MSK PROTOCOL COVER SHEET

An Open Label Phase II Study of Romiplostim for Chemotherapy Induced Thrombocytopenia

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

TARGET PATIENTS

- Locally advanced or metastatic solid tumors, and
- Chemotherapy Induced Thrombocytopenia,
  - Thrombocytopenia has persisted for at least 4 weeks despite:
  - Delay in chemotherapy, and/or
  - Modification of chemotherapy dose/regimen.
- Meets Inclusion/Exclusion criteria
- No mutations associated with myelodysplasia or leukemia by peripheral blood bone marrow cytogenetics and FISH panel.

Intervention:
Romiplostim (Weekly, SQ Treatment)
Initial dose: 2 mcg/kg, then titrate per protocol section 9.0, "Treatment/ Intervention Plan"

- Weekly monitoring on Romiplostim per section 9.0, "Treatment/ Intervention Plan:
- First 3 weeks on treatment: Weekly CBC, COMP, LDH, PT, aPTT
- Maintenance on Treatment:
  Weekly CBC and monthly Comprehensive Chemistry Panel, LDH, PT, aPTT

Primary Endpoint: At 3 Weeks	**Proportion of patients achieving ≥100,000/mcL platelets by the end of 3 weeks of treatment.**
Within 3 weeks	**Romiplostim (Treatment)**
<100,000/mcL	Failure: terminate from study **or** continue at the discretion of the investigator.
≥100,000/mcL	Success: Continue romiplostim at the discretion of the investigator and oncologist.

At Successful Achievement of Primary Endpoint: Achieve a platelet count of ≥100,000/mcL within 3 weeks.

- Resume chemotherapy regimen at the discretion of the oncologist.
- Continue weekly romiplostim

Secondary Endpoints:

1. Ability to resume and continue two cycles (or 8 weeks, whichever comes first) of chemotherapy without recurrence of Chemotherapy-Induced Thrombocytopenia. We will also observe the following events:12 months of chemotherapy without recurrence of Chemotherapy-Induced Thrombocytopenia.
2. Change in chemotherapy regimen for toxicity unrelated to thrombocytopenia.
3. Change in chemotherapy regiment for progression of disease or other cancer-related conditions.
4. Death from any cause.

NOTES:

- All Romiplostim treatment will be given as weekly, subcutaneous injections, and doses titrated per protocol section 9.0, “Treatment/ Intervention Plan”.
- After the initial 3 weeks of romiplostim on romiplostim, patients who remain on weekly romiplostim will continue to have routine monitoring of weekly CBC and monthly COMP, LDH, and PT/aPTT at discretion of study investigator or oncologist.
- Patients who remain on Romiplostim for 4 or more months, will undergo one marrow aspirate and biopsy or peripheral blood test, with cytogenetics, and FISH panel for MDS, in the 30 day period after completion of the 4th month.
- Throughout this protocol, to allow for patient scheduling limitations and needs, treatment schedules will be 7 days +/- 2 days.
- Treatment can be held up to 16 days if patient develops an intercurrent medical illness or symptom that is unrelated. Treatment may be held up to 20 days if the patient is unavailable for non-medical reasons, such as vacation or travel.
- If the patient receives romiplostim therapy for ≥12 months, the scheduling of routine labs and treatment dosing will be at the discretion of the investigator.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

The primary objective for this study is:

1. To evaluate whether romiplostim can improve the recovery of persistent, isolated Chemotherapy-Induced Thrombocytopenia (CIT), to a platelet count ≥100,000/mcL within 3 weeks after initiation of therapy.

Secondary Objectives
The secondary objectives for this study are:

1. In patients whose platelet counts have recovered within three weeks on romiplostim treatment, we will observe for:
    a. Ability to resume at least two cycles (or eight weeks, whichever comes first) of chemotherapy without recurrence of chemotherapy-induced thrombocytopenia leading to chemotherapy dose delay or reduction.
        i. Note the duration of off-chemotherapy time.
    b. Change in chemotherapy for progression of disease or other cancer related conditions.
    c. Change in chemotherapy for other toxicities unrelated to thrombocytopenia.
    d. Censor patients who have tolerated chemotherapy with romiplostim support for up to 12 months.
    e. Death due to all causes.
2. The safety profile of romiplostim will be assessed in this patient population at specified time-points during the course of study as per section 11.0 Toxicities/Side Effects.

3.0 BACKGROUND AND RATIONALE

3.1 Chemotherapy-induced thrombocytopenia

Chemotherapy-induced thrombocytopenia (CIT) is defined as a single hematopoietic lineage depression resulting in a low platelet count (< 100,000/mcL) despite adequate recovery time from prior chemotherapy. Not uncommonly, CIT can result in subsequent dose reductions and can adversely affect on time delivery of subsequent chemotherapy cycles. In a retrospective series of 609 patients with solid tumors or lymphoma who exhibited CIT (platelets of <50,000/mcL), delay in subsequent chemotherapy occurred during 6% of cycles. The CIT cohort used more resources, but outcomes were not impacted when compared to those who did not experience CIT[1]. In the same report, dose reduction occurred in 15% of patients with CIT [1]. Currently, the management of CIT is supportive with platelet transfusions per the discretion of the treating medical oncologist. Presently, there is no specific standard of care for CIT.

3.2 Romiplostim: Mechanism of action

Romiplostim (Npate®) is a thrombopoietin (TPO) mimetic that is Food and Drug Administration (FDA) approved for use in patients with chronic immune thrombocytopenia (ITP) [2]. Romiplostim bears no structural or biochemical resemblance to TPO, but mimics the TPO binding to the TPO receptor (Mpl). [3] Romiplostim is a 'peptibody' formed by the fusion of the Fc portion of an IgG1 monoclonal antibody with four TPO mimetic peptides. Romiplostim binds the distal cytokine homology region of the TPO receptor leading to activation of the JAK/STAT pathway. Simultaneously, romiplostim has been shown to engage the MAP kinase pathway leading to activation of anti-apoptotic pathways resulting in increased platelet production[4,5].

3.3 Romiplostim: Clinical activity

Romiplostim has been shown to increase and maintain platelet counts in splenectomized and non-splenectomized patient with ITP with few adverse effects. [6] No anti-TPO antibody formation of clinical significance has been reported to date. [6] In several trials of patients with ITP, the mean therapeutic dose of romiplostim to achieve a platelet count of 50-200,000/mcL was 3-4 mcg/kg. [5]

3.4 Rationale for Romiplostim in CIT

At MSKCC, Soff, Parameswaran, and Mantha have treated over 50 patients with romiplostim for CIT. Our initial case series of 20 patients was published in 2014, indicating 19 of 20 treated patients meeting the goal of normalization of platelet count to >100,000/mcL (Parameswaran et al, 2014).

Our interim observations of this current clinical trial suggests that romiplostim is effective and safe to improve platelet counts in patients with CIT. Of the treatment patients, 13 of the 14 (93%) romiplostim patients normalized their platelet count within the three-week primary endpoint. From our initial 21 patients who enrolled on this trial, 1 out of 7 (14.3%) observation patients have corrected her platelet counts within 3 weeks. (P= 0.0009 by two-tailed Fisher's Exact Test). Of the 5 observation patients who crossed over to romiplostim and were evaluable, all 5 corrected their platelet count within 3 weeks. Of all patients receiving romiplostim, 18 of 19 patients (95%) reach platelet counts of 100,000/mcL or greater within 3 weeks of treatment. No patients who resumed chemotherapy while receiving romiplostim (N=14) had a recurrence of CIT. We continue to see efficacy and safety within our patients currently on romiplostim. Based on highly significant efficacy and no further spontaneous correction of platelets, it was felt inappropriate to continue randomizing to the observation control arm.

No toxicity attributable to the romiplostim has been observed in our initial cases. Three of the initial 20 courses of treatment (19 patients) developed deep vein thrombosis which is within the historical range of between 10% and 30% [7] in comparable patients with metastatic cancer on chemotherapy. Further, one of the two patients with DVT had a previous history of DVT, prior to initiation of romiplostim, and had been off anticoagulation when the second thrombosis occurred.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

Primary objective:

This is an intent-to-treat multicenter phase II open label trial. Once appropriate patients are identified and enrolled, 60 patients will be enrolled.

During the initial 3-week period, the enrolled patients will receive romiplostim, titrated as per protocol (Section 9.0). Assessment for the primary endpoint will take place at week 3 and denote the proportion of patients that achieves a platelet count of $\geq$100,000/mcL within 3 weeks of initiation.

Safety Analysis will be performed at specified time-points (Section 11.0 Toxicities/Side Effects) including possible adverse events such as thrombosis, peripheral blood abnormalities and evidence of organ dysfunction.

Secondary objective:

In patients whose platelet counts have recovered within three weeks, we will observe for patient's ability to receive two cycles (or eight weeks, whichever comes first) of cytotoxic chemotherapy without recurrence of chemotherapy-induced thrombocytopenia leading to chemotherapy dose delay or reduction; change in chemotherapy for progression of disease or other cancer related conditions; change in chemotherapy for other toxicities unrelated to thrombocytopenia; and death due to all causes. The duration for patients off-chemotherapy will also be noted. In addition we are also censoring patients who have tolerated chemotherapy with romiplostim support for up to 12 months.

Safety endpoints will include possible adverse events such as thrombosis, evidence of marrow toxicity, and evidence of organ dysfunction.

4.2 Intervention

I. Initial Phase of Study: Intervention For Primary Endpoint.

Romiplostim, n=60.
All patients will begin weekly romiplostim at 2 mcg/kg, subcutaneously. The romiplostim dose will be titrated as per Section 9.0, based on weekly CBC/platelet counts. For titration purposes, the target platelet count is 150,000-200,000/mcL.

II. Maintenance romiplostim, During Resumed Chemotherapy/Secondary Efficacy Endpoint

All patients on romiplostim who achieve a platelet count adequate ($\geq$100,000/mcL) and resume chemotherapy will be followed with continuation of weekly, titrated romiplostim.

In patients whose platelet counts have recovered within three weeks, we are observing for ability to resume 2 cycles (or eight weeks, whichever comes first) of cytotoxic chemotherapy without recurrence of chemotherapy-induced thrombocytopenia leading to chemotherapy dose delay or reduction; change in chemotherapy for progression of disease or other cancer related conditions; change in chemotherapy for other toxicities unrelated to thrombocytopenia; and death due to all causes. The duration for patients off chemotherapy will be noted. In addition we are also censoring patients who have tolerated chemotherapy with romiplostim support for up to 12 months.

Patients who are benefitting from the romiplostim, will be able to remain on treatment beyond the completion of 12 months on study, at the discretion of their oncologist and the study participating hematologist.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Romiplostim, a member of the TPO mimetic class, is an Fc-peptide fusion protein (peptibody) that activates intracellular transcriptional pathways leading to increased platelet production via the TPO receptor (also known as cMpl). The peptibody molecule contains two identical single-chain subunits, each consisting of human immunoglobulin IgG1 Fc domain, covalently linked at the C-terminus to a peptide containing two thrombopoietin receptor-binding domains. Romiplostim has no amino acid sequence homology to endogenous TPO. Romiplostim is produced by recombinant DNA technology in *Escherichia coli (E coli)*.

Romiplostim is approximately 59 kilodalton and is comprised of 4 Mpl-binding domains and an Fc fragment. The peptibody is produced by recombinant DNA technology in Escherichia coli (E coli). Though it has no amino acid sequence homology to endogenous thrombopoietin (eTPO), romiplostim is an agonist of the thrombopoietin (TPO) receptor and signals and activates intracellular transcriptional pathways to increase platelet production.

Romiplostim is supplied as a sterile, preservative-free lyophilized white powder ready for reconstitution. It is supplied for single use in 5 cc Type I glass vials containing 625 µg of romiplostim, 500 µg deliverable drug product. When reconstituted with the appropriate volume of sWFI, romiplostim is at a concentration of 0.5 mg/mL in 10 mM histidine, 4% (w/v) mannitol, 2% (w/v) sucrose, and 0.004% (w/v) polysorbate 20 at a pH of 5.0. The product, when reconstituted, is a clear colorless solution practically free from particles.

Prior to administration, romiplostim is reconstituted in the vial to 0.5 mg/mL (1.2 ml of sWFI is added to vials containing 625 µg (500 µg) of romiplostim), and drawn into a syringe for subcutaneous injection.

Romiplostim vials will be stored in their carton to protect from light until the time of use. Keep romiplostim vials refrigerated at 2°to 8°C (36° to 46°F). Do not freeze.

A. Romiplostim is an FDA approved drug, approved for the indication of chronic immune (idiopathic) thrombocytopenic purpura (ITP). The investigators Brochure, provided by Amgen, is attached as Appendix C. The product insert is also provided as Appendix B.

B. Relevant statements from the Product Insert:
   1. INDICATIONS AND USAGE: “Romiplostim is a thrombopoietin receptor agonist indicated for the treatment of thrombocytopenia in patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.”

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

1. Patients (18 years of age or greater) with active non-hematological cancer:
   A. The patients have previously received a chemotherapy regimen including one or more of the following agents:
      1. Nucleoside Analogue, including gemcitabine and fluorouracil
      2. Carboplatin or cisplatin
      3. Anthracycline
      4. Alkylating agent
      5. Other chemotherapy agents with thrombocytopenia as known common toxicity.
2. Patients who have not had any cytotoxic chemotherapy within 14 days of beginning the study.
3. Thrombocytopenia:
   A. Defined as platelet count <100,000/mcL.
   B. The patient will have had at least 2 CBCs with platelet counts <100,000/mcL separated by at least 4 weeks, and no platelet count $\geq$100,000/mcL in the prior 6 week period, despite (1) delay or (2) modification of chemotherapeutic regimen.
   C. A platelet count of >100,000/mcL, that follows within 7 days of a platelet transfusion, will not make the patient ineligible, as long as one or more subsequent platelet counts confirms thrombocytopenia (<100,000/mcL).

D. Patients have undergone bone marrow aspirate and biopsy, or peripheral blood test in the prior 3 months, without evidence of leukemia or myelodysplasia by fluorescent in situ-hybridization (FISH).
E. Dysplastic changes, based on morphology only, will not exclude the patient if FISH panel for MDS is normal.

4. KPS $\geq$ 50 or ECOG performance status $\leq$2 .
5. Ability to provide written informed consent.

6.2 Subject Exclusion Criteria

1. Patients with history of hematologic malignancies, including leukemia, myeloma, myeloproliferative disease, lymphoma, or myelodysplastic diseases. Romiplostim has been associated with transient increases in immature blood cell counts and a higher risk for progression to acute myeloid leukemia in Myelodysplastic Syndrome patients treated with Nplate.
2. Patients with known bone metastases, with evidence of corticol bone damage/lytric lesions/blastic lesions on standard imaging studies (CT/MR).
3. Anemia (Hgb <8.0 gm/dl) or leukopenia (absolute neutrophil count (ANC) <1,000/mcL). Use of red cell transfusions, erythropoietin, or G-CSF, as ordered by the managing oncology service, is acceptable and does not preclude participation.
4. Patients with underlying liver disease, such as cirrhosis or chronic hepatitis, and do not have primary or metastatic cancer in the liver will be excluded if ALT/AST >3X ULN or Total Bili >3X ULN. In the presence of primary or metastatic liver cancer, patients will be excluded if ALT/AST >5X ULN or Total Bili >5X ULN.
5. Patients with a history of a prior symptomatic venous thrombotic event such as DVT or pulmonary embolism and symptomatic arterial thrombotic events such as myocardial infarction, ischemic cerebral vascular accident or transient ischemic attack will be ineligible if they have not tolerated anticoagulation therapy. If patients remain on anticoagulation, or have completed the prescribed course of anticoagulation, they will be eligible for enrollment. A venous thrombotic event associated with a central venous catheter will not make the patient ineligible.
6. Serious concomitant medical condition that could interfere with the conduct of the clinical trial, such as unstable angina, renal failure requiring hemodialysis, or active infection requiring IV antibiotics
7. Pregnant women/lactating mothers
8. Patients unwilling to use contraception.

7.0 RECRUITMENT PLAN

This study will be conducted at MSKCC and participating institutions. Potential research subjects will be identified by members of the solid tumor oncology services. Fortunately, this will be based on existing referral patterns to the Hematology Service.

After the consultation and results of the cytogenetics and FISH, if a patient qualifies for the trial, the consulting hematologist will discuss the possibility of participation in the study. If consent is offered, the risks: benefits will be presented to the patient by an investigator prior to the patient consenting. If the patient consents, they will be enrolled by a study RSA (see section 15.1). Similar recruitment procedures will be followed at participating institutions.

This study does not compete with any existing or planned other studies for CIT and therefore, we anticipate a high percent of the appropriate patients will be referred. It is expected that a total of 60 patients will be recruited to this study.

8.0 PRETREATMENT EVALUATION

Documentation of tests resulted and/or verification will be completed within the following guidelines before enrolling on trial

Within 28 days prior to enrollment:

- Hematologic consultation with an institutional hematologist.
- Record current medications
- Physical examination

Within 48 hours prior to enrollment:

- CBC with peripheral smear (must have 2 tests) (CBC must include: WBC, Hgb, platelet, MCV, cell differential.)
- Comprehensive Metabolic Panel (also referred to as a Comprehensive Chemistry Panel (CCP)) (must include: BUN, Creatinine, sodium, potassium, chloride, CO2, calcium, glucose, total Bilirubin, total protein, albumin, alkaline phosphatase, AST, ALT)
- LDH
- PT
- aPTT
- Negative pregnancy test (serum hCG or urine) result in women of child bearing potential.

Prior to enrollment:

- CT or MRI performed within the prior 60 days of enrollment indicating active cancer **or**
- Positive serum marker within the prior 30 days of enrollment.

Within 90 days prior to enrollment:

- Bone marrow aspirate and biopsy, or peripheral blood test
  - FISH panel does not indicate MDS
  - Morphology and FISH does not indicate leukemia

9.0 TREATMENT/INTERVENTION PLAN

I. Initial Phase of Study: Intervention For Primary Endpoint. Romiplostim, n=60 .

A. Patients will begin weekly romiplostim treatment at 2 mcg/kg, subcutaneously.

B. Weekly CBC, comprehensive chemistry panel, LDH, PT, and aPTT will be performed, (as well as monitoring laboratory tests) for the first 3 weeks on treatment.

The romiplostim dose will be titrated by a study investigator.

The target platelet count for romiplostim dose titration is 150,000/mcL. A platelet count of ≥100,000/mcL is the threshold for successful response and the range of acceptable platelet

counts is 100-200k/mcL. These target platelet values have been used by investigators since the opening of this trial. Language specifying exact values was added in Amendment 16.

In the initial 3 successive weeks, the weekly romiplostim dose will be increased by 1 mcg/kg, until the platelet count 100,000-200,000/mcL. With romiplostim dose escalation, if the platelet count reaches ≥100,000/mcL, (adequate to resume chemotherapy), but not ≥150,000/mcL, the dose of romiplostim will not be escalated above 5 mcg/kg.

The dose of romiplostim may be modified at the discretion of the study investigator in consultation with the PI. Smaller dose increment (or decreases) may be needed to titrate the platelet count to the 100,000- 200,000/ mcL target.

C. 3 Week: Primary Endpoint.

The anticipated recovery of the platelets is within 3 weeks of initiation of romiplostim. The initial endpoint will be at 3 weeks.

The proportion of patients who have achieved a platelet count of ≥100,000/mcL within 3 weeks, (adequate to resume chemotherapy) and the weekly absolute platelet counts are recorded.

II. Maintenance Romiplostim, During Resumed Chemotherapy/Secondary Efficacy Endpoint

A. All patients who achieve an adequate platelet count to resume chemotherapy (≥100,000/mcL) and resume chemotherapy will be followed with continuation of weekly, titrated romiplostim. If the patient receives romiplostim therapy for ≥12 months, the scheduling of routine labs and treatment dosing will be at the discretion of the investigator.

B. The secondary endpoint will be documented for patients whose platelet counts have recovered within three weeks. We will observe for ability to resume 2 cycles (or eight weeks, whichever comes first) of cytotoxic chemotherapy without recurrence of chemotherapy-induced thrombocytopenia leading to chemotherapy dose delay or reduction; change in chemotherapy for progression of disease or other cancer related conditions; change in chemotherapy for other toxicities unrelated to thrombocytopenia; and death due to all causes. The duration for patients off chemotherapy will be noted. In addition we are also censoring patients who have tolerated chemotherapy with romiplostim support for up to 12 months.

C. Romiplostim dose titration. After resumption of full-dose chemotherapy, the romiplostim dose can be further titrated based on platelet count at beginning of each chemotherapy cycle. The dose adjustments are from the prior week's romiplostim dose. The below dose titration refers to the initial 2 cycles of resumed chemotherapy as well as the continuation phase for patients who successfully complete the study through 2 cycles.
   1. The target platelet count, at initiation of a cycle of chemotherapy is 100,000-200,000/mcL.
   2. If the pre-chemotherapy cycle platelet count is >200,000/mcL, the romiplostim dose will be reduced by 0.5 mcg/kg.
   3. If the pre-chemotherapy cycle platelet count is >250,000/mcL, the romiplostim dose will be reduced by 1.0 mcg/kg

4. If the pre-chemotherapy cycle platelet count is <100,000/mcL, the romiplostim dose will be increased by 1.0 mcg/kg.
5. The dose of romiplostim may be rounded off to the nearest 50 mcg.
6. The dose of romiplostim may be modified at the discretion of the study investigator in consultation with the MSKCC P.I. Smaller dose increments (or decreases) may be needed to titrate the platelet count to the 100,000-200,000/mcL target.

III. Discontinuation of Romiplostim.

A. Discontinuation of Cancer Therapy. After the 3 week period of the initial endpoint is reached, if the treating medical oncologist discontinues chemotherapy or switches to a cancer therapy not associated with thrombocytopenia, the romiplostim may be discontinued.

B. If a patient develops a Grade 3/4 adverse event, attributable to Romiplostim, based on the Common Terminology Criteria for Adverse Events (CTCAE), the Romiplostim will be discontinued.

C. If a patient develops a symptomatic deep vein thrombosis and/or pulmonary embolism, not associated with hemodynamic instability, and not considered life-threatening, the romiplostim may be continued if there is consensus of judgment of the treating oncologist and study investigator.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Patients will come for visits to the study-center/hematologist on a weekly basis during the study. The intervals of the weekly visits will be 7 +/- 2 days. These visits will be for the purpose of monitoring the safety and efficacy of the romiplostim intervention, as well as to allow for further dose titration. Treatment can be held up to 16 days if a patient develops an intercurrent medical illness or symptom that is unrelated to study drug therapy. Treatment may be held up to 20 days if the patient is unavailable for non-medical reasons, such as vacation or travel.

For the first 3 weeks on treatment, patients will receive weekly CBC, COMP, LDH, PT, and aPTT. During consecutive weeks, CBCs will be obtained weekly, for the purpose of monitoring the platelet recovery and to allow for further dose titration. Once per month (30 days +/- 10 days),,comprehensive metabolic panel (see above for itemization), LDH, Prothrombin Time, and activated Partial Thromboplastin Time will be monitored. If at any time the automated hematology analyzer flags possible morphological abnormalities, peripheral smears will be ordered for further analyze in order to monitor the platelet recovery and continue dose titration.

Patients who remain on romiplostim for 4 or more months, will undergo bone marrow aspirate and biopsy, or peripheral blood test, with reticulin stain, cytogenetics, and FISH panel for MDS, in the 30 day period after completion of the 4th month.

Patients will have a CBC performed within 1-4 weeks after the last dose of romiplostim.

11.0 TOXICITIES/SIDE EFFECTS

Based on our initial experience, we have not observed treatment-related toxicities in our first 40+ patients. Based on the romiplostim Prescribing Information, the most common adverse

reactions (≥ 5% higher patient incidence in romiplostim versus placebo) are arthralgia, dizziness, insomnia, myalgia, pain in extremity, abdominal pain, shoulder pain, dyspepsia, and paresthesia.

Individual cases of thrombosis and been reported in patients receiving romiplostim, but in one recent review of long-term use of romiplostim, "The thrombotic adverse event rate across all studies was 0.09 events per 100 patient-weeks on romiplostim therapy,"[8] markedly lower than would expected in patients with active cancer receiving chemotherapy. We have not observed an increased thrombosis rate compared with expected rates in patients with metastatic cancer, on chemotherapy, however, we will monitor any clinical evidence of thrombosis as well as hemorrhage.

Assessment of potential toxicity will be based on the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. We will monitor for evidence of marrow toxicity, with weekly CBC (CBC must include: WBC, Hgb, platelet, MCV, cell differential) and lab toxicities of grade 3/4 will be adjudicated on a regular basis by the PI or Co-PI of the study. In addition, cytogenetics testing through bone marrow aspirate or peripheral blood will be performed within 30 days after the completion of the 4th month on treatment.

Patients will be monitored for Adverse Events throughout the study at the following time points: Toxicity Assessments will be completed at 3-weeks from enrollment (3-weeks from initiation of romiplostim in cross-over patients), and every 3 months while on romiplostim. A final toxicity assessment will be completed 1 month after the last dose of romiplostim. However, if the patient is discontinuing chemotherapy and going to hospice/ comfort care, the final toxicity assessment will be omitted if toxicities were managed regularly. For purposes of toxicity assessment, 3 months will be defined as 90 days +/- 15 days, 1 month is defined as 30 days +/- 15 days, and 3 weeks will be defined as 21 days + 9 days.

The study will report only those toxicities that are <u>not</u> known to be linked to the patient's prior chemotherapy treatment or underlying disease. All toxicities meeting this criteria should be reported to MSKCC as an Adverse Event in CRDBi-Multicenter with supporting source documentation.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

The primary therapeutic response is assessed by the platelet count within 3 weeks of treatment.

1. Achievement of platelet counts of <u>≥</u>100,000/mcL in patients who receive romiplostim will serve as the primary endpoint.

The secondary therapeutic response endpoints are:

For patients who successfully achieve platelet counts of <u>≥</u>100,000/mcL, and resume chemotherapy, we will observe the:

1. Ability to resume two cycles (or eight weeks, whichever comes first) of cytotoxic chemotherapy without recurrence of chemotherapy-induced thrombocytopenia leading to delay or dose reduction in chemotherapy.
    a. Dose reduction/ delay for pancytopenia or drop in hemoglobin or neutrophil count will not count.

   b. The day of chemotherapy dose delay/ reduction will be considered the secondary endpoint.
   c. Duration of the off-chemotherapy time will be recorded.
2. Change in chemotherapy for progression of disease or other cancer related conditions.
   a. The start of a new chemotherapy is the day that will be considered the secondary endpoint.
3. Change in chemotherapy for other toxicities unrelated to thrombocytopenia.
   a. The start of a new chemotherapy is the day that will be considered the secondary endpoint.
4. Censoring patients who have tolerated chemotherapy with romiplostim support for 12 months.

13.0 CRITERIA FOR REMOVAL FROM STUDY

Treatment will continue until the occurrence of any of the following events:

- Continuation is no longer in the patient's best interest as determined by the patient's oncologist.
- Patient withdraws consent
- Death
- Lost to follow-up
- Major violation of study protocol, such as non-compliance.
- Adverse event(s) that, in the judgment of the Investigator or treating oncologist, may cause severe or permanent harm or which rule out continuation of the trial.
- Discontinuation of chemotherapy for reason other than CIT. If the patient is discontinuing chemotherapy regimen and beginning a different regimen, the patient may remain on study.
- Note: (Patients on romiplostim who fail to achieve ≥100,000/mcL within the first 3 weeks of treatment are considered a primary treatment failure. However, patients can continue on treatment per protocol if the treating physician believes the patient will benefit for secondary endpoints.)

14.0 BIOSTATISTICS

This study was originally designed as a phase II randomized study where patients were randomized 2:1 to respectively receive romiplostim and observational control. The primary endpoint was the achievement of a platelet count of ≥ 100,000/mcL within three weeks of study enrollment, and any patient removed from study during evaluation window without count recovery was considered a treatment failure. Based on earlier MSKCC data, it was estimated that the probability of a success in the romiplostim arm is at least 90%, while the probability of a spontaneous recovery in the control arm is 60% or less.

Due to preliminary trial results, the protocol was amended on 4/13/2016 and the observation control arm was dropped. At that point, the study became a single arm phase II study of romiplostim. The sections below represent the new single arm study design.

Analysis of these data will only be done with 60 evaluable patients enrolled on the trial. There was one patient enrolled during this time who was inevaluable and therefore there were 61 patients enrolled for 60 spots.

Primary endpoint:
This study is a single arm phase II design to evaluate romiplostim mediated improvements in platelet counts in patients who have experienced CIT. The primary endpoint is the achievement of a platelet count of ≥ 100,000/mcL within three weeks of study enrollment. Any patient who is removed from study before the evaluation of the primary endpoint will be considered a treatment failure. A total of sixty patients will be enrolled and treated with romiplostim. Based on preliminary MSKCC data, it is estimated that the probability of a success in patients on romiplostim treatment is at least 90%. Therefore, we will consider the trial promising and worthy of further intervention if at least 54 out of 60 achieve platelet count recovery. The operating characteristics of this design rule are provided in the table below.

	True Rate of Count Recovery				
	0.85	0.875	0.9	0.925	0.95
Probability of Observing >= 54/60	17%	40%	60%	81%	97%

Secondary endpoints:

Patients who achieve a platelet recovery may be allowed to resume chemotherapy. In these patients, we are observing for recurrence of chemotherapy-induced thrombocytopenia leading to chemotherapy dose delay or reduction; change in chemotherapy for progression of disease or other cancer related conditions; change in chemotherapy for other toxicities unrelated to thrombocytopenia; and death due to all causes.

Lastly, the frequency of thrombosis, marrow toxicity, and organ dysfunction will be tabulated.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section titled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.1.1 Registration for Participating Sites

Central registration for this study will take place at Memorial Sloan Kettering Cancer Center

To complete registration and enroll a participant from another institution, the site must contact the designated research staff at MSK to notify him/her of the participant registration.

Registration documents should be submitted per the contact information provided by the MSK study coordinator.

The following documents must be sent for each enrollment **within 24 hours** of the informed consent form being signed:

- The completed or partially completed MSK eligibility checklist
- The signed informed consent and HIPAA Authorization form
- Supporting source documentation for eligibility questions (laboratory results, radiology reports, MD notes, physical exam sheets, medical history, prior treatment records)

Upon receipt, the research staff at MSK will conduct an interim review of all documents. If the eligibility checklist is not complete or source documentation is missing, the participant will be registered PENDING and the site will be responsible for sending the completed registration documents within 45 days of the consent.

If the external registration submission is complete, the participating site IRB has granted approval for the protocol, and the site is in good standing, the MSK research staff will enter the completed registration documents to MSK CTMS for participant enrollment as stated in section 15.1.

Once the participant is registered, the participant will be assigned a number in the MSK Clinical Research Database (CRDB). This number is unique to the participant and must be written on all data and correspondence for the participant. This protocol participant number will be relayed back to study staff at the registering site via e-mail and will serves as the enrollment confirmation.

15.2 Randomization

There will be no randomization in this study.

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study at MSKCC. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secure database, CRDB. Source documentation will be available to support the computerized patient record.

Investigators will permit study-related audits by the sponsor, IRB review, and regulatory inspection(s) (e.g., FDA, EMEA, TPP), providing direct access to the facilities where the study took place, to the source documents, and to all other study documents.

16.0.1 Data and Source Documentation for Participating Sites

Data
The participating sites will enter data remotely into electronic Case Report Forms (eCRFs) using the internet based system CRDBi-Multicenter. Data entry guidelines have been generated for this study and the site staff will receive database training prior to enrolling its first participant. The participating

site PI is responsible for ensuring these forms are completed accurately in a timely manner. A schedule of required forms is shown in section 16.0.3

Source Documentation
Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data. Source documentation should be consistent with data entered into eCRFs. Relevant source documentation to be submitted throughout the study includes:

- Baseline measures to assess pre-protocol disease status (ex. CT, PSA, bone marrow)
- Treatment records
- Toxicities/adverse events that meet study reporting requirements not previously submitted with SAE reports
- Response designation

Source documentation should include a minimum of two identifiers to allow for data verification. MSK will maintain the confidentiality of any subject-identifiable information it may encounter.

16.0.2 Data and Source Documentation Submission for Participating Sites

Participating sites should enter data directly into CRDBi-Multicenter. Source documentation should be sent to MSK at the contact information provided by the MSK study coordinator. Submissions should include a cover page listing relevant records enclosed per participant.

16.0.3 Data and Source Documentation Submission Timelines for Participating Sites

Data and source documentation to support data should be transmitted to MSK according to the chart below.

Chart: Data and Source Submission Requirements and Timelines

	Baseline	Week 1	Week 2	Week 3	After Week 3	SAE	Off Study
Submission Schedule							
Source Documentation	Within 24 hours (see section 15.1.1)	within 14 days of visit				Within 3 days of event (see section 17.2.1); updates to be submitted as available	Within 14 days of visit
eCRFs	Within 7 days of visit						
Required Forms							
Minimal Dataset	**X**						**X**
Disease Form	**X**						
Physical Exam Form	**X**						
Prior Therapy Form	**X**						
Concomitant Medications Form	**X**	**X**	**X**	**X**	**X**		
Treatment Form		**X**	**X**	**X**	**X**		

Laboratory Form	**X**	**X**	**X**	**X**	**X**		**X**
Diagnostic Test Form	**X**						
Adverse Event Form*		**X**	**X**	**X**	**X**	**X**	**X**
Serious Adverse Event						**X**	
Hospitalization Form						**X**	

*Toxicities/adverse events that meet reporting requirements as outlined in section 11

16.0.4 Data Review and Queries for Participating Site Data

Research staff at MSK will review data and source documentation as it is submitted. Data will monitored against source documentation and discrepancies will be sent as queries to the participating sites. Queries will be sent by MSK Research staff twice a month.

Participating sites should respond to data queries within 14 days of receipt.

Data analysis being performed by the site(s): "Clinical, laboratory and radiographic data will be shared with SYLVESTER COMPREHENSIVE CANCER CENTER, including but not limited to: cancer therapy, COVID-19 treatment, demographic information, and assessment values."

Dr. Gerald A Soff MD (Clinical Director, Hemostasis, Thrombosis and Transfusion Services, University of Miami Health System/Sylvester Comprehensive Cancer Center) will serve as a Data Collaborator for this study. In this capacity, he will participate in analysis, presentation, and publication of the data and findings of the study. He will also contribute to the language for amendments to the protocols, if necessary.

Dr. Soff will not have access to any Protected Health Information (PHI) on any patient. He will have access to aggregated data only. All correspondences between the MSKCC investigators and Dr. Soff will be conducted via secure email. Data will be made available to Dr. Soff throughout the performance of the study, as well as during the period when the data are analyzed and written up for presentation and publication.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates, the extent and accuracy of evaluations and follow-ups will be monitored periodically throughout the study period for potential problems, which will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, or more frequently if indicated.

16.1.1 Quality Assurance for Participating Sites

Each site accruing participants to this protocol will be audited by the staff of the MSK study team for protocol and regulatory compliance, data verification and source documentation.

Audits will be conducted annually during the study (or more frequently if indicated) and at the end or closeout of the trial. Ideally the first audit will occur shortly after the first patients are enrolled. The number of participants audited will be determined by auditor availability and the complexity of the protocol. Each audit will be summarized and a final report will be sent to the PI at the audited participating site within 30 days of the audit.

16.1.1 Response Review

Since therapeutic efficacy is a stated primary objective, participant's responses are subject to review by MSKCC's Therapeutic Response Review Committee (TRRC). Radiology, additional lab reports and possibly bone marrow biopsies and/or aspirates will be submitted for MSKCC TRRC review and confirmation of response assessment.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering were approved by the National Cancer Institute in August 2018. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials."

There are several different mechanisms by which clinical studies are monitored for data, safety and quality. At a departmental/PI level there exists procedures for quality control by the research team(s). Institutional processes in place for quality assurance include protocol monitoring, compliance and data verification audits, staff education on clinical research QA and two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Deputy Physician-in-Chief, Clinical Research.

The degree of monitoring required will be determined based on level of risk and documented.

The MSK DSMB monitors phase III trials and the DSMC monitors non-phase III trials. The DSMB/C have oversight over the following trials:

- MSK Investigator Initiated Trials (IITs; MSK as sponsor)
- External studies where MSK is the data coordinating center
- Low risk studies identified as requiring DSMB/C review

The DSMC will initiate review following the enrollment of the first participant/or by the end of the year one if no accruals and will continue for the study lifecycle until there are no participants under active therapy and the protocol has closed to accrual. The DSMB will initiate review once the protocol is open to accrual

16.3 Regulatory Documentation

Prior to implementing this protocol at MSK, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSK Institutional Review Board/Privacy Board (IRB/PB). There will be one protocol document and each participating site will utilize that document.

The following documents must be provided to MSK before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved informed consent form and HIPAA authorization
- Participating Site IRB membership list
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical licenses for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key staff members at the participating site
- Documentation of Good Clinical Practice (GCP) training for the PI and co-PI at the participating site
- Participating site laboratory certifications and normals

Upon receipt of the required documents, MSK will formally contact the site and grant permission to proceed with enrollment.

Prior to implementing this protocol at MSK, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSK Institutional Review Board/Privacy Board (IRB/PB). There will be one protocol document and each participating site will utilize that document.

Participating sites that are conducting data analysis should submit this protocol to their IRB according to local guidelines. Copies of any site IRB correspondence should be forwarded to MSK

16.3.1 Amendments

Each change to the protocol document must be organized and documented by MSK and first approved by the MSK IRB/PB. Upon receipt of MSK IRB/PB approval, MSK will immediately distribute all non expedited amendments to the participating sites, for submissions to their local IRBs.

Participating sites must obtain approval for all non expedited amendments from their IRB within 90 calendar day of MSK IRB/PB approval. If the amendment is the results of a safety issue or makes eligibility criteria more restrictive, sites will not be permitted to continue enrolling new participants until the participating site IRB approval has been granted.

The following documents must be provided to MSK for each amendment within the stated timelines:

- Participating Site IRB approval
- Participating Site IRB approved informed consent form and HIPAA authorization

16.3.2 Additional Correspondence

Continuing Review Approval
The Continuing Review Approval letter from the participating site's IRB and the most current approved version of the informed consent form should be submitted to MSK within 7 days of expiration. Failure to submit the re-approval in the stated timeline will result in suspension of new participant enrollment.

16.4 Document maintenance

The MSK PI and participating site PI will maintain adequate and accurate records to enable the implementation of the protocol to be fully documented and the data to be subsequently verified.

The participating sites will ensure that all regulatory documents and participating site IRB correspondences are maintained in an on site regulatory binder and sent to MSK as outlined within the protocol. The regulatory binder on site will be reviewed by the MSK designated study monitor at monitoring visits. A regulatory binder for each site will also be maintained at MSK this binder may be paper or electronic.

After study closure, the participating sites will maintain all source documents, study related documents and CRFs for 3 years.

16.5 Noncompliance

If a participating site is noncompliant with the protocol document, accrual privileges may be suspended and/or contract payments may be withheld, until the outstanding issues have been resolved.

17.0 PROTECTION OF HUMAN SUBJECTS

Inclusion of Children in Research
This protocol/project does not include children because the number of children is limited and the majority are already accessed by a nationwide pediatric cancer research network. This statement is based on exclusion 4b of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.

Incentives/Costs/Benefits
No incentives will be offered to patients/subjects for participation in this study. Participation is voluntary. The potential benefits of participation in the study will be weighed against other treatment options (see below) including supportive care. The patient/subject or their health insurance provider will be responsible for the costs of standard medical care including MD visits, routine blood tests, administration of the study drug, and bone marrow biopsies and aspirates. The patient/subject or their health insurance provider will not be charged for the study drug romiplostim.

Alternative Treatments: N/A

Alternative treatment of patients: Usual care with delay or dose reduction in chemotherapy.

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.2 Serious Adverse Event (SAE) Reporting

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

For all other trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following

  - A explanation of how the AE was handled
  - A description of the subject's condition
  - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

17.2.1 Report SAEs to Amgen by MSKCC

The MSKCC research staff must inform Amgen, Inc. of any SAE as soon as possible but no later than 5 calendar days of the MSKCC principal investigator becoming aware of the event. Participating sites should submit SAEs to MSKCC as indicated in section 17.3 and MSKCC will report these events to Amgen as appropriate. Participating sites should not submit SAEs directly to Amgen. All SAE's will be reported up to 30 days after the last dose of treatment.

Definitions

Adverse Event Definition

Adverse event (AE) means any untoward medical occurrence(s) in a patient/subject attributed to a pharmaceutical product. (The untoward medical occurrence does not necessarily have a causal relationship with this treatment.) An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

Serious Adverse Event Definition

Serious adverse event (SAE) means any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening (refers to an AE in which the patient 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 inpatient hospitalization, with the exception of a planned procedure.
- Requires prolongation of an existing hospitalization.
- Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is a medically important event. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent one of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent.

Clarification should be made between the terms *serious* and *severe* because they ARE NOT the same. The term *severe* is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above and is usually associated with events that pose a threat to a patient's life or functioning. A severe AE does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but may not be considered an SAE. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild but would be defined as an SAE based on the above noted criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

17.3 SAE Reporting for Participating Sites

Responsibilities of Participating Sites

- Participating sites are responsible for reporting all SAEs to their local IRB per local guidelines. Local IRB SAE approvals/acknowledgements must be sent to MSK upon receipt.
- Participating sites are responsible for submitting the SAE Report form found in MSK's internet based Clinical Research Database to MSK within 3 calendar days of learning of the event.
- When a death is unforeseen and indicates participants or others are at increased risk of harm, participating sites should notify the MSK PI as soon as possible but within 24 hours of the time the site becomes aware of the event.

SAE contact information:
Email: medmctcore@mskcc.org to the attention of 13-132 Research Staff

AND

Email: wilkinsc@mskcc.org

Responsibilities of MSK

- MSK Research Staff are responsible for submitting all SAEs to the MSK IRB/PB as specified in 17.2 and to Amgen as described in 17.2.1
- The MSK PI is responsible for informing all participating sites about all unexpected SAEs that are either possibly, probably, or definitely related to the study intervention within 30 days of receiving the stamped SAE from the MSK IRB/PB
- The MSK PI is responsible for informing all participating sites within 24 hours or on the next business day about a death that is unforeseen and indicates participants or others are at increased risk of harm.

17.5 Safety Reports

MSK must submit external safety reports to the MSK IRB/PB according to institutional guidelines. All external safety reports will be made available to the participating sites. For those safety reports that require an amendment, the participating sites will receive a special alert.

Participating sites are responsible for submitting safety reports to their local IRB per their local IRB guidelines. All local IRB approvals/acknowledgments of safety reports must be sent to MSK upon receipt.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

18.1 Informed Consent Procedures for Participating Sites

The investigators listed on the Consenting Professionals Lists at each participating site may obtain informed consent and care for the participants according to good clinical practice and protocol guidelines.

A note will be place in the medical record documenting that informed consent was obtained for this study, and that the participant acknowledges the risk of participation.

19.0 REFERENCES

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20.0 APPENDICES

Appendices will be stored in a separate file and will be submitted in electronic format.

Appendix A: Manuscript under editorial review

Appendix B: Romiplostim Product Information

Appendix C: Investigators Brochure