values if multiple tests are done in the same day or $\pm$ 1 day

- Add thrombocytopenia-related dose modification guidance per chemotherapy and tumor type
- Update the number of investigative sites to 100 instead of 125, and remove Canada as a separate site
- Update the study duration for subjects to be consistent with the rest of the protocol
- Revise exclusion criterion 220 to exclude only patients with severe renal impairment (creatinine clearance < 30 mL/min)
- Update exclusion criteria by excluding subjects with thrombocytopenia due to another etiology other than chemotherapy-induced thrombocytopenia (exclusion criterion 215)
- Update the General Study Periods in the protocol by adding language to accommodate for rescreening that occurs less than 30 days after the original signing of the informed consent
- Add a 15% minimum cap regarding enrollment of subjects for each tumor type
- Update the treatment period considering the chemotherapy cycles and the investigational product dose adjustment guidelines
- Update the proposed analysis plan to include sensitivity analyses using different cutoff values to evaluate the robustness of analysis results
- Revise the strategy for handling missing data to be consistent between the two cycles, and for the patients whose cycle 2 or cycle 3 status is missing, sensitivity analyses will be explored by imputing the missing observations in cycle 2 and/or cycle 3 using the same rule based on the last platelet count assessment when calculating the primary endpoint
- Revise relevant language in Section 10 (Statistical Considerations) and respective text in synopsis, since secondary endpoint is no longer considered in sample size/power calculation
- Make editorial and administrative changes for grammatical reasons as well as for internal consistency within the protocol

**Amendment 1**

**Protocol Title: A Phase 3 Randomized Placebo-controlled Double-blind Study of Romiplostim for the Treatment of Chemotherapy-induced Thrombocytopenia in Patients Receiving FOLFOX-based Chemotherapy for Treatment of Gastrointestinal or Colorectal Cancer**

Amgen Protocol Number Romiplostim 20140346

EudraCT number 2017-002992-25

NCT number NCT03362177

Amendment Date: 12 March 2018

**Rationale:**

This amendment was revised to:

- Specified the chemotherapy regimen and type of cancer to state that romipostim will be studied for the treatment of chemotherapy-induced thrombocytopenia in patients receiving a FOLFOX-based chemotherapy regimen for treatment of gastrointestinal or colorectal cancer:
  - Limit the chemotherapy regimen to 'FOLFOX-based regimen'.
  - Removed lung and ovarian cancer.
  - Enrollment stratified by gastrointestinal and colorectal cancer.
- Added a secondary endpoint to measure overall survival.
- Added the benefit/risk Assessment.
- Editorial changes (ie, typographic, grammatical, and formatting errors) and abbreviation corrections were made throughout the protocol in accordance with Amgen Inc. Style Guide.