Official Title of Study:

A Phase 2, Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Luspatercept (ACE-536) in Subjects With Myeloproliferative Neoplasm-Associated Myelofibrosis and Anemia With and Without Red Blood Cell-Transfusion Dependence

PROTOCOL(S) ACE-536-MF-001

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A PHASE 2, MULTICENTER, OPEN-LABEL STUDY TO EVALUATE THE EFFICACY AND SAFETY OF LUSPATERCEPT (ACE-536) IN SUBJECTS WITH MYELOPROLIFERATIVE NEOPLASM-ASSOCIATED MYELOFIBROSIS AND ANEMIA WITH AND WITHOUT RED BLOOD CELL-TRANSFUSION DEPENDENCE

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CONFIDENTIAL

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{See appended electronic signature page}
Signature of Celgene Therapeutic Area Head **dd mmm yyyy**
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By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.

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Signature of Site Principal Investigator	**dd mmm yyyy**
Printed Name of Site Principal Investigator **Institution Name:** _____ By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Celgene representatives, the Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

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PROTOCOL SUMMARY

Study Title

A Phase 2, Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Luspatercept (ACE-536) in Subjects With Myeloproliferative Neoplasm-Associated Myelofibrosis and Anemia With and Without Red Blood Cell-Transfusion Dependence

Indication

Treatment of anemia associated with myeloproliferative neoplasm (MPN)-associated myelofibrosis in subjects with and without red blood cell (RBC)-transfusion dependence

Objectives

The **primary objective** of this study is:

- to evaluate the efficacy and safety of luspatercept for the treatment of anemia in subjects with MPN-associated myelofibrosis with and without RBC-transfusion dependence.

The **secondary objectives** of this study are:

- To evaluate the safety of luspatercept in MPN-associated myelofibrosis
- To evaluate the effect of luspatercept in MPN-associated myelofibrosis:
  - on the time to and duration of anemia response
  - on frequency of RBC transfusions and transfusion dependence
  - on symptom response improvement via the Myeloproliferative Neoplasms Symptom Assessment Form Total Symptom Score (MPN-SAF TSS)
  - on health-related quality of life (HRQoL) via the EQ-5D-5L and Functional Assessment of Cancer Therapy – Anemia (FACT-An) questionnaires
  - on the changes in hemoglobin and mean hemoglobin increase
- To evaluate population pharmacokinetics of luspatercept in subjects with MPN-associated myelofibrosis with and without RBC-transfusion dependence

[redacted]

[redacted]

Study Population and Design

This is a Phase 2, multicenter, multicohort, open-label study that will be conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practices (GCPs). Subjects satisfying the eligibility criteria will be assigned to 1 of the following cohorts:

> **Cohort 1**: will contain up to 20 subjects with anemia only that are not currently receiving RBC transfusions (these subjects will be referred to as "anemia only" throughout the protocol, defined as 0 RBC units/84 days immediately prior to the C1D1 date)
>
> **Cohort 2**: will contain up to 20 subjects that are RBC-transfusion dependent (these subjects will be referred to as "RBC-transfusion dependent" throughout the protocol, defined as an average RBC transfusion frequency of 2 to 4 RBC units/28 days over at least the 84 days immediately up to the C1D1 date)
>
> **Cohort 3A**: will contain ≥ 10 subjects who meet the eligibility criteria for Cohort 1 (anemia only) while being on a stable dose of ruxolitinib for at least 112 days immediately prior to the enrollment date
>
> **Cohort 3B:** will contain approximately 46 subjects who meet the eligibility criteria for Cohort 2 (RBC-transfusion dependent) while being on a stable dose of ruxolitinib for at least 112 days immediately prior to the enrollment date. Effective from Protocol Amendment 3, additional subjects for this cohort must also have a minimum prior treatment with ruxolitinib per their local standard-of-care for at least 280 days (40 weeks) without interruptions exceeding 2 consecutive weeks, while being on a stable ruxolitinib dose for at least 112 days (16 weeks) immediately prior to the enrollment date.

Overall, the study will enroll approximately 100 subjects worldwide across these parallel-enrolling cohorts.

The study will consist of a:

- Maximum 28-day Screening Period
- Up to a 2-year Treatment Period (consisting of a 168-day Primary Phase, a Day 169 Disease Response Assessment, and approximately 2-years or more for Extension Phase following the Cycle 1 Day 1 (C1D1) date, defined as the date of first dose of luspatercept)
- At least a 3-year Posttreatment Follow-up Period (consisting of 42-Day Follow-up Period and Long-term Follow-up Period)

Refer to Section 3.1 for more information.

Length of Study

The expected duration of the study for an individual subject is up to 5 years, consisting of a maximum 28-day Screening Period, a Primary Phase of Treatment Period of 168 days, a

potential Extension Phase of Treatment Period for approximately 2 years or more (if the subject continues to receive clinical benefit) from first dose of luspatercept, and a Posttreatment Follow-up Period of 3 years. A roll-over study will provide continued access for subjects benefiting from luspatercept in the Extension Phase of the Treatment Period and ensures the Posttreatment Follow-up Period will also be captured.

The expected total study duration is approximately 6 years, which includes an enrollment period of approximately 26 months.

The Screening Period

Screening procedures are to take place over a maximum of 28 days immediately prior to the enrollment date, which is defined as the date in which subjects have been assigned a treatment cohort via Integrated Response Technology (IRT).

Review of historical bone marrow biopsy information will be used to confirm MPN-associated myelofibrosis diagnosis. The report(s) should come from the most recent local bone marrow biopsy performed and should contain the mutational status of the disease (eg, Janus kinase 2 [*JAK2*] gene, calreticulin [*CALR*] gene, and thrombopoietin receptor [*MPL*] gene).

Transfusion history must be available for at least the 84 days immediately prior to the subject's C1D1 date. Transfusion data should include, but not be limited to, the number of units, volume of transfusion, pretransfusion hemoglobin (Hgb) values, and date of transfusion. Red blood cell transfusions given at outside local institutions must also be collected.

Primary Phase of Treatment Period: Day 1 to Day 168

The first dose of luspatercept should be administered as soon as possible (at the latest 3 calendar days) following the enrollment date and will be given on Day 1 of each 21-day treatment cycle (unless there are dose delays). In all cohorts, best supportive care (BSC) may be used in combination with study treatment when clinically indicated per Investigator.

Day 169 Disease Response Assessment

The Day 169 Disease Response Assessment visit should be completed 169 days after the date of first dose, regardless of dose delays.

Extension Phase of Treatment Period: Day 169 through approximately 2 years or more from the date of C1D1, if the subject continues to receive clinical benefit

Subjects who meet the clinical benefit criteria (refer to Section 6.2.2 for more information) to remain on luspatercept treatment may continue dosing on Day 1 of each 21-day treatment cycle in the Extension Phase of the Treatment Period for approximately 2 years or more until the subject is no longer receiving clinical benefit, experiences unacceptable toxicities, has disease progression, withdraws consent, or meets any other discontinuation criteria (refer to Section 11 for more information). Best supportive care (BSC) may continue to be used in combination with study treatment when clinically indicated per Investigator.

The Disease Response Assessment should be completed on Day 1 of every Cycle in the Extension Phase until the subject is discontinued from treatment or withdraws consent.

Serial measurements of safety and efficacy will continue on scheduled study visits in the Extension Phase of the Treatment Period. Refer to Section 6 for full list of study procedures/assessments.

The same dose titration, delay and/or reduction, and treatment discontinuation criteria will still apply in the Extension Phase of the Treatment Period. See Section 7.3 for dose modification rules and Section 11 for discontinuation criteria.

All subjects who have received at least 1 dose of study treatment should undergo end of treatment (EOT) evaluations when luspatercept is discontinued.

Posttreatment Follow-up Period

The Posttreatment Follow-up Period includes a 42-Day Follow-up Period and Long-term Follow-up Period, beginning from the date of last dose of luspatercept.

42-Day Follow-up Period

All adverse events (AEs) will be recorded by the Investigator from the time the subject signs informed consent until 42 days after the last dose of luspatercept including serious adverse events (SAEs) made known to the Investigator at any time thereafter that are suspected of being related to luspatercept.

Long-term Follow-up Period

For all subjects who receive at least 1 dose of luspatercept, continuation of monitoring for transformation to blast phase will occur in the Posttreatment Follow-up Period along with data collection of subsequent MPN-associated myelofibrosis therapies, and overall survival for at least 3 years from the date of last dose of luspatercept unless the subject withdraws consent from the study, dies, or is lost to follow up. Refer to Section 6.5 for additional details.

The End of Trial is defined as either the date of the last visit of the last subject to complete the Posttreatment Follow-up Period, or the date of receipt of the last data point from the last subject that is required for primary, secondary [redacted] analysis, as prespecified in the protocol, whichever is the later date.

Refer to Section 3.1 for more information.

Study Treatments

Each subject will receive a starting dose level of luspatercept at 1.0 mg/kg subcutaneous injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle). The starting dose can be titrated (increased) during the Treatment Period (Primary Phase and Extension Phase) to 1.33 mg/kg, up to a maximum of 1.75 mg/kg, provided that the subject meets the appropriate criteria (refer to Section 7.3). The subject's dose may also be delayed, reduced, or discontinued, depending on the specific criteria (refer to Section 7.3).

Subjects enrolling into Cohort 3B following implementation of Protocol Amendment 3 will begin luspatercept treatment at a starting dose of 1.33 mg/kg and can have their dose increased to a maximum dose of 1.75 mg/kg (with the total dose not to exceed 168 mg).

Overview of Key Efficacy Assessments

Key efficacy assessments include:

- RBC transfusions
- Hematology parameters (eg, Hgb)
- HRQoL information
- Disease Response Assessment

Overview of Key Safety Assessments

Key safety assessments include:

- AE/SAE reporting
- Concomitant medications/procedures
- Hematology parameters
- Serum chemistry
- Urinalysis
- Pregnancy testing
- 12-lead electrocardiogram (ECG)
- Physical examination
- Eastern Cooperative Oncology Group (ECOG) performance status
- Vital signs and body weight

Statistical Methods

For more specific information, please refer to Section 9 of the protocol.

The analysis populations for this protocol are the intent-to-treat (ITT) population, the efficacy evaluable (EE) population, and the safety population.

A sample size of approximately 100 subjects will be enrolled as follows:

- **Cohort 1**: approximately 20 subjects, but no less than 14 EE subjects
- **Cohort 2**: approximately 20 subjects
- **Cohort 3**: up to 60 subjects

A subject who meets all of the inclusion/exclusion criteria will be considered "efficacy evaluable" upon receiving ≥ 3 cycles of luspatercept and remain in the study for ≥ 21 days following the third dose of luspatercept. Subjects who attain Hgb values > 13 g/dL in < 3 cycles will also be considered efficacy evaluable. Subjects not considered "efficacy evaluable" are in general those that receive < 3 cycles of luspatercept in which luspatercept is held or discontinued or who receive < 3 cycles due to a treatment-emergent adverse event (TEAE) or discontinued treatment for any other reason (these subjects will be scored as a nonresponder).

Subjects will become nonefficacy evaluable in certain cases (eg, prohibited concomitant medication/s was/were used during the study). Subjects specifically in Cohort 3 become nonefficacy evaluable in certain cases (eg, the ruxolitinib dose was modified during the study).

The study steering committee will review the allocation of all subjects to the EE population.

The Sponsor estimates that out of 20 enrolled subjects in Cohort 1, at least 14 will become efficacy evaluable. For Cohort 1, the probability of observing no responses among 14 subjects is less than 0.05 if the response probability is greater than 20%. If no responses are observed in the first 14 evaluable subjects, the trial will be stopped because it can be concluded that the response rate for the primary endpoint is less than 20% in Cohort 1, and not worthy of further investigation. Cohorts 2 and 3 will also be stopped due to clinical considerations.

The sample size of Cohort 3 is increased to approximately 60 ITT subjects by the addition of up to 27 additional subjects (a total of approximately 46 subjects) in Cohort 3B. The sample size of Cohort 3A remains the same. A total of 46 subjects in Cohort 3B would provide for 80% power to detect a 15% increase in response rate for luspatercept over a null response rate of 17%. This assumes a one-sided *z* test of a binomial proportion (with a 5% significance level).

All efficacy analyses will be conducted primarily in the ITT population. Confirmatory analyses will be conducted in the EE population.

The primary efficacy endpoint is the proportion of subjects that achieved anemia response as defined below:

Cohorts 1 (anemia only) and 3A:

Proportion of subjects achieving ≥ 1.5 g/dL hemoglobin increase from baseline over any consecutive 84-day period without an RBC transfusion from Day 1 up through and including Day 168. This 84-day period will begin as soon as the ≥ 1.5 g/dL hemoglobin increase is detected. There must be ≥ 3 determinations of ≥ 1.5 g/dL hemoglobin increase from baseline in this interval with no value showing a < 1.5 g/dL hemoglobin increase from baseline and no 2 measurements are ≥ 42 days apart.

Cohorts 2 (RBC-transfusion dependent) and 3B:

Proportion of subjects who become RBC-transfusion free over any consecutive 84-day period from Day 1 up through and including Day 168. This 84-day period will begin from the date of the prior RBC transfusion that is given for a Hgb value ≤ 9.5 g/dL.

Anemia response rate, together with a 95% confidence interval, will be calculated for each cohort.

Secondary efficacy endpoint analyses will include:

Time to anemia response will be summarized only for subjects who achieved anemia response. It is defined as time from first dose to first onset of anemia response, calculated from Day 1 through and including Day 168.

Duration of anemia response will be summarized only for subjects who achieved anemia response. It is defined as maximum duration of modified anemia response, calculated from Day 1 through end of treatment.

Frequency of RBC transfusions will be assessed for Cohort 2 subjects and RBC-transfusion dependent subjects in Cohort 3B. It is defined as the mean number of RBC units transfused per subject per 28 days. It will be calculated from Day 1 through and including Day 168 and Day 1 through end of treatment.

Frequency of RBC transfusion dependence will be assessed for Cohort 2 subjects and RBC-transfusion dependent subjects in Cohort 3B. It is defined as the proportion of subjects who reduce their transfusion burden by ≥ 50% from baseline over any consecutive 84-day period. It will be calculated from Day 1 through and including Day 168 and Day 1 through end of treatment.

Symptoms response improvement will be assessed using the proportion of subjects who achieve ≥ 50% reduction in fatigue symptom as measured by the MPN-SAF TSS, calculated from Day 1 through and including Day 168 and Day 1 through end of treatment. The proportion of subjects who achieve ≥ 50% reduction in total symptom score (TSS) will also calculated.

Health-related quality of life (HRQoL) will be assessed via the mean changes in domain scores over the study compared to baseline using the FACT-An and EQ-5D-5L, calculated from Day 1 through and including Day 168 and Day 1 through end of treatment.

Changes in hemoglobin will be assessed for Cohorts 1 and 3A subjects over the study compared to baseline in the absence of RBC transfusions, calculated from Day 1 through and including Day 168 and Day 1 through end of treatment.

Mean hemoglobin increase of ≥ 1.5 g/dL from baseline over any consecutive 84-day period without an RBC transfusion will be assessed for Cohorts 1 and 3A subjects, calculated from Day 1 through and including Day 168 and Day 1 through end of treatment.

No formal interim analysis is planned for the study.

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1. INTRODUCTION

1.1. Myeloproliferative Neoplasm-associated Myelofibrosis

Myeloproliferative neoplasm (MPN)-associated myelofibrosis is a clonal myeloid neoplasm characterized by defective bone marrow function, bone marrow fibrosis, extramedullary hematopoiesis, a propensity for transformation to blast phase, and an inflammatory state. Levels of hematopoietic stem and progenitor cells in the blood are increased, reflecting abnormal homing of hematopoietic stem and progenitor cells. Hematopoiesis in MPN-associated myelofibrosis is clonal arising from a transformed multipotent hematopoietic progenitor cell.

The cause of MPN-associated myelofibrosis is unknown and there are no known etiological factors. About 50% of patients with MPN-associated myelofibrosis have a mutation in the Janus kinase 2 (*JAK2*) gene, about 33% of patients have a mutation in the calreticulin (*CALR*) gene, and about 5% of patients have a mutation in the thrombopoietin receptor (*MPL*) gene. About 25% of patients have no detectable mutation and are referred to as *triple-negative*. Mutations in other genes such as *TET2, ASXL1* and *DMT3A* are also sometimes found and can precede or follow development of the *driver* mutations.

Myeloproliferative neoplasm (MPN)-associated myelofibrosis can develop directly (primary myelofibrosis [PMF]) or evolve from other MPNs, including polycythemia vera (PV) and essential thrombocythemia (ET). For purposes of this study, MPN-associated myelofibrosis is defined as PMF, post-polycythemia vera myelofibrosis (post-PV MF), and post-essential thrombocythemia myelofibrosis (post-ET MF).

1.1.1. Signs and Symptoms

Myeloproliferative neoplasm (MPN)-associated myelofibrosis is predominately a disease of the elderly with a median age at onset in a range of 69 to 76 years (Moulard, 2013). Erythropoiesis is qualitatively and quantitatively abnormal resulting in anemia in about 30% of affected patients at diagnosis. However, eventually all affected patients develop anemia. Anemia is often confounded by comorbidities typical of an older population like atherosclerotic cardiovascular disease and cerebrovascular disease. Severe anemia unresponsive to therapy can be fatal. Myelopoiesis is also qualitatively and quantitatively abnormal resulting in decreased or increased granulocytes and/or platelets. Infection risk is increased because of decreased numbers of and/or dysfunctional granulocytes. Furthermore, there may be bleeding from decreased numbers of and/or dysfunctional platelets. Extramedullary hematopoiesis, typical of MPN-associated myelofibrosis, results in spleen and liver enlargement (splenomegaly and hepatomegaly, respectively) in about 60% of affected patients at diagnosis resulting in early satiety, weight loss, and constitutional symptoms. Myeloproliferative neoplasm (MPN)-associated myelofibrosis is a progressive disorder such that many of the signs and symptoms discussed above will develop with time even in patients in whom they are absent at diagnosis.

1.1.2. Prognosis

Median survival of patients with MPN-associated myelofibrosis is 5 to 6 years from diagnosis. Several prognostic scores are used that combine independent prognostic variables including age, gender, spleen and/or liver enlargement, hemoglobin (Hgb) level, red blood cell (RBC)-transfusion dependence, numbers of leukocytes and/or platelets, numbers of monocytes or

immature myeloid cells, clonal cytogenetic abnormalities and bone marrow histology (Cervantes, 2009; Dupriez, 1996; Tefferi, 2007; Tefferi, 2009). In a recent study involving > 1000 subjects, multivariate analysis of parameters obtained at diagnosis identified age > 65 years, constitutional symptoms, hemoglobin concentration < 10 g/dL, leukocyte levels > 25 x 10^9/L and blood myeloblasts ≥ 1% as predictors of shortened survival. Several of these parameters are also associated with an increased risk of transformation to blast phase. In this study, the yearly incidence rates for transformation to blast phase was 3.7% and deaths due to transformation to blast phase within a 10-year period was 18% (Quintas-Cardama, 2013; updated by personal communication with Srdan Verstovsek 01 May 2017).

Patients developing MPN-associated myelofibrosis after PV or ET have the same prognosis to those with PMF.

Recently, associations are reported between prognosis and mutational landscape. For example, patients with *CALR* mutations have the best prognosis whereas those with no detectable mutation (*triple negative*) have the worst prognosis. The concomitant presence of *non-driver* mutations, such as those in *ASXL1*, *TET2* and *DNMT3A*, are also associated with a worse prognosis.

1.2. Treatment of MPN-associated Myelofibrosis

Two types of therapies are used in MPN-associated myelofibrosis: (1) targeting the cancer clone and (2) targeting signs and symptoms of the disease. Current therapies have little impact on survival. Commonly used therapies include drugs to reverse anemia (refer to below), drugs to decrease the size of the neoplastic clone, and anti-inflammatory drugs, where sometimes these targets overlap. Splenectomy and/or spleen radiation are also sometimes done, whereas hematopoietic cell transplants are rarely used because of advanced age and co-morbidities.

In 2011 and 2012, the Food and Drug Administration (FDA) and European Medicines Agency (EMA), respectively, approved ruxolitinib, a Janus kinase (*JAK*) inhibitor intended for therapy of MPN-associated myelofibrosis. Currently, it is the standard of care for treating splenomegaly and constitutional symptoms, offering significant improvements in spleen shrinkage, symptom mitigation, and overall survival. However, therapy-induced cytopenias like anemia may impair administration of optimal therapeutic doses as they can occur transiently.

Several other *JAK* or signal transducers and activators of transcription (STAT) inhibitors are currently in development, and though they are not targeted, they are effective in reducing splenomegaly and constitutional symptoms in patients with and without the *JAK2* mutation. However, there is controversy whether they improve survival. Several other drug classes are in development including telomerase inhibitors and anti-fibrotic drugs (eg, pentraxin).

1.2.1. Treatment for Anemia

Anemia is present at diagnosis in about 30% of patients with MPN-associated myelofibrosis and develops in almost all patients. The etiology of anemia in MPN-associated myelofibrosis is complex, as several mechanisms may operate in an affected person (Barosi, 2010). Some drugs used to treat MPN-associated myelofibrosis, such as hydroxyurea (hydroxycarbamide) and ruxolitinib, worsen anemia.

Overall, anemia and RBC-transfusion dependence are strong, independent prognostic variables for survival and for risk of transformation to blast phase (Passamonti, 2010; Elena, 2011).

Therapy of anemia in MPN-associated myelofibrosis is problematic, and there are no proven or approved therapies. Currently, there are no FDA- or EMA-approved drugs for the treatment of anemia with or without RBC-transfusion dependence in patients with MPN-associated myelofibrosis, but commonly used interventions include therapies such as corticosteroids, androgenic steroids, erythropoietin, thalidomide, and pomalidomide. None have been proven effective in an adequately powered, double-blind, randomized clinical trial. A recent large randomized trial of pomalidomide reported no benefit, but other investigational studies of pomalidomide and corticosteroids report contradictory data (Tefferi, 2017; Schlenk, 2016).

In summary, no therapy has been proven safe and effective to treat anemia in patients with MPN-associated myelofibrosis.

1.2.1.1. Erythropoiesis Stimulating Agents

Erythropoiesis stimulating agents (ESAs) are widely used for the treatment of anemia associated with both lymphoid and myeloid neoplasms. In general, serum erythropoietin (EPO) levels in patients with MPN-associated myelofibrosis are elevated for the degree of anemia and exogenous use of ESAs are of limited value (Barosi, 1993).

Some patients with EPO levels < 500 IU/L receive pharmacological doses of recombinant human EPO. Response rates are < 20% and complete responses are uncommon, while most responses are transient. Currently, there are no randomized clinical trials of recombinant human EPO in patients with MPN-associated myelofibrosis who are RBC-transfusion dependent. Retrospective series in such patients treated with EPO or darbepoetin reported occasional response (Cervantes, 2004; Cervantes, 2006; Rodriguez, 1998; Tsiara, 2007). The data suggest ESAs have limited therapeutic activity in RBC-transfusion dependent patients with MPN-associated myelofibrosis and anemia regardless of serum EPO levels (Huang, 2009).

1.2.1.2. Androgenic Steroids

Androgenic steroids are sometimes used to treat anemia in patients with MPN-associated myelofibrosis. A retrospective analysis of case reports identified 5 of 27 (18%) subjects with MPN-associated myelofibrosis and RBC-transfusion-dependence responding to treatment with danazol (Cervantes, 2015). Complete responses are uncommon and often transient, which are in line with earlier studies. Additionally, androgenic steroids are associated with risks of liver toxicity and liver and prostate cancers. Based on these data, use of androgenic steroids in this setting is not proven safe and effective in patients with MPN-associated myelofibrosis who are RBC-transfusion dependent (Branda, 1977; Brubaker, 1982; Cervantes, 2005; Levy, 1996).

1.2.1.3. Corticosteroids

Corticosteroids do not produce sustained improvement in hemoglobin concentrations in patients with MPN-associated myelofibrosis. Corticosteroids are poorly-tolerated, especially in older patients, and increase infection risk in patients with decreased normal spleen function and in patients who have been splenectomized (Odenike, 2005).

1.2.1.4. Thalidomide, Lenalidomide, and Pomalidomide

Thalidomide and other immunomodulatory compounds, such as lenalidomide and pomalidomide, modulate levels of cytokines and growth factors in the bone marrow and may be

of benefit in patients with MPN-associated myelofibrosis. Thalidomide and lenalidomide are reported to improve outcomes with MPN-associated myelofibrosis in nonrandomized clinical trials. However, the efficacy of thalidomide and lenalidomide are severely limited by adverse effects, toxicities that are uncommon with pomalidomide. Furthermore, pomalidomide is more active in modulating levels of inflammatory cytokines and growth factors. Data from experimental models and a Celgene-sponsored trial indicate pomalidomide increases erythropoiesis in mice with sickle cell disease and humans with MPN-associated myelofibrosis. A randomized Phase 3 study showed no benefit of low-dose pomalidomide over placebo in subjects with RBC-transfusion dependence (Tefferi, 2017). However, a Phase 2 study of a higher dose of pomalidomide combined with prednisone reported activity (Schlenk, 2016).

1.2.1.5. Sotatercept

Sotatercept (ACE-011) is a novel soluble receptor fusion protein (activin receptor type IIA linked to Fc fragment of human immunoglobulin [Ig]G1) that "traps" ligands that bind to the activin type IIA receptor.

Sotatercept is extensively studied in humans and is active in treating anemia in patients associated with β-thalassemia and myelodysplastic syndrome (MDS). Like luspatercept, sotatercept targets molecules in the transforming growth factor-beta (TGF-β) superfamily, but sotatercept contains the human activin type IIA receptor whereas luspatercept contains the activin type IIB receptor.

Sotatercept is currently being studied in subjects with MPN-associated myelofibrosis and anemia receiving or not receiving ruxolitinib. Preliminary results suggest sotatercept improves anemia and RBC-transfusion dependence in patients with MPN-associated myelofibrosis and is well-tolerated (Bose, 2016).

1.3. Luspatercept Background

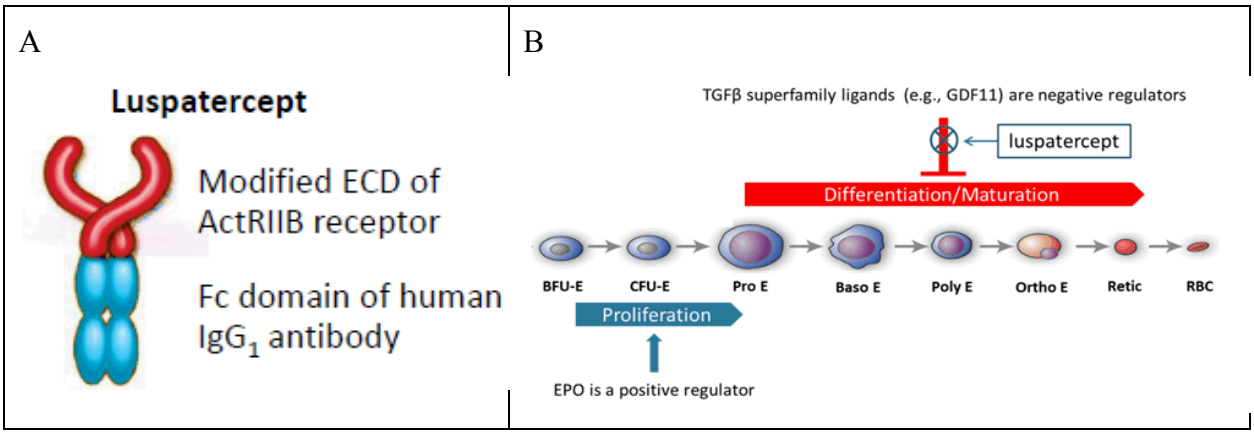
Luspatercept (ACE-536) is a recombinant fusion protein consisting of a modified form of the extracellular domain (ECD) of the human activin receptor type IIB (ActRIIB) linked to the IgG1 Fc domain (Figure 1A). The ActRIIB receptor and its ligands are members of the transforming growth factor-β (TGF-β) superfamily, a group of proteins involved in the development, differentiation, and/or maturation of various tissues. No species differences have been described in the ligand-receptor interactions among members of the TGF-β family as the ligands and receptors are highly conserved across species (Massague, 1998). Thus, observations from pharmacology studies of luspatercept or its murine ortholog RAP-536 in animal models provide significant insight into the potential of luspatercept to treat human disease.

Members of the TGF-β ligands, through their binding to activin receptors, are involved in modulating the differentiation of late-stage erythrocyte precursors (normoblasts) in the bone marrow. In particular, luspatercept acts as a ligand trap for growth differentiation factor 11 (GDF11) and other TGF-β family ligands to suppress Smad2/3 signaling. In nonclinical experiments, luspatercept has been shown to bind with high affinity to some TGF-β ligands (eg, GDF11, bone morphogenetic protein 6 [BMP6] and activin B) but substantially less to others (eg, bone morphogenetic protein 9 [BMP9] and activin A). The mechanism of action of luspatercept is independent from that of erythropoietin (EPO) (Suragani, 2014). While EPO stimulates proliferation and differentiation of early erythroid progenitors, luspatercept promotes

stimulation of the later, maturation phase of erythroblast differentiation and maturation in the bone marrow (refer to Figure 1B).

During normal erythropoiesis, GDF11 appears to inhibit differentiation and maintain the survival of immature erythroid progenitors, but its expression is decreased as cells mature, and thus its effect is transient. In a mouse model of thalassemia, defects in erythroid differentiation led to an accumulation of GDF11 expressing cells that maintained their own survival (Dussiot, 2014). Recent studies (Dussiot, 2014; Suragani, 2014) identified GDF11 as a regulator of erythropoiesis and showed that its inhibition in mouse models of anemia with ineffective erythropoiesis restores normal erythropoietic differentiation and improves anemia.

Figure 1: Luspatercept Schematic Representation and Mechanism of Action



ActRIIB = activin receptor type IIB; ECD = extracellular domain; EPO = erythropoietin; GDF11 = growth differentiation factor 11; IgG1 = immunoglobulin G1; RBC = red blood cell; TGF-b = transforming growth factor-beta.

Please refer to the Investigator's Brochure for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of luspatercept.

1.3.1. Summary of Nonclinical Studies with Luspatercept

A brief summary of key findings from pharmacology and toxicology studies is provided below. Please refer to the Investigator's Brochure (IB) for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of luspatercept. The most recent version of the luspatercept IB should be reviewed prior to initiating the study.

[redacted]

1.3.2. Summary of Clinical Experience

Luspatercept is currently in Phase 3 of clinical development in MDS and beta-thalassemia.

Luspatercept is currently being assessed in two Phase 2 studies in subjects with MDS. In these studies, the preliminary International Working Group (IWG) hematologic improvement – erythroid (HI-E) response for subjects treated with luspatercept dose levels of ≥ 0.75 mg/kg in the base study (A536-03) and the extension study (A536-05) respectively were seen in 18 out of 29 (62%) and 19 out of 23 (83%) subjects with ring sideroblasts (RS+) with EPO levels < 200 U/L, as well as 5 out of 11 (46%) and 7 out of 8 (88%) RS+ subjects with EPO levels 200 to 500 U/L. Subjects were also evaluated on the basis of whether they achieved RBC-transfusion independence (RBC-TI) for ≥ 8 weeks. The RBC-TI response for subjects treated with luspatercept dose levels of ≥ 0.75 mg/kg in the base study and extension study respectively were seen in 13 out of 19 (68%) and 10 out of 14 (71%) RS+ subjects with EPO levels < 200 U/L, as well as 3 out of 9 (33%) and 3 out of 5 (60%) RS+ subjects with EPO levels 200 to 500 U/L. Furthermore, in the extension study, 17 out of 28 (61%) subjects overall had achieved transfusion independence, in which the longest duration of erythroid response was up to 22 months (treatment ongoing) (Platzbecker, 2016).

Preliminary data for RS- subjects is encouraging for both HI-E response and RBC-TI.

In a Phase 3 (MEDALIST) trial, luspatercept resulted in a significantly reduced transfusion burden compared with placebo in patients with anemia due to Revised International Prognostic Scoring System (IPSS-R) very low-, low-, or intermediate-risk MDS with ring sideroblasts who require RBC transfusions, and overall, was generally well tolerated. Data demonstrated that 58 out of 153 (37.9%) subjects in the luspatercept arm achieved RBC transfusion independence for ≥ 8 weeks compared to 10 out of 76 (13.2%) subjects in the placebo arm (Fenaux, 2018).

Luspatercept is currently being assessed in two Phase 2 studies in subjects with β-thalassemia. In these studies, 25 out of 31 (81%) transfusion-dependent (TD) subjects treated with ≥ 0.6 mg/kg had a ≥ 20% reduction and 17 out of 31 subjects (55%) had a ≥ 50% reduction in transfusion burden over any 12-week period during the 3-month study (A536-04). For nontransfusion dependent (NTD) subjects treated with ≥ 0.6 mg/kg, 7 out of 21 subjects (33%) achieved an increase in Hgb ≥ 1.5 g/dL sustained for ≥ 14 days and 13 out of 21 subjects (62%) achieved a mean increase in Hgb ≥ 1.0 g/dL sustained for ≥ 12 weeks in the 3-month treatment study (Piga, 2016).

In a Phase 3 (BELIEVE) trial, luspatercept resulted in significantly reduced transfusion burden in adults with transfusion-dependent β-thalassemia, and overall, was generally well tolerated. Data demonstrated that 48 out of 224 (21.4%) subjects in the luspatercept arm achieved a ≥ 33% reduction from baseline in transfusion burden during weeks 13 to 24 compared to 5 out of 112 (4.5%) subjects in the placebo arm (Cappellini, 2018).

Until now, no clinical trials investigating the efficacy of luspatercept in MPN-associated myelofibrosis have been initiated/completed.

Additional information regarding clinical experience with luspatercept is summarized in the current version of the luspatercept IB.

1.3.3. Potential Risks of Human Use

Increases in hematologic parameters (ie, RBC, Hgb, hematocrit, reticulocytes) are expected pharmacologic effects of luspatercept treatment. Increases in systolic and diastolic blood pressures may occur in concert with increases in hemoglobin values. Excessive or rapid increases in hemoglobin or blood pressure may occur and will be monitored. Dose modification rules for individual subjects, including dose delay and/or dose reduction, will be utilized to minimize risks associated with increased RBC parameters.

Adverse events observed in the Phase 1 study in healthy volunteers and the ongoing Phase 2 studies that were considered probably or possibly related to investigational product included injection site reactions (hemorrhage, pruritus, rash), skin rash, hyperesthesia, muscle spasms, myalgia, pruritus, and hyperkalemia.

As with all biologics, there is the potential for antidrug antibodies (ADA) that can be associated with increased drug clearance and hypersensitivity reactions. Antidrug antibody (ADA) formation against luspatercept as well as human ActRIIB protein will be monitored in the initial clinical studies.

Luspatercept has exhibited maternal and developmental toxicity in reproductive toxicity studies in preclinical species and therefore luspatercept should not be administered to pregnant or nursing women. Male and female subjects of childbearing potential participating in studies of luspatercept must be willing to abstain from sexual intercourse or use adequate contraception during the treatment and follow-up period of the study. Please refer to the IB for additional information regarding findings from toxicology studies. It is unknown if humans will experience any of the effects of luspatercept that were noted in the rat and monkey toxicology studies. Safety effects will be monitored closely through adverse event (AE) reporting, clinical laboratory tests, vital signs, and physical examinations.

A comprehensive review of luspatercept, as well as details regarding the information summarized above, is provided in the IB. The most recent version of the luspatercept IB should be reviewed prior to initiating the study.

1.4. Rationale

1.4.1. Study Rationale and Purpose

Anemia and related symptoms are important features of MPN-associated myelofibrosis. Patients with anemia and those receiving RBC transfusions have significantly worse survival and an increased risk of transformation to blast phase. Therapies such as ESAs, androgenic steroids, and corticosteroids are rarely effective with most responses transient, while data regarding efficacy of pomalidomide is controversial. No drug is approved to treat anemia in patients with MPN-associated myelofibrosis.

Luspatercept is a novel recombinant fusion protein consisting of a modified form of the extracellular domain (ECD) of the human activin receptor type IIB (ActRIIB). Luspatercept stimulates the later, maturation phase of erythropoiesis and improves anemia in patients with MDS and beta-thalassemia. Sotatercept, active in patients with MPN-associated myelofibrosis and anemia, is structurally similar to luspatercept.

The purpose of this Phase 2 study is to evaluate safety and efficacy of luspatercept in subjects with MPN-associated myelofibrosis and anemia with and without RBC-transfusion dependence.

1.4.2. Rationale for the Study Design

This study is a multicenter, multicohort, parallel-enrolling, single-arm, Phase 2 study of anemia response, where the multicenter nature of the study provides assurance that the results are likely to have applicability for planning a confirmatory Phase 3 study.

Three cohorts with distinct entry criteria are included. The rationale for each of the cohorts is as follows:

- **Cohort 1 (anemia only)**: [redacted]
- **Cohort 2 (RBC-transfusion dependent)**: [redacted]
- **Cohort 3 (subjects on ruxolitinib as part of their standard-of-care therapy)**: [redacted]

Beginning with Protocol Amendment 3, in addition to RBC-transfusion dependent subjects with a defined average RBC-transfusion frequency of 6 to 12 RBC units/84 days, subjects with an RBC transfusion burden of 4 to 5 RBC units/84 days may also be eligible for enrollment.

Eligibility criteria are consistent with those in other studies of this population. Safety is assessed by evaluating adverse events and laboratory data. Adverse events and abnormal laboratory value severity will be graded using version 4.03 of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).

[redacted]

2. STUDY OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives

Primary Objective
The primary objective of the study is to evaluate the efficacy and safety of luspatercept for the treatment of anemia in subjects with myeloproliferative neoplasm (MPN)-associated myelofibrosis with and without red blood cell (RBC)-transfusion dependence.
Secondary Objectives
The secondary objectives of the study are: - To evaluate the safety of luspatercept in MPN-associated myelofibrosis - To evaluate the effect of luspatercept in MPN-associated myelofibrosis: o on the time to and duration of anemia response o on frequency of RBC transfusions and transfusion dependence o on symptom response improvement via the Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) o on health-related quality of life (HRQoL) via the EQ-5D-5L and Functional Assessment of Cancer Therapy – Anemia (FACT-An) questionnaires o on the changes in hemoglobin and mean hemoglobin increase - To evaluate population pharmacokinetics of luspatercept in subjects with MPN-associated myelofibrosis with and without RBC-transfusion dependence
[redacted]
[redacted]

Table 2: Study Endpoints

Endpoint	Name	Description	Timeframe
Primary Endpoint **refer to Section 3.1 for more information on each cohort*	Anemia response as it relates to hemoglobin (Hgb) increase and red blood cell (RBC)-transfusion independence	Cohorts 1 and 3A*: Proportion of subjects achieving ≥ 1.5 g/dL hemoglobin increase from baseline over any consecutive 84-day period without an RBC transfusion	Any consecutive "rolling" 84-day period from Day 1 through and including Day 168
		Cohorts 2 and 3B*: Proportion of subjects who become RBC-transfusion free over any consecutive 84-day period	Any consecutive "rolling" 84-day period from Day 1 through and including Day 168
Secondary Endpoints	Time to anemia response	Time from first luspatercept dose to first onset of anemia response in each of the cohorts	Day 1 through and including Day 168
	Duration of anemia response	Maximum duration of anemia response in each of the cohorts	Day 1 through end of treatment
	Frequency of RBC transfusions	Cohorts 2 and 3B: Mean number of RBC units transfused per subject per 28 days	Day 1 through and including Day 168; Day 1 through end of treatment
	Frequency of RBC-transfusion dependence	Cohorts 2 and 3B: Proportion of RBC-transfusion dependent subjects who reduce their transfusion burden by ≥ 50% from baseline over any consecutive 84-day period	Day 1 through and including Day 168; Day 1 through end of treatment
	Symptoms response improvement	Proportion of subjects who achieve ≥ 50% reduction in fatigue symptom as measured by the Myeloproliferative Neoplasms Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) The proportion of subjects who achieve ≥ 50% reduction in total symptom score (TSS)	Day 1 through and including Day 168; Day 1 through end of treatment

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
	Health-related quality of life (HRQoL) improvement via the Functional Assessment of Cancer Therapy – Anemia (FACT-An) and EQ-5D-5L questionnaires	Mean changes in HRQoL domain scores over the study compared to baseline	Day 1 through and including Day 168; Day 1 through end of treatment
	Safety	Type, frequency, severity of AEs and relationship of AEs to luspatercept	Screening through 42 days post last dose
	A population pharmacokinetic (PK) model	A population PK model that describes the PK exposure data of luspatercept and associated variability	Day 1 up to 1 year
	Antidrug antibodies (ADA)	Frequency of antidrug antibodies and effects on efficacy, safety, or PK	Day 1 up to 1 year for ADA-negative subjects; Day 1 up to 2 years for ADA-positive subjects
	Changes in hemoglobin	Cohorts 1 and 3A: Changes in hemoglobin over the study compared to baseline in the absence of RBC transfusions	Day 1 through and including Day 168; Day 1 through end of treatment
	Mean hemoglobin increase	Cohorts 1 and 3A: Proportion of subjects achieving a mean $\geq$ 1.5 g/dL hemoglobin increase from baseline over any consecutive 84-day period without an RBC transfusion	Any consecutive "rolling" 84-day period from Day 1 through and including Day 168; Day 1 through end of treatment

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

3. OVERALL STUDY DESIGN

3.1. Study Design

The study will be conducted in compliance with the International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

This is a Phase 2, multicenter, open-label study to evaluate the efficacy and safety of luspatercept in subjects with MPN-associated myelofibrosis and anemia with and without RBC-transfusion dependence. The study is divided into a Screening Period, a Treatment Period (consisting of a Primary Phase, a Day 169 Disease Response Assessment, and an Extension Phase), followed by a Posttreatment Follow-up Period. The overall study design is described in Figure 2, with more detailed descriptions for each phase of the study design found in Section 6.

Subjects satisfying the eligibility criteria will be assigned to 1 of the following cohorts (which are enrolling in parallel) based on their eligibility:

- **Cohort 1**: will contain up to 20 subjects with anemia only that are not currently receiving RBC transfusions (these subjects will be referred to as "anemia only" throughout the protocol, defined as 0 RBC units/84 days immediately up to the C1D1 date)
- **Cohort 2**: will contain up to 20 subjects that are RBC-transfusion dependent (these subjects will be referred to as "RBC-transfusion dependent" throughout the protocol, defined as an average RBC transfusion frequency of 2 to 4 RBC units/28 days over at least the 84 days immediately up to the C1D1 date)
- **Cohort 3A**: will contain ≥ 10 subjects who meet the eligibility criteria for Cohort 1 (anemia only) while being on a stable dose of ruxolitinib for at least 112 days immediately prior to the enrollment date
- **Cohort 3B**: will contain approximately 46 subjects who meet the eligibility criteria for Cohort 2 (RBC-transfusion dependent) while being on a stable dose of ruxolitinib for at least 112 days immediately prior to the enrollment date. Effective from Protocol Amendment 3, additional subjects for this cohort must also have a minimum prior treatment with ruxolitinib per their local standard-of-care for at least 280 days (40 weeks) without interruptions exceeding 2 consecutive weeks, while being on a stable ruxolitinib dose for at least 112 days (16 weeks) immediately prior to the enrollment date.

Refer to the eligibility criteria (Section 4) for full cohort specifications.

The subject must be enrolled at the latest 28 days from signing the informed consent form (ICF), designated as the enrollment date. The first dose of luspatercept (designated as Cycle 1 Day 1 [C1D1]) should be administered as soon as possible (at the latest 3 calendar days) following the enrollment date (but can occur on the same day as the enrollment date).

Subjects across each cohort will receive a starting dose level of luspatercept at 1.0 mg/kg subcutaneous injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle).

Subjects enrolling into Cohort 3B following implementation of Protocol Amendment 3 will begin luspatercept treatment at a starting dose of 1.33 mg/kg and can have their dose increased to a maximum dose of 1.75 mg/kg (with the total dose not to exceed 168 mg).

The starting dose can be titrated (increased), reduced, or delayed during the Treatment Period (Primary Phase and Extension Phase). Please refer to Section 7.3 for more information regarding dose modifications.

During the Primary Phase of the Treatment Period, subjects will receive luspatercept on Day 1 of each 21-day treatment cycle (unless there are dose delays) through at least Day 168 following the C1D1 date unless the subject experiences unacceptable toxicities, withdraws consent, or meets any other treatment discontinuation criteria (Section 11.1) prior to the Day 169 Disease Response Assessment.

At the Day 169 Disease Response Assessment, which should be completed 169 days after the C1D1 date regardless of dose delays, subjects will be assessed by the Investigator to see if they may continue receiving luspatercept treatment in the Extension Phase of the Treatment Period. The following criteria must be met:

Cohorts 1 (anemia only) and 3A

Subjects with ≥ 3 determinations showing a ≥ 1.5 g/dL hemoglobin increase above the baseline value (defined as the subject's Hgb value observed on the C1D1 date prior to luspatercept administration) absent of RBC transfusions over a consecutive ≥ 84-day period with no 2 measurements ≥ 42 days apart (and no determination < 1.5 g/dL above the baseline value) at the time of the Day 169 Disease Response Assessment will have the opportunity to move into the Extension Phase of the Treatment Period. The subject may remain on treatment for approximately 2 years or more from date of C1D1, until a determination shows a value < 1.5 g/dL hemoglobin increase above the baseline value (absent of bleeding or infection), there is receipt of an RBC transfusion, disease progression, or any of the other criteria for treatment discontinuation are met.

If, at the Day 169 Disease Response Assessment, the subject has ≥ 3 determinations showing a ≥ 1.5 g/dL hemoglobin increase above the baseline value with no 2 measurements ≥ 42 days apart (and no determination < 1.5 g/dL above the baseline value) in the absence of RBC transfusions over the preceding 56 days, the subject may continue on in the Extension Phase of the Treatment Period for an additional 28 days. If, after this additional 28 days, the subject meets the response criteria, the subject can continue on in the Extension Phase of the Treatment Period and remain on treatment at the Investigator's discretion for approximately 2 years or more from the date of C1D1, until a determination shows a value < 1.5 g/dL hemoglobin increase above the baseline value (absent of bleeding or infection), there is receipt of an RBC transfusion, disease progression, or any of the other criteria for treatment discontinuation are met.

Cohorts 2 (RBC-transfusion dependent) and 3B

Subjects who are transfusion free over ≥ 84 consecutive days at the time of the Day 169 Disease Response Assessment can enter the Extension Phase of the Treatment Period and remain on treatment for approximately 2 years or more from the C1D1 date at the

Investigator's discretion, until they receive the next RBC transfusion (absent of bleeding or infection), disease progression, or meet other criteria for treatment discontinuation.

If, at the Day 169 Disease Response Assessment, the subject is RBC-transfusion free for the preceding 56 days, they may continue on in the Extension Phase of the Treatment Period for an additional 28 days. If, after this additional 28 days, the subject meets the response criteria, they can continue on in the Extension Phase of the Treatment Period and remain on treatment for approximately 2 years or more from the C1D1 date at Investigator's discretion until the subject receives an RBC transfusion (absent of bleeding or infection), disease progression, or meets of other criteria for treatment discontinuation.

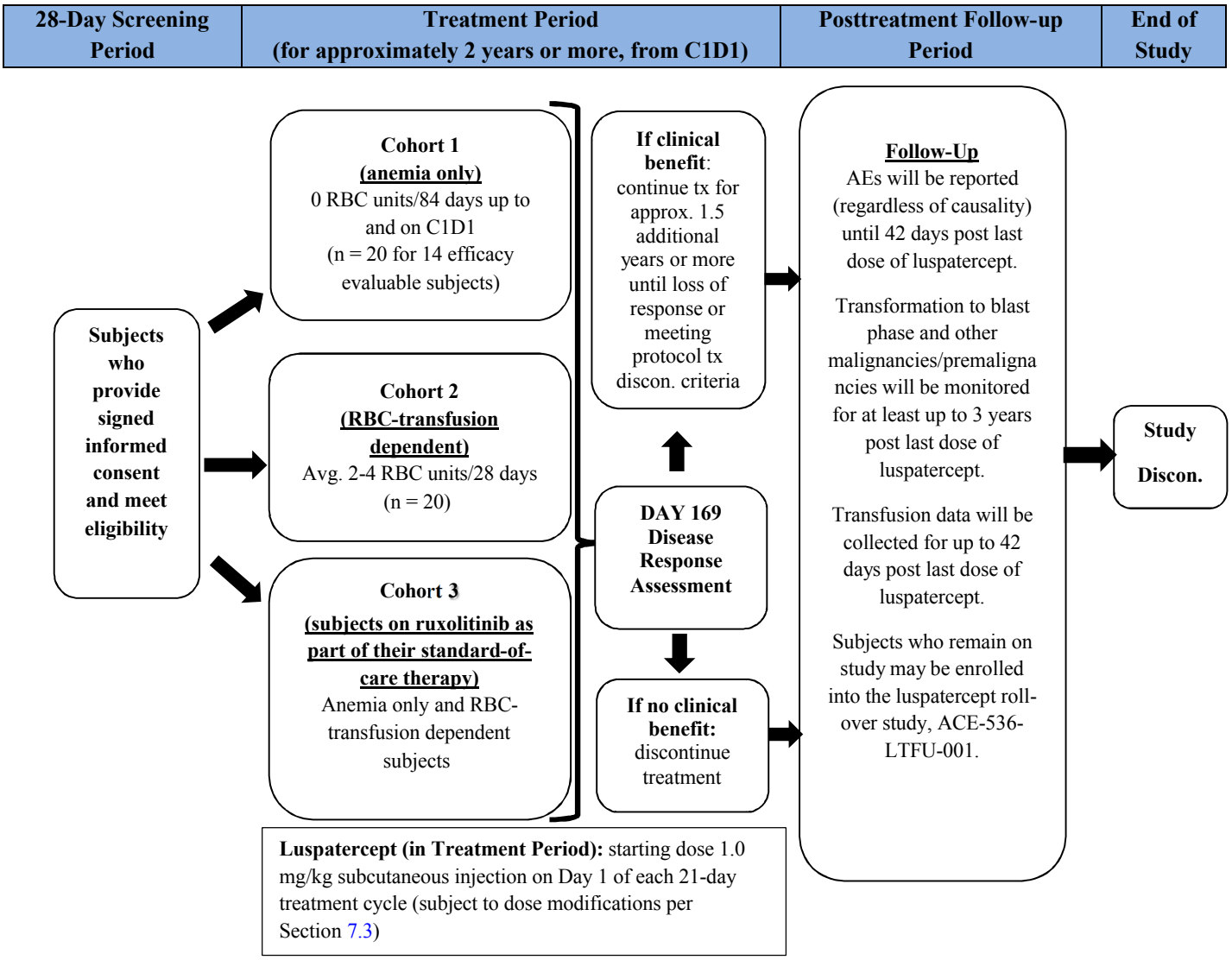
Should subjects from each respective cohort not meet the clinical benefit criteria outlined above, they should discontinue treatment with luspatercept and enter the Posttreatment Follow-up Period. Otherwise, subjects may begin luspatercept treatment in the Extension Phase of the Treatment Period, receiving luspatercept on Day 1 of each 21-day treatment cycle (unless there are dose delays), and remain on treatment at the Investigator's discretion for approximately 2 years or more (if the subject continues to receive benefit) following the C1D1 date or until the next RBC transfusion, disease progression, or any of the other criteria for treatment discontinuation are met. If, according to the assessment of the investigator, the subject is benefiting from treatment not reflected by the criteria above (eg, a clinically significant reduction of the transfusion burden or clinically significant improvement of a subject's symptom burden), this should be discussed with the Medical Monitor for the potential continuation of the subject in the Extension Phase.

Subjects will enter the Posttreatment Follow-up Period following the last dose of luspatercept for at least 3 years. This Posttreatment Follow-up Period will be inclusive of a 42-Day Follow-up Period and Long-term Follow-up Period.

In all cohorts throughout the Treatment Period, best supportive care (BSC) may be used in combination with study treatment when clinically indicated per Investigator. Best supportive care includes, but is not limited to, antibiotic, antiviral and/or antifungal therapy, and nutritional support as needed. Best supportive care for this study excludes the use of ESAs. Refer to Section 8 for additional details.

A steering committee (SC) will be established by charter for this study, in which SC members will have the opportunity to review efficacy and safety data on an ongoing basis. The SC will serve in an advisory capacity to the Sponsor. Please refer to Section 9.9.3 for additional details.

Figure 2: Study Design



AEs = adverse events; Approx. = approximately; Avg. = average; C1D1 = Cycle 1 Day 1; Discon. = discontinuation; RBC = red blood cell; tx = treatment.

3.2. Study Duration for Subjects

After a Screening Period of at most 28 days immediately prior to their enrollment date, eligible subjects should receive luspatercept treatment through at least the first 168 days of the study unless the subject experiences unacceptable toxicities, has disease progression, withdraws consent, or meets any other discontinuation criteria (refer to Section 11).

Subjects who experience clinical benefit or become responders (refer to Section 6.2.2 for detailed definition) as determined by the Day 169 Disease Response Assessment may continue luspatercept treatment beyond the Day 169 visit (ie, in the Extension Phase of the Treatment Period) for approximately 2 years or more from the C1D1 date or until the subject is no longer

receiving clinical benefit, experiences unacceptable toxicities, has disease progression, withdraws consent, or meets any other discontinuation criteria (refer to Section 11).

For all subjects who receive at least 1 dose of luspatercept, continuation of monitoring for transformation to blast phase will occur in the Posttreatment Follow-up Period, along with data collection of subsequent MPN-associated myelofibrosis therapies and overall survival for at least 3 years from the date of last dose of luspatercept unless the subject withdraws consent from the study, dies, or is lost to follow up. Refer to Section 6 for additional details.

3.3. End of Trial

The End of Trial is defined as either the date of the last visit of the last subject to complete the Posttreatment Follow-up Period, or the date of receipt of the last data point from the last subject that is required for primary, secondary [redacted] analysis, as prespecified in the protocol, whichever is the later date.

The Sponsor may end the trial when all key endpoints and objectives of the study have been analyzed.

At the End of Trial, any subjects who remain on study may be consented and enrolled on the luspatercept roll-over study, ACE-536-LTFU-001. This study is intended to evaluate long-term safety (including progression to acute myeloid leukemia [AML] and/or other malignancies/pre-malignancies) of luspatercept. The roll-over study will also provide continued access for subjects on luspatercept treatment who continue to receive benefit. Additionally, subjects who have completed the Primary Phase of the Treatment Period and the Day 169 Disease Response Assessment may be considered for consent and transition over to the ACE-536-LTFU-001 study prior to the End of Trial if agreed to by the Sponsor.

4. STUDY POPULATION

4.1. Numbers of Subjects

Approximately 100 subjects with MPN-associated myelofibrosis (primary myelofibrosis [PMF], post-polycythemia vera myelofibrosis [post-PV MF], or post-essential thrombocythemia myelofibrosis [post-ET MF]) with or without RBC-transfusion dependence will be enrolled worldwide. Refer to Section 3.1 for additional information regarding subject enrollment in each cohort.

4.2. Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study (with the enrollment date defined as the date in which the subject is assigned a cohort in Integrated Response Technology [IRT]) and receive their first dose of luspatercept:

1. Subject is ≥18 years of age at the time of signing the informed consent form (ICF).
2. Subject has MPN-associated myelofibrosis (PMF, post-PV MF, and/or post-ET MF) as confirmed from the most recent local bone marrow biopsy report according to the World Health Organization 2016 criteria (Arber, 2016).
3. Subject has anemia defined as:
   - **a. Cohorts 1 and 3A**
     - i. Obtain ≥ 3 Hgb levels of ≤ 9.5 g/dL recorded on ≥ 3 different days, including the day of dosing, in the 84-day period immediately up to the C1D1 date. There must be ≥ 14 days in between each Hgb measurement. No subjects with an interval ≥ 42 days between hemoglobin measurements will be enrolled.
     - ii. There must not be any RBC transfusions within the 84-day period immediately up to the C1D1 date.
   - **b. Cohorts 2 and 3B**
     - i. Average RBC-transfusion frequency: 4 to 12 RBC units/84 days immediately up to the C1D1 date. There must be no interval > 56 days without ≥ 1 RBC transfusion.
     - ii. Subjects must have a Hgb value of < 13 g/dL on C1D1 prior to luspatercept administration.
     - iii. Only RBC transfusions given when the Hgb ≤ 9.5 g/dL are scored in determining eligibility.
     - iv. RBC transfusions given because of bleeding, infection, or chemotherapy-induced anemia are not scored in determining eligibility.
4. Subject has an Eastern Cooperative Oncology Group (ECOG) performance score of ≤ 2.
5. Subject is not anticipated during the 6 months from the C1D1 date to receive a hematopoietic cell transplant.

6. A female of childbearing potential (FCBP) for this study is defined as a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months). FCBP participating in the study must:
    a. Have 2 negative pregnancy tests as verified by the Investigator prior to starting study therapy. She must agree to ongoing pregnancy testing during the course of the study, and after end of study treatment. This applies even if the subject practices true abstinence* from heterosexual contact.
    b. Either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agree to use, and be able to comply with, effective contraception** without interruption, 28 days prior to starting investigational product, during the study therapy (including dose interruptions), and for 12 weeks (approximately 5 times the mean terminal half-life of luspatercept based on multiple-dose pharmacokinetics [PK] data) after discontinuation of study therapy.
7. Male subjects must:
    a. Practice true abstinence* (which must be reviewed on a monthly basis) or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential** while participating in the study, during dose interruptions and for at least 12 weeks (approximately 5 times the mean terminal half-life of luspatercept based on multiple-dose PK data) following investigational product discontinuation, even if he has undergone a successful vasectomy

    * True abstinence is acceptable when it is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.]

    ** Agreement to use highly effective methods of contraception that alone or in combination resulting in a failure rate of a Pearl index of less than 1% per year when used consistently and correctly throughout the course of the study. Such methods include: Combined (estrogen and progestogen containing) hormonal contraception: Oral; Intravaginal; Transdermal; Progestogen-only hormonal contraception associated with inhibition of ovulation: Oral; Injectable hormonal contraception; Implantable hormonal contraception; Placement of an intrauterine device (IUD); Placement of an intrauterine hormone-releasing system (IUS); Bilateral tubal occlusion; Vasectomized partner; Sexual Abstinence.
8. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.
9. Subject is willing and able to adhere to the study visit schedule and other protocol requirements.

4.3. Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment (with the enrollment date defined as the date in which the subject is assigned a cohort in IRT):

1. Subject use of hydroxyurea or other drugs with potential effects on hematopoiesis (refer to Section 8.2 for prohibited medications) or ongoing adverse events from previous treatment ≤ 112 days immediately up to the enrollment date.
    a. Systemic corticosteroids are permitted for nonhematological conditions providing the subject is receiving a stable or decreasing dose for ≥ 84 days immediately up to enrollment and is receiving a constant dose equivalent to ≤ 10 mg prednisone for the 28 days immediately up to enrollment.
2. **Cohort 1 and 2 only**: subjects treated with *JAK2* inhibitors ≤ 112 days immediately up to the enrollment date or if anticipated/substantial likelihood for subject to receive ruxolitinib within the first 168 days on the study.
3. **Cohort 3 only**: subjects not receiving ruxolitinib:
    a. for at least 280 days (40 weeks) without interruptions exceeding 2 consecutive weeks
    b. on a stable daily dose for at least 112 days (16 weeks)

    immediately up to the enrollment date as part of their standard-of-care therapy.
4. Subject use of ESAs or androgenic steroids ≤ 112 days immediately up to the enrollment date.
5. Starting iron chelation therapy (ICT) or changing the ICT dose within ≤ 112 days up to the enrollment date.
6. Subject with anemia from iron deficiency, B12 and folate deficiencies, hemolytic anemia, infection, or bleeding.
7. Pregnant or breastfeeding females.
8. Subject with blood myeloblasts ≥ 5%.
9. Subject with major surgery within 8 weeks up to the enrollment date. Subject must have completely recovered from any previous surgery immediately up to the enrollment date.
10. Subject with prior history of malignancies, other than disease under study, unless the subject has been free of the disease for ≥ 5 years. However, subject with the following history/concurrent conditions is allowed:
    - Basal or squamous cell carcinoma of the skin
    - Carcinoma in situ of the cervix
    - Carcinoma in situ of the breast
    - Incidental histologic finding of prostate cancer (T1a or T1b using the tumor, nodes, metastasis [TNM] clinical staging system)
11. Subject with prior therapy of luspatercept or sotatercept.

12. Subject participation in any other clinical protocol or investigational trial that involves administration of experimental therapy and/or therapeutic devices within 30 days immediately up to the enrollment date.
13. Subject with prior hematopoietic cell transplant.
14. Subject with any of the following laboratory abnormalities at screening:
    - Neutrophils < 1 x 10^9/L
    - White blood count (WBC) > 100 x 10^9/L
    - Platelets
        i. **Cohorts 1 and 2**: < 25 x 10^9/L
        ii. **Cohort 3A and 3B**: < 50 x 10^9/L
        iii. **All Cohorts**: > 1000 x 10^9/L
    - Estimated glomerular filtration rate < 45 mL/min/1.73 m^2 (via the 4-variable modification of diet in renal disease [MDRD] formula)
    - Aspartate aminotransferase (AST) or alanine transaminase (ALT) > 3.0 x upper limit of normal (ULN)
    - Direct bilirubin ≥ 2 x ULN
        i. higher levels are acceptable if these can be attributed to active red blood cell precursor destruction within the bone marrow (ie, ineffective erythropoiesis)
    - Uncontrolled hyperthyroidism or hypothyroidism
15. Subject with stroke, deep venous thrombosis, pulmonary or arterial embolism within 6 months immediately up to the enrollment date.
16. Subject with diastolic blood pressure ≥ 90 mmHg or systolic blood pressure ≥ 140 mmHg measured during the Screening Period despite appropriate treatment.
17. Subject with inadequately controlled heart disease and/or have a known left ventricular ejection fraction < 35%.
18. Subject with history of severe allergic or anaphylactic reactions or hypersensitivity to recombinant proteins or excipients in the investigational product (see luspatercept IB).
19. Subject with uncontrolled systemic fungal, bacterial, or viral infection (defined as ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics, antiviral therapy, and/or other treatment).
20. Subject with human immunodeficiency virus (HIV), evidence of active infectious Hepatitis B (HepB), and/or evidence of active Hepatitis C (HepC).
21. Subject with any significant medical condition, laboratory abnormality, psychiatric illness, or is considered vulnerable by local regulations (eg, imprisoned or institutionalized) that would prevent the subject from participating in the study.

22. Subject with any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study.
23. Subject with any condition or concomitant medication that confounds the ability to interpret data from the study.
24. Subject on anticoagulant therapy not under appropriate control or subject not on a stable dose of anticoagulant therapy for ≥ 8 weeks up to the enrollment date.
25. Subject on anagrelide within 28 days immediately up to the enrollment date.
26. Subject with a major bleeding event (defined as symptomatic bleeding in a critical area or organ and/or bleeding causing a decrease in Hgb of ≥ 2 g/dL or leading to transfusion of ≥ 2 units of packed red cells) in the last 6 months prior to enrollment.

5. TABLE OF EVENTS

Table 3: Table of Events

	Reference Section	Screening Period[a]	Treatment Period									Posttreatment Follow-up Period (± 14 days)		
			Primary Phase *First 168 days of treatment Up to maximum of 8 Treatment Cycles (if no dose delays)* (± 3 days)				Day 169[b] Assessment *169 calendar days after C1D1 regardless of dose delays* (± 14 days)	Extension Phase *Continuation of treatment beyond Day 169* (± 3 days)			EOT Visit[b]	• **42-Day Follow-up Period** = Occurs 42 days from last dose of luspatercept • **Long-term Follow-up Period** = Occurs every 3 months after 42-Day Follow-up until at least 3 years post last dose of luspatercept		
		Day -28 to Enrollment	Every Cycle (ie, 1, 2, 3+ up to max 8 cycles) Day 1	Every Other Cycle Only) (ie, 1, 3, 5, 7) Day 1	Cycles 1 and 5 Only Day 8	Cycle 1 Only Day 15		Every Cycle; X, X+1, etc. Day 1	Every 4th Cycle; X, X+4, etc. Day 1	Every 8th Cycle; X, X+8, etc. Day 1		42-Day Follow-up Period	Long-term Follow-up Period	End of Study
STUDY ENTRY AND GENERAL ASSESSMENTS														
Informed consent	6.1	X	--	--	--	--	--	--	--	--	--	--	--	--
Inclusion/Exclusion evaluations	6.1	X	--	--	--	--	--	--	--	--	--	--	--	--
Physical examination (including liver/spleen assessment)	6.1	X	X	--	--	--	X	X	--	--	X	--	--	--
Demographics	6.1	X	--	--	--	--	--	--	--	--	--	--	--	--
Medical history	6.1	X	--	--	--	--	--	--	--	--	--	--	--	--
Prior anemia treatment	6.1	X	--	--	--	--	--	--	--	--	--	--	--	--
Prior RBC transfusions	6.1	X	--	--	--	--	--	--	--	--	--	--	--	--
INVESTIGATIONAL PRODUCT														
Luspatercept administration and accountability[c]	6.2	--	X	--	--	--	--	X	--	--	--	--	--	--

Table 3: Table of Events (Continued)

	Reference Section	Screening Period[a]	Treatment Period: Primary Phase (First 168 days of treatment, Up to maximum of 8 Treatment Cycles, (if no dose delays), (± 3 days))				Day 169[b] Assessment (169 calendar days after C1D1 regardless of dose delays (± 14 days)	Treatment Period: Extension Phase (Continuation of treatment beyond Day 169, (± 3 days))			EOT Visit[b]	Posttreatment Follow-up Period (± 14 days)		
			Every Cycle (ie, 1, 2, 3+ up to max 8 cycles	Every Other Cycle Only) (ie, 1, 3, 5, 7)	Cycles 1 and 5 Only	Cycle 1 Only		Every Cycle; X, X+1, etc.	Every 4th Cycle; X, X+4, etc.	Every 8th Cycle; X, X+8, etc.		42-Day Follow-up Period	Long-term Follow-up Period	End of Study
		Day -28 to Enrollment	Day 1	Day 1	Day 8	Day 15		Day 1	Day 1	Day 1				
SAFETY ASSESSMENTS														
ECOG performance status	6.1	X	--	X	--	--	X	Ext. C1D1, then D1 of every other cycle until treatment discontinuation (eg, Ext. C1D1, C3D1, etc.)			X	--	--	--
Urinalysis	6.1	X	C1D1 and D1 of every 4th cycle thereafter (eg, C1D1, C5D1, etc.)				X	--	X	--	X	--	--	--
Assessment of HIV/HepB/HepC status[d]	6.1	X	--	--	--	--	--	--	--	--	--	--	--	--
Electrocardiogram (ECG), 12-lead	6.1	X	--	--	C5D8 only	--	--	--	--	--	X	--	--	--
Pregnancy testing	6.1	X	X	--	--	--	X	X	--	--	X	--	--	--
Adverse events	6.1	Continuous, from signing informed consent until 42 days after last luspatercept administration[e]											--	--
Prior and concomitant medications/procedures	6.1	X	Continuous until 42 days after last luspatercept administration or until the EOT visit, whichever occurs later										--	--

Table 3: Table of Events (Continued)

	Reference Section	Screening Period[a]	Treatment Period									Posttreatment Follow-up Period (± 14 days) • **42-Day Follow-up Period** = Occurs 42 days from last dose of luspatercept • **Long-term Follow-up Period** = Occurs every 3 months after 42-Day Follow-up until at least 3 years post last dose of luspatercept		
			Primary Phase *First 168 days of treatment Up to maximum of 8 Treatment Cycles (if no dose delays)* (± 3 days)				Day 169[b] Assessment *169 calendar days after C1D1 regardless of dose delays* (± 14 days)	Extension Phase *Continuation of treatment beyond Day 169* (± 3 days)			EOT Visit[b]			
		Day -28 to Enrollment	Every Cycle (ie, 1, 2, 3+ up to max 8 cycles Day 1	Every Other Cycle Only) (ie, 1, 3, 5, 7) Day 1	Cycles 1 and 5 Only Day 8	Cycle 1 Only Day 15		Every Cycle; X, X+1, etc. Day 1	Every 4th Cycle; X, X+4, etc. Day 1	Every 8th Cycle; X, X+8, etc. Day 1		42-Day Follow-up Period	Long-term Follow-up Period	End of Study
Vital signs, height (measured at screening), weight (measured at screening and prior to every luspatercept administration)	6.1	X	X	--	X	X	X	X	--	--	X	--	--	--
Serum chemistry	6.1	X	X	--	--	--	X	X	--	--	X	--	--	--
EFFICACY ASSESSMENTS														
Hematology[c]	6.1	X	X	--	X	X	X	X	--	--	X	--	--	--
Serum erythropoietin (EPO)	6.1	X	--	X	--	--	X	--	--	--	X	--	--	--
Serum ferritin	6.1	X	X	--	--	--	X	--	X	--	X	--	--	--
Transfusion data collection and assessment[f]	6.2, 6.5	--	Assess and record on ongoing basis (prior to each dose of luspatercept) until end of treatment or 42 days after last dose of luspatercept, whichever occurs later.										--	--
Disease response assessment[g]	6.2.2	--	--	--	--	--	X	X	--	--	X	--	--	--

Table 3: Table of Events (Continued)

			Treatment Period									Posttreatment Follow-up Period (± 14 days) • **42-Day Follow-up Period** = Occurs 42 days from last dose of luspatercept • **Long-term Follow-up Period** = Occurs every 3 months after 42-Day Follow-up until at least 3 years post last dose of luspatercept		
			Primary Phase *First 168 days of treatment Up to maximum of 8 Treatment Cycles (if no dose delays)* (± 3 days)				Day 169[b] Assessment *169 calendar days after C1D1 regardless of dose delays* (± 14 days)	Extension Phase *Continuation of treatment beyond Day 169* (± 3 days)			EOT Visit[b]			
	Reference Section	Screening Period[a] Day -28 to Enrollment	Every Cycle (ie, 1, 2, 3+ up to max 8 cycles Day 1	Every Other Cycle Only) (ie, 1, 3, 5, 7) Day 1	Cycles 1 and 5 Only Day 8	Cycle 1 Only Day 15		Every Cycle; X, X+1, etc. Day 1	Every 4th Cycle; X, X+4, etc. Day 1	Every 8th Cycle; X, X+8, etc. Day 1		42-Day Follow-up Period	Long-term Follow-up Period	End of Study
[redacted]														
[redacted]														
PK and ADA														
PK sample collection	6.7	--	C1, C2, C4, C5, C6, C8 Only	--	X	X	X	D1 of every 4th Extension Cycle thereafter (eg, Ext. C4, C8, etc.) for up to 1-year post first dose of luspatercept.			X	--	--	--

Table 3: Table of Events (Continued)

	Reference Section	Screening Period[a]	Treatment Period								EOT Visit[b]	Posttreatment Follow-up Period (± 14 days) • **42-Day Follow-up Period** = Occurs 42 days from last dose of luspatercept • **Long-term Follow-up Period** = Occurs every 3 months after 42-Day Follow-up until at least 3 years post last dose of luspatercept		
			Primary Phase *First 168 days of treatment Up to maximum of 8 Treatment Cycles (if no dose delays)* **(± 3 days)**				**Day 169[b] Assessment** *169 calendar days after C1D1 regardless of dose delays* **(± 14 days)**	**Extension Phase** *Continuation of treatment beyond Day 169* **(± 3 days)**						
			Every Cycle (ie, 1, 2, 3+ up to max 8 cycles **Day 1**	**Every Other Cycle Only)** (ie, 1, 3, 5, 7) **Day 1**	**Cycles 1 and 5 Only** **Day 8**	**Cycle 1 Only** **Day 15**		**Every Cycle; X, X+1, etc.** **Day 1**	**Every 4th Cycle; X, X+4, etc.** **Day 1**	**Every 8th Cycle; X, X+8, etc.** **Day 1**		**42-Day Follow-up Period**	**Long-term Follow-up Period**	**End of Study**
ADA sample collection	6.8	--	C1, C2, C4, C6, C8 Only (collect C1D1 sample prior to luspat-ercept dose)	--	--	--	--	D1 of every 4th Cycle thereafter (eg, Ext. C4, C8, C12, C16+, etc.) for up to 1 year post first dose of luspatercept			X	ADA sample collection to continue every 12 weeks for positive subjects for up to 2 years post first dose of luspatercept or until return to baseline, whichever comes first.		--
QUALITY OF LIFE														
EQ-5D-5L and FACT-An questionnaire completion	6.10	--	--	X	--	--	X	Day 1 of Every Other Cycle (X, X+2, etc.)			X	--	--	--
MPN-SAF TSS completion	6.10	--	Completed weekly during the first 6 months of treatment				X	Day 1 of Every Other Cycle (X, X+2, etc.)			X	--	--	--

Table 3: Table of Events (Continued)

	Reference Section	Screening Period[a]	Treatment Period: Primary Phase (First 168 days of treatment, Up to maximum of 8 Treatment Cycles (if no dose delays)) (± 3 days)				Day 169[b] Assessment (169 calendar days after C1D1 regardless of dose delays) (± 14 days)	Treatment Period: Extension Phase (Continuation of treatment beyond Day 169) (± 3 days)			EOT Visit[b]	Posttreatment Follow-up Period (± 14 days)		
			Every Cycle (ie, 1, 2, 3+ up to max 8 cycles	Every Other Cycle Only) (ie, 1, 3, 5, 7)	Cycles 1 and 5 Only	Cycle 1 Only		Every Cycle; X, X+1, etc.	Every 4th Cycle; X, X+4, etc.	Every 8th Cycle; X, X+8, etc.		42-Day Follow-up Period	Long-term Follow-up Period	End of Study
		Day -28 to Enrollment	Day 1	Day 1	Day 8	Day 15		Day 1	Day 1	Day 1				
FOLLOW UP														
Monitoring for transformation to blast phase and other malignancies/ Premalignancies[h]	6.1, 6.5	After signing ICF and until at least 3 years post last dose of luspatercept or until death, lost to follow up, withdrawal of consent for further data collection.												
Posttreatment myelofibrosis therapies[h]	6.5	--	--	--	--	--	--	--	--	--	--	X	X	X
Survival follow up[h]	6.5	--	--	--	--	--	--	--	--	--	--	X	X	X

ADA = antidrug antibody; C1D1 = Cycle 1 Day 1; ECOG = Eastern Cooperative Oncology Group; EOT = End of Treatment; FACT-An = Functional Assessment of Cancer Therapy – Anemia; Hgb = hemoglobin; HepB = Hepatitis B; HepC = Hepatitis C; HIV = human immunodeficiency virus; MPN-SAF TSS = Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; [redacted]; PK = pharmacokinetic; RBC = red blood cell; TSS = total symptom score; WBC = white blood count.

[a] If screening assessments are performed within 72 hours of the C1D1 date, safety laboratory and physical examinations would not need to be repeated during the C1D1 date, with the exception of blood pressure measurements, hematology, serum ferritin, and serum EPO sample collections.

[b] Day 169 and beyond visit procedures/assessments may not need to be repeated if previously performed within ± 7 days of the scheduled visit. End of Treatment (EOT) Visit procedures/assessments will be performed as soon as possible for subjects who are withdrawn from treatment for any reason as soon as possible (but, at the latest, at the next projected planned study visit) after the decision to permanently discontinue treatment has been made. Furthermore, the EOT evaluations may not need to be repeated if previously performed within ± 7 days of EOT visit (with the exception of blood pressure assessment and sample collection for hematology, chemistry, and urinalysis). If a subject is discontinued during a regular scheduled visit, all EOT procedures should be completed at that visit.

[c] On dosing days, local laboratory sample should be collected, with white blood count (WBC) and Hgb levels assessed prior to each luspatercept administration to ensure dose modification rules are followed. Blood myeloblasts should also be assessed prior to luspatercept dosing. In case a subject had an elevated blood myeloblast percentage at the previous treatment cycle (≥ 10%), the blood myeloblast percentage needs to be assessed within a week prior to the next treatment cycle. In these circumstances, a split sample should also be collected and sent to the central laboratory for analysis. Subjects must have blood pressure assessed prior to each luspatercept administration. Should a dose delay occur on the day of dosing, refer to Section 7.3 for more information.

[d] Central assessments are not required when local test results confirming HIV, HepB, Hep C are available within 8 weeks immediately prior to the enrollment date. If beyond this window, additional central laboratory testing will be requested.

[e] Only serious adverse events (SAEs) related to luspatercept will be captured post the 42-Day Follow-up Period.

[f] Clinical site staff should confirm if any transfusions were received by the subject (including any at outside institutions in between study visits) prior to each dose of luspatercept via use of a transfusion diary or other local procedure in place at the investigational site. Subjects should record information relating to transfusions (eg, date of transfusion, pretransfusion Hgb levels, number of units transfused, volume of transfusion, etc.) they may have received outside the study site. In addition to local procedures that may be in place at the site to capture this information, a transfusion diary will be provided to all subjects and will be reviewed by the site when/if returned by the subject.

[g] During the Treatment Period, the Day 169 Disease Response Assessment should be completed by the Investigator. At Day 169, based on the outcome of the Disease Response Assessment, subjects will either be discontinued from treatment and enter the Posttreatment Follow-up Period or continue treatment with luspatercept in the Extension Phase of the Treatment Period.

[h] The Long-term Follow-up Period for transformation to blast phase, other malignancies/premalignancies, and data collection for subsequent myelofibrosis therapies may be conducted by record review (including public records if allowed by local regulations) and/or telephone contact with the subject, family, or the subject's treating physician. The Investigator must make every effort to obtain information regarding the subject's survival status before determining the subject is lost to follow up.

6. PROCEDURES

Any questions regarding the protocol should be directed to the Celgene Medical Monitor or designee.

All of the protocol required assessments are listed in Section 5, Table 3, with an "X" indicating at which visits the assessments are to be performed. All data obtained from these assessments must be recorded in the subject's source documentation. Except for the Day 169 Disease Response Assessment, all study visits during the Treatment Period (both Primary and Extension Phases) must occur within ± 3 days of the scheduled day. A 14-day window is allowed for the Day 169 Disease Response Assessment and Posttreatment Follow-up Period assessments (ie, transformation to blast phase, posttreatment myelofibrosis therapies). Procedures are described in detail below.

Safety laboratory analyses and all laboratory assessments will be performed centrally (except otherwise stated in this section) during the Treatment Period.

Local laboratories are only allowed in cases when timely results are needed (eg, study treatment dosing decisions, hematology assessments between clinic visits, adverse events). In these circumstances, a split sample should still be collected and sent to the central laboratory for analysis. Local laboratory data should be collected in the electronic case report form (eCRF) if relevant to dose administration, dose modification, an AE, or when no central laboratory results were obtained.

Refer to the eCRF completion guidelines for additional information related to data entry requirements of local laboratories.

Sample collection, processing, storage, and shipment procedures will be provided in the Study Laboratory Manual.

6.1. Screening Period

Upon giving written informed consent, subjects enter the Screening Period to determine eligibility. Subject screening procedures (performed locally/centrally) are to take place over a maximum of 28 days immediately prior to their enrollment date, which will be defined in this protocol as the date in which they have been assigned a treatment cohort via IRT. The first dose of luspatercept (designated as the C1D1 date) should be administered as soon as possible (at the latest 3 calendar days) following the enrollment date. During the Screening Period, the subject will undergo safety and other assessments to determine eligibility for the study. Screening laboratory values must demonstrate subject eligibility but may be repeated within the screening window if clinically justified. Subjects that have met all eligibility criteria during the Screening Period will be eligible for enrollment.

Review of historical bone marrow biopsy information will be used to confirm MPN-associated myelofibrosis diagnosis. The report should come from the most recent local bone marrow biopsy performed and should contain the mutational status of the disease (eg, *JAK2*, *MPL*, and *CALR*).

These data will be recorded in the subject's electronic case report form (eCRF). Subjects who do not meet the eligibility criteria prior to enrollment will be considered screening failures and will not be eligible for enrollment. Subjects who fail screening may undergo rescreening.

Screening evaluations will be performed (locally/centrally) for all subjects to determine study eligibility. These evaluations must be completed within the 28 days prior to the enrollment date (refer to Table of Events, Section 5, Table 3 for further information) unless noted otherwise below.

Waivers to the protocol eligibility criteria will not be granted during the conduct of this trial.

The following will be performed during the 28-day Screening Period as specified in the Table of Events (Section 5, Table 3) after informed consent has been obtained:

- **Assessment of inclusion/exclusion criteria for study eligibility**

  Screening evaluations will be performed for all subjects to determine eligibility. Screening laboratory values must demonstrate subject eligibility, but may be repeated within the screening window, if necessary.

- **Physical examination**

  Information about the physical examination (which will also include liver and spleen palpation, as well as spleen size assessment) to be captured in the eCRF.

- **Demographics and medical history**

  Information about the subject's demographics (if allowed per local country regulations; including, but not limited to: date of birth, sex, race, and ethnicity) to be recorded on the appropriate eCRF.

  Complete medical history documenting specific information regarding all relevant medical conditions diagnosed (occurring prior to Screening Period) to be recorded on the appropriate eCRF.

- **Prior anemia treatment**

  Information on therapies to treat anemia prior to the Screening Period to be recorded on the appropriate eCRF. Refer to Section 8 for more information.

- **RBC transfusion history**

  Information regarding RBC transfusion history (≥ 84 days prior to and including the C1D1 date), including, but not limited to, pretransfusion Hgb levels, number of units transfused, volume of transfusion, and dates of transfusions, will be collected and reported in the appropriate eCRF. Any transfusions given at outside institutions must also be collected. Source documentation of RBC transfusion history must be available for source document verification. Transfusions given when Hgb ≤ 9.5 g/dL will be counted towards eligibility, while transfusions given because of bleeding, infection, or chemotherapy-induced anemia will not be counted towards eligibility.

- **Eastern Cooperative Oncology Group (ECOG) performance status**

  Performance status will be assessed by the Investigator using the ECOG criteria provided in Appendix B.

- **Urinalysis**

  Information regarding urinalysis to include microscopic, quantitative analysis of urine (eg, albumin, protein, creatinine, albumin/creatinine ratio), and will be tested by the central laboratory.

- **Human immunodeficiency virus (HIV), Hepatitis B (HepB), and Hepatitis C (HepC)**

  Testing for HIV, HepB, and HepC will be completed by the central laboratory unless local lab results are available within 8 weeks immediately prior to the enrollment date. If beyond this window, additional central laboratory testing will be requested.

- **Electrocardiogram (ECG)**

  A 12-lead ECG to be performed locally at site. The following ECG parameters will be recorded on the respective eCRF(s): heart rate (HR), PR interval, QRS duration, QT, QTc. The Investigator will review the results and assess as normal, abnormal – not clinically significant, or abnormal – clinically significant, and report the abnormal finding(s) on the appropriate eCRF. If the ECG is abnormal, the Investigator should consult a cardiologist if deemed appropriate.

- **Pregnancy testing**

  Pregnancy testing (conducted at the central laboratory or locally) to be completed for all female subjects of childbearing potential (FCBP), in which the serum beta subunit of the human chorionic gonadotropic (β-hCG) pregnancy test (which must be negative) with a minimum sensitivity of 25 mIU/mL will be performed. This assessment will be used to confirm eligibility. Urine (or serum) pregnancy test will be performed to assess subject eligibility within 72 hours prior to the C1D1 date, if the initial serum pregnancy test did not already occur with 72 hours of dosing (negative results required for luspatercept administration). During the Treatment Period, a urine or serum pregnancy test is allowed. The Investigator will appraise a female subject as a FCBP according to the definition provided in Section 4.2. Justification must be recorded in the eCRF and the source document. Pregnancy testing is not required for non-FCBP subjects.

- **Adverse event assessment**

  Information regarding adverse event assessment and reporting initiated from the time the subject signs the informed consent form will occur on an ongoing basis and must be documented on the appropriate eCRF. Refer to Section 10 for more information.

- **Prior/concomitant medications and procedures**

  Information relating to prior/concomitant medications and procedures to be reported on the appropriate eCRF. Refer to Section 8 for more information.

- **Vital signs, height, and weight**

  Information regarding vital signs including height (measured only during screening), weight (measured during screening and prior to each luspatercept administration), seated blood pressure (documented as mean of 2 readings obtained approximately 10

minutes apart with the subject seated for approximately 10 minutes prior to initial reading; on dosing days, blood pressure must be assessed prior to luspatercept administration), temperature, heart rate, and respiratory rate are to be reported on the appropriate eCRF.

- **Serum chemistry**

  Information regarding serum chemistry including labs such as sodium, potassium, chloride, bicarbonate (if available), calcium, magnesium, phosphorus, blood urea nitrogen, creatinine and creatinine clearance, glucose, albumin, total protein, alkaline phosphatase, direct/indirect total bilirubin, AST/serum glutamic oxaloacetic transaminase (SGOT) or ALT/serum glutamic pyruvic transaminase (SGPT), lactate dehydrogenase, and uric acid are to be reported on the appropriate eCRF and will be tested by the central laboratory.

- **Hematology**

  Information regarding hematology assessments including red blood cell (RBC) count, complete blood count, white blood count (WBC) with differential (including myeloblasts), Hgb, hematocrit, nucleated red blood cells, absolute reticulocyte count, platelet count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and red blood cell distribution width are to be reported on the appropriate eCRF and will be tested by the central laboratory.

- **Serum erythropoietin (EPO)**

  Serum EPO collected during the Screening Period should be collected on the same day as a planned RBC transfusion, prior to the transfusion, or 7 days after any RBC transfusion due to possible reduction of the serum level related to the hemoglobin level achieved after the last transfusion. Serum EPO samples will be analyzed by the central laboratory.

- **Serum ferritin**

  Serum ferritin should be collected within the Screening Period and analyzed by the central laboratory. Historic serum ferritin levels from previous local laboratory reports (within the 84-day window prior to and including the enrollment date) should be collected, if available in the medical records, and entered on the appropriate eCRF.

  On dosing days, serum ferritin samples should be collected prior to luspatercept administration and analyzed by the central laboratory.

- [redacted]

- **Monitoring for transformation to blast phase and other malignancies/premalignancies**

  Monitoring for transformation to blast phase as per International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) criteria (Tefferi, 2013) will be included as part of the safety assessment throughout the course of the study. Transformation to blast phase should be monitored from time of signing of

informed consent through at least 3 years after last dose of luspatercept or until death, lost to follow up, or withdrawal of consent from the study, whichever occurs first. The occurrence of a new malignancy or premalignant lesion will be monitored as an event of interest and should be included as part of the assessment of adverse events throughout the course of the study. Investigators are to report the development of any new malignancy or premalignant lesion as a serious adverse event, regardless of causal relationship to luspatercept, occurring at any time for the duration of the study, from the time of signing the ICF for up to and including at least 3 years of long-term follow up, or until death, lost to follow up, or withdrawal of consent for further data collection. Documentation supporting the diagnosis of transformation to blast phase and other malignancies/pre-malignancies (eg, confirmatory histology or cytology results) may be requested. Appropriate information related to the diagnosis of transformation to blast phase and other malignancies/premalignancies should be captured on the eCRF and in the subject's source documents.

6.2. Treatment Period

The subject will be enrolled into the study following Sponsor review of eligibility.

The subject must be enrolled at the latest 28 days from signing the ICF. The first dose of luspatercept (designated as C1D1) should be administered as soon as possible (at the latest 3 calendar days) following the enrollment date. In case a subject should become ineligible after being enrolled but prior to receiving the first dose of luspatercept, they must be discontinued from the study. These subjects will be replaced.

If screening assessments are performed within 72 hours of the C1D1 date, safety laboratory and physical examinations would not need to be repeated during the C1D1 date, with the exception of blood pressure measurements, hematology, serum ferritin, and serum EPO sample collections.

On dosing days, local laboratory WBC and Hgb levels should be assessed prior to each luspatercept administration. In case a subject had an elevated blood myeloblast percentage at the previous treatment cycle, the blood myeloblast percentage needs to be assessed within a week prior to the next treatment cycle. These parameters are to ensure the dose modification rules are followed as outlined in Section 7.

In these circumstances, a split sample should also be collected and sent to the central laboratory for analysis. Subjects should also have blood pressure assessed (as detailed in Section 6.1) and the clinical site must confirm with the subject if any transfusions were received at outside local centers in between study visits prior to each luspatercept administration.

6.2.1. Primary Phase of the Treatment Period

Subjects will receive luspatercept on Day 1 of each 21-day treatment cycle (unless there are dose delays) through at least Day 168 following the C1D1 date unless the subject experiences unacceptable toxicities, withdraws consent, or meets any other treatment discontinuation criteria (refer to Section 11.1) prior to the Day 169 Disease Response Assessment. Treatment cycles are 21 days in duration.

The following procedures/evaluations will be performed at the frequency specified in the Table of Events (Table 3) during the Primary Phase of the Treatment Period. The

procedures/evaluations should be performed prior to dosing on the visit day, unless otherwise specified:

- Physical examination (as detailed in Section 6.1)
- Administration/accountability of luspatercept
- ECOG performance status
- Urinalysis (as detailed in Section 6.1)
- 12-lead electrocardiogram (ECG) to be performed locally
- Pregnancy testing (as detailed in Section 6.1)
- Adverse event assessment and reporting on an ongoing basis
- Concomitant medications and procedures on an ongoing basis
- Vital signs (as detailed in Section 6.1)
- Serum chemistry (as detailed in Section 6.1)
- Hematology assessments (as detailed in Section 6.1)
- Serum EPO level
- Serum ferritin level
- Transfusion data collection and assessment

  During the study, the following, but not limited to, information will be recorded for all transfusions (including any transfusions received at outside institutions in between study visits) the subject receives starting from the C1D1 date until end of treatment or end of the 42-Day Follow-up Period, whichever occurs later: date of transfusion, pretransfusion Hgb levels, number of units transfused, and volume of transfusion. In addition to local procedures that may be in place at the site to capture this information, a transfusion diary will be provided to all subjects and will be reviewed by the site when/if returned by the subject. Source documentation of transfusions given during the study must be available for source document verification.
- [redacted]
- PK and ADA sample collection (as detailed in Sections 6.7 and 6.8)
- Subject reported outcomes via the EQ-5D-5L, FACT-An, and MPN-SAF TSS (as detailed in Section 6.10)
- Monitoring for transformation to blast phase and other malignancies/premalignancies

6.2.2. Day 169 Disease Response Assessment

The Day 169 Disease Response Assessment should be completed 169 days after the C1D1 date, regardless of dose delays. As central laboratory results and assessments are required for the Day 169 Disease Response Assessment, a 14-day window is allowed for the Day 169 Disease Response Assessment.

In order for subjects to remain on luspatercept treatment beyond Day 169, the following criteria must be confirmed upon the completion of the Disease Response Assessment by the Investigator at the Day 169 visit:

Cohorts 1 (anemia only) and 3A

Subjects with ≥ 3 determinations showing a ≥ 1.5 g/dL hemoglobin increase above the baseline value (defined as the subject's Hgb value observed on the C1D1 date prior to luspatercept administration) absent of RBC transfusions over a consecutive ≥ 84-day period with no 2 measurements ≥ 42 days apart (and no determination < 1.5 g/dL above the baseline value) at the time of the Day 169 Disease Response Assessment will have the opportunity to move into the Extension Phase of the Treatment Period. The subject may remain on treatment for approximately 2 years or more from date of C1D1 at the Investigator's discretion until a determination shows a value < 1.5 g/dL hemoglobin increase from the baseline value (absent of bleeding or infection), there is receipt of an RBC transfusion, disease progression, or any of the other criteria for treatment discontinuation are met.

If, at the Day 169 Disease Response Assessment, the subject has ≥ 3 determinations showing a ≥ 1.5 g/dL hemoglobin increase above the baseline value with no 2 measurements ≥ 42 days apart (and no determination < 1.5 g/dL above the baseline value) in the absence of RBC transfusions over the preceding 56 days, the subject may continue on in the Extension Phase of the Treatment Period for an additional 28 days. If, after this additional 28 days, the subject meets the response criteria, the subject can continue on in the Extension Phase of the Treatment Period and remain on treatment for approximately 2 years or more from the C1D1 date at the Investigator's discretion until a determination shows a value < 1.5 g/dL hemoglobin increase above the baseline value (absent of bleeding or infection), there is receipt of an RBC transfusion, disease progression, or any of the other criteria for treatment discontinuation are met.

Cohorts 2 (RBC-transfusion dependent) and 3B

Subjects who are transfusion-free over ≥ 84 consecutive days at the time of the Day 169 Disease Response Assessment can enter the Extension Phase of the Treatment Period and remain on treatment for approximately 2 years or more from the C1D1 date at the Investigator's discretion until they receive the next RBC transfusion (absent of bleeding or infection), disease progression, or meet other criteria for treatment discontinuation.

If, at the Day 169 Disease Response Assessment, the subject is RBC-transfusion free for the preceding 56 days, they may continue on in the Extension Phase of the Treatment Period for an additional 28 days. If, after this additional 28 days, the subject meets the response criteria, they can continue on in the Extension Phase of the Treatment Period and remain on treatment for approximately 2 years or more from the C1D1 date at Investigator's discretion until the subject receives an RBC transfusion (absent of bleeding or infection), disease progression, or meets of other criteria for treatment discontinuation.

Should subjects from each respective cohort not meet the clinical benefit criteria outlined above, they should discontinue treatment with luspatercept and enter the Posttreatment Follow-up Period. Otherwise, subjects may begin luspatercept treatment in the Extension Phase of the Treatment Period to remain on treatment at the Investigator's discretion until the next RBC transfusion, disease progression, or any of the other criteria for treatment discontinuation are

met. If, according to the assessment of the investigator, the subject is benefiting from treatment not reflected by the criteria above (eg, a clinically significant reduction of the transfusion burden or clinically significant improvement of a subject's symptom burden), this should be discussed with the Medical Monitor for the potential continuation of the subject in the Extension Phase.

The following procedures/evaluations will be performed at the Day 169 Disease Response Assessment visit:

- Physical examination (as detailed in Section 6.1)
- ECOG performance status
- Urinalysis (as detailed in Section 6.1)
- Pregnancy testing (as detailed in Section 6.1)
- Adverse event assessment and reporting on an ongoing basis
- Concomitant medications and procedures on an ongoing basis
- Vital signs (as detailed in Section 6.1)
- Serum chemistry (as detailed in Section 6.1)
- Hematology assessments (as detailed in Section 6.1)
- Serum EPO level
- Serum ferritin level
- Transfusion data collection and assessment

  During the study, the following, but not limited to, information will be recorded for all transfusions (including any transfusions received at outside institutions in between study visits) the subject receives starting from the C1D1 date until end of treatment or end of the 42-Day Follow-up Period, whichever occurs later: date of transfusion, pretransfusion Hgb levels, number of units transfused, and volume of transfusion. In addition to local procedures that may be in place at the site to capture this information, a transfusion diary will be provided to all subjects and will be reviewed by the site when/if returned by the subject. Source documentation of transfusions given during the study must be available for source document verification.
- [redacted]
- PK sample collection (as detailed in Sections 6.7 and 6.8)
- Subject reported outcomes via the EQ-5D-5L, FACT-An, and MPN-SAF TSS (as detailed in Section 6.10)
- Monitoring for transformation to blast phase and other malignancies/premalignancies will occur on an ongoing basis

6.2.3. Extension Phase of the Treatment Period

Subjects who meet the criteria to remain on luspatercept treatment after completion of the Day 169 Disease Response Assessment may continue dosing on Day 1 of each 21-day treatment cycle

in the Extension Phase of the Treatment Period for approximately 2 years or more from the C1D1 date until the subject is no longer receiving clinical benefit according to the Investigator's assessment (eg, loss of ≥ 50% reduction of transfusion burden from baseline), experiences unacceptable toxicities, has disease progression, withdraws consent, or meets any other discontinuation criteria (Section 11).

The Disease Response Assessment should be completed on Day 1 of every treatment cycle in the Extension Phase of the Treatment Period until the subject is discontinued from treatment and should confirm continued clinical benefit per the criteria outlined in Section 6.2.2.

All subjects who have received at least 1 dose of study treatment should undergo end of treatment (EOT) evaluations when luspatercept is discontinued (refer to Section 6.4 for more information). The reason for discontinuation will be recorded in the eCRF pages and in the source documents.

Serial measurements of safety and efficacy will continue on scheduled study visits in the Extension Phase of the Treatment Period, of which the following procedures/evaluations should be performed prior to dosing on the visit day, unless otherwise specified:

- Physical examination (as detailed in Section 6.1)
- Administration/accountability of luspatercept on Day 1 of each treatment cycle
- ECOG performance status
- Urinalysis (as detailed in Section 6.1)
- Pregnancy testing (as detailed in Section 6.1)
- Adverse event assessment and reporting on an ongoing basis
- Concomitant medications and procedures on an ongoing basis
- Vital signs (as detailed in Section 6.1)
- Serum chemistry (as detailed in Section 6.1)
- Hematology assessments (as detailed in Section 6.1)
- Serum ferritin level assessed on Day 1 of every 4th Extension Phase treatment cycle
- Transfusion data collection and assessment

  During the study, the following, but not limited to, information will be recorded for all transfusions (including any transfusions received at outside institutions in between study visits) the subject receives starting from the C1D1 date until end of treatment or end of the 42-Day Follow-up Period, whichever occurs later: date of transfusion, pretransfusion Hgb levels, number of units transfused, and volume of transfusion. In addition to local procedures that may be in place at the site to capture this information, a transfusion diary will be provided to all subjects and will be reviewed by the site when/if returned by the subject. Source documentation of transfusions given during the study must be available for source document verification.
- PK and ADA sample collection (as detailed in Sections 6.7 and 6.8)

- Subject reported outcomes via the EQ-5D-5L, FACT-An, and MPN-SAF TSS (as detailed in Section 6.10)
- Monitoring for transformation to blast phase and other malignancies/premalignancies will occur on an ongoing basis

6.3. Dose Delays in Treatment Period

On days when subjects return to the investigational site for luspatercept administration, but luspatercept is not administered (eg, due to protocol dose modification, dose delay rules [Section 7.3]), all required assessments and procedures should be performed, regardless if luspatercept is administered. During the time period of dose delay, the following assessments/procedures should be performed:

- If dose delay is due to a laboratory or vital signs abnormality, the assessment that was the reason for the dose delay should be repeated at least on a weekly basis.
- If dose delay is due to increased Hgb level, perform hematology assessments at least weekly.
- If dose delay is due to an AE, perform hematology, serum chemistry, and serum ferritin assessments at least every 3 weeks thereafter and before next dose administration.
- Pharmacokinetic (PK)/ADA samples should be collected on the first day of dose delay and prior to luspatercept administration on day dosing resumes.

Refer to the eCRF completion guidelines for detailed instructions related to eCRF data entry.

6.4. End of Treatment Visit

An end of treatment (EOT) evaluation will be performed as soon as possible for subjects who are withdrawn from treatment for any reason (but, at the latest, at the next projected planned study visit) after the decision to permanently discontinue treatment has been made. Evaluations will be performed as specified in Table 3.

If a subject is discontinued during a regular scheduled visit, all EOT procedures should be completed at that visit. If a procedure had been performed within ± 7 days of the EOT visit, it does not need to be repeated unless clinically indicated per Investigator discretion (with the exception of blood pressure assessment and sample collection for hematology, chemistry, and urinalysis).

The reason for discontinuation will be recorded in the eCRF and in the source document for all enrolled subjects, regardless of whether they are dosed or not. Reasons for treatment discontinuation are provided in Section 11.

The following procedures/evaluations (including a Disease Response Assessment evaluation) should be performed:

- Physical examination (as detailed in Section 6.1)
- ECOG performance status
- Urinalysis (as detailed in Section 6.1)

- 12-lead electrocardiogram (ECG) to be performed locally
- Pregnancy testing (as detailed in Section 6.1)
- Adverse event assessment and reporting on an ongoing basis
- Concomitant medications and procedures on an ongoing basis
- Vital signs (as detailed in Section 6.1)
- Serum chemistry (as detailed in Section 6.1)
- Hematology assessments (as detailed in Section 6.1)
- Serum EPO level
- Serum ferritin level
- Transfusion data collection and assessment

  During the study, the following, but not limited to, information will be recorded for all transfusions (including any transfusions received at outside institutions in between study visits) the subject receives starting from the C1D1 date until end of treatment or end of the 42-Day Follow-up Period, whichever occurs later: date of transfusion, pretransfusion Hgb levels, number of units transfused, and volume of transfusion. In addition to local procedures that may be in place at the site to capture this information, a transfusion diary will be provided to all subjects and will be reviewed by the site when/if returned by the subject. Source documentation of transfusions given during the study must be available for source document verification.
- Disease response assessment (as detailed in Section 6.2.2)
- [redacted]
- PK and ADA sample collection (as detailed in Sections 6.7 and 6.8)
- Subject reported outcomes via the EQ-5D-5L, FACT-An, and MPN-SAF TSS (as detailed in Section 6.10)
- Monitoring for transformation to blast phase and other malignancies/pre-malignancies will occur on an ongoing basis

6.5. Posttreatment Follow-up Period

The Posttreatment Follow-up Period will be inclusive of a 42-Day Follow-up Period and a Long-term Follow-up Period, beginning from the date of last dose of luspatercept.

6.5.1. 42-Day Follow-up Period (referred to as the Safety Follow-up)

All AEs (including serious adverse events [SAEs]), regardless of causal relationship to luspatercept, will be recorded by the Investigator from the time the subject signs informed consent until 42 days after the last dose of luspatercept.

Females of childbearing potential (FCBPs) will be advised to avoid becoming pregnant during study and for 12 weeks after the last dose of luspatercept. Males will be advised to use a latex condom during any sexual contact with an FCBP prior to study entry and continue for 12 weeks

following the last dose of luspatercept, even if he has undergone a successful vasectomy. Refer to Section 10.5.

Antidrug antibodies (ADA) sample(s) may be required in the Posttreatment Follow-up Period if a subject is ADA positive at the time of treatment discontinuation. Refer to Section 6.8.

Additionally, the following should also be captured:

- Concomitant medications and procedures
- Transfusion data collection and assessment

  During the study, the following, but not limited to, information will be recorded for all transfusions (including any transfusions received at outside institutions in between study visits) the subject receives starting from the C1D1 date until end of treatment or end of the 42-Day Follow-up Period, whichever occurs later: date of transfusion, pretransfusion Hgb levels, number of units transfused, and volume of transfusion. In addition to local procedures that may be in place at the site to capture this information, a transfusion diary will be provided to all subjects and will be reviewed by the site when/if returned by the subject. Source documentation of transfusions given during the study must be available for source document verification.
- Monitoring for transformation to blast phase and other malignancies/pre-malignancies
- Post-luspatercept treatment MPN-associated myelofibrosis therapies
- Survival follow up

6.5.2. Long-term Follow-up and End of Study

After the 42-Day Follow-up Period, only those serious adverse events (SAEs) made known to the Investigator that are suspected of being related to luspatercept will be recorded by the Investigator.

Females of childbearing potential (FCBPs) will be advised to avoid becoming pregnant during study and for 12 weeks after the last dose of luspatercept. Males will be advised to use a latex condom during any sexual contact with an FCBP prior to study entry and continue for 12 weeks following the last dose of luspatercept, even if he has undergone a successful vasectomy. Refer to Section 10.5.

For all subjects who receive at least 1 dose of luspatercept, continuation of monitoring for transformation to blast phase will occur in the Posttreatment Follow-up Period, along with data collection of new MPN-associated myelofibrosis disease therapies and overall survival for at least 3 years from the date of last dose of luspatercept unless the subject withdraws consent from the study, dies, or is lost to follow up, whichever occurs first. This information will be collected until the End of Study and recorded in the eCRF. During this time, all subjects will be followed approximately every 3 months following the 42-Day Follow-up Period. The Investigator must make every effort to obtain information regarding the subject's survival status before determining the subject is lost to follow up. Survival follow up can be performed via the telephone.

Long-term follow up may be conducted by record review (including public records, if available and allowed by local regulations) and/or telephone contact with the subject, family, or the subject's treating physician.

6.6. Unscheduled Visits

An unscheduled visit in this protocol refers to any assessment or procedure that is completed outside of the designated time points and frequencies outlined in Section 5, Table 3. Should it become necessary to repeat an evaluation (eg, laboratory tests or vital signs), the results of the repeat evaluation should be entered as an additional unscheduled visit in the eCRF.

Refer to the eCRF completion guidelines for detailed instructions related to eCRF data entry.

6.7. Pharmacokinetics

Blood samples will be collected to analyze luspatercept concentrations in serum in all subjects as indicated in Section 5, Table 3. At each pharmacokinetic (PK) time point, approximately 3 mL of blood will be collected and serum prepared as described in the study reference guide. Blood samples for PK will be taken at the following visits during the study:

- **Primary Phase of Treatment Period**: C1D1 (must be collected before the first dose), C1D8, C1D15, C2D1, C4D1, C5D1, C5D8, C6D1, and C8D1 (collect samples only if the subject is still in the Primary Phase)
- **Day 169 Disease Response Assessment**
- **Extension Phase of Treatment Period (if applicable)**: Day 1 of every 4th Extension Phase treatment cycle for up to 1 year post the date of first dose of luspatercept

The dose level and dosing time of luspatercept on the PK visit days should be recorded in eCRF.

Detailed procedures of PK sample collection, processing, and shipping are provided in the study reference guide.

6.7.1. Unscheduled Pharmacokinetic Visits

Pharmacokinetic (PK) sampling per Investigator's or Sponsor's discretion is allowed and should be recorded as an unscheduled visit.

6.8. Antidrug Antibody

Blood samples will be collected for assessment of antidrug antibodies (ADA) against luspatercept in serum in all subjects. The maximum ADA monitoring period will be 2 years from Cycle 1 Day 1 of the Treatment Period. At each ADA time point, approximately 3 mL of blood will be collected and serum prepared as described in the study reference guide. However, during the first year of treatment, an additional blood draw may not be needed for the ADA test, as the ADA test may be conducted utilizing the PK samples obtained at the same visit. Blood samples for ADA will be taken at the following visits during the study (also see Table 3):

- **Primary Phase of Treatment Period**: C1D1 (must be collected before the first dose), C2D1, C4D1, C6D1, and C8D1

- **Extension Phase of Treatment Period (if applicable)**: Day 1 of every 4th Extension Phase treatment cycle for up to 1 year post the date of first dose of luspatercept. If the last available antiluspatercept antibody result is positive at the end of 1 year, subjects may be asked to return for ADA sample collection every 12 weeks for up to 2 years post the date of first dose of luspatercept or until the ADA level returns to baseline, whichever comes first.
- **End of Treatment Visit**
- **Posttreatment Follow-up Period**: If the last available antiluspatercept antibody result is positive at the end of treatment, subjects may be asked to return for ADA sample collection every 12 weeks for up to 2 years post the date of first dose of luspatercept or until the ADA level returns to baseline, whichever comes first.

Antidrug antibodies (ADA) sampling per Investigator's or Sponsor's discretion is allowed and should be recorded as an unscheduled visit.

Detailed procedures of ADA sample collection, processing, and shipping are provided in the study reference guide.

6.10. Subject Reported Outcomes or Quality of Life Measurements

Myeloproliferative neoplasm (MPN)-associated myelofibrosis-related symptoms (fatigue, night sweats, itchiness, abdominal discomfort, pain under the ribs on the left side, early satiety, and bone pain) will be recorded using the MPN-SAF TSS, which will be completed on a weekly basis and prior to luspatercept administration on Day 1 of dosing in the Primary Phase of the Treatment Period, in addition to the Day 169 Disease Response Assessment, and on Day 1 of every other treatment cycle prior to luspatercept administration thereafter during the Extension Phase of the Treatment Period, as well as the End of Treatment Visit.

Fatigue-related symptoms and their impact on subjects' functionality will be measured via the FACT-An, which will be completed on Day 1 during every other treatment cycle prior to luspatercept administration during the Primary Phase of the Treatment Period, in addition to the Day 169 Disease Response Assessment, and Day 1 of every other treatment cycle prior to luspatercept administration thereafter during the Extension Phase of the Treatment Period, as well as the End of Treatment Visit.

Information on general quality of life (eg, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) will be assessed via the EQ-5D-5L, which will be completed on Day 1 during every other treatment cycle prior to luspatercept administration during the Primary Phase of the Treatment Period, in addition to the Day 169 Disease Response Assessment, and Day 1 of every other treatment cycle prior to luspatercept administration thereafter during the Extension Phase of the Treatment Period, as well as the End of Treatment Visit.

6.11. Screen Failures

For all subjects determined as screen failures, the following information is to be captured in the subject's source documents and eCRF page(s): the date the informed consent form (ICF) was signed, demographics, the reason subject did not qualify for the study, and the Investigator's signature for the eCRF pages. The adverse events experienced by screen failure subjects will be collected from the date of signing consent to the day the subject is confirmed as a screen failure. Relevant information will also be recorded on the Screening Log.

7. DESCRIPTION OF STUDY TREATMENTS

7.1. Description of Investigational Product(s)

Luspatercept will be provided by the Sponsor. Luspatercept for injection is formulated as a sterile, preservative-free, lyophilized cake/powder. Luspatercept for injection is available in 25 mg and 75 mg vials and when reconstituted, each consists of 50 mg/mL luspatercept in a [redacted] mM citrate buffer-based solution ([redacted] mM citrate, pH [redacted] % sucrose, [redacted] % polysorbate 80).

The recommended storage condition for luspatercept for injection (25 mg/vial and 75 mg/vial; lyophilized powder formulation) is 2°C to 8°C. Reconstituted luspatercept in its original container closure system may be held for up to 10 hours at 2°C to 8°C, however it should be administered at room temperature. It is recommended that the reconstituted luspatercept for injection be used immediately. If not used immediately, the total in-use time of the reconstituted luspatercept for injection, from reconstitution to administration, must not exceed 10 hours.

Samples of luspatercept drug product, held at the recommended storage condition, have been shown to be stable through the labeled shelf-life.

Subjects enrolled in Cohort 3 are receiving ruxolitinib as prescribed by their physician. Celgene will not be supplying ruxolitinib for this study. Instead, ruxolitinib will be obtained by the sites according to local clinical study agreement and in accordance with local guidelines.

7.2. Treatment Administration and Schedule

Luspatercept will be administered on Day 1 of every 21-day cycle, at an initial dose level of 1.0 mg/kg (***Note for Protocol Amendment 3**: Additional subjects enrolling into Cohort 3B will begin luspatercept treatment at a starting dose of 1.33 mg/kg and can have their dose increased to a maximum dose of 1.75 mg/kg [with the total dose not to exceed 168 mg]). Doses may be titrated up starting in Cycle 3 as described in Section 7.3. Luspatercept will be administered as a subcutaneous injection to subjects by the study staff at the clinical site and administration will be documented in the subject's source record. Subjects must have their Hgb, WBC, blood myeloblast percentage, and blood pressure assessed prior to each luspatercept administration.

Subcutaneous injections will be given in the upper arm, thigh, and/or abdomen. Calculated doses requiring reconstituted volume greater than 1.2 mL should be divided into separate, similar volume injections across 2 or 3 separate sites using the same anatomical location, but on opposite sides of the body (example left thigh and right thigh). The maximum volume per subcutaneous injection should not exceed 1.2 mL. The injection sites can be rotated according to Investigator judgment, and the injections can be given in the following order as needed, for example: 1) right upper arm, 2) left upper arm, 3) right upper thigh, 4) left upper thigh.

7.3. Dose Modifications: Dose Titration, Dose Reduction, and Dose Delay

Starting dose with dose increases and reductions are presented below for reference (refer to Table 4). The total dose administered should not exceed 168 mg.

Table 4: Starting Dose Level with Dose Reductions and Dose Titration

3rd Dose Reduction (~25% reduction)	2nd Dose Reduction (~25% reduction)	1st Dose Reduction (~20% reduction)	Starting Dose Level[a]	1st Dose Titration Increase	2nd Dose Titration Increase
0.45 mg/kg	0.6 mg/kg	0.8 mg/kg	1.0 mg/kg	1.33 mg/kg	1.75 mg/kg

[a] Note for Protocol Amendment 3: Additional subjects enrolling into Cohort 3B will begin luspatercept treatment at a starting dose of 1.33 mg/kg and can have their dose increased to a maximum dose of 1.75 mg/kg (with the total dose not to exceed 168 mg).

7.3.1. Dose Titration

Starting as soon as Cycle 3 Day 1 and assessed by the Investigator prior to every subsequent treatment cycle, subjects may have the dose level increased in a stepwise manner beyond the starting dose level of 1.0 mg/kg to 1.33 mg/kg, and up to a maximum of 1.75 mg/kg (but no more than 168 mg) during the Treatment Period.

***Note for Protocol Amendment 3**: Additional subjects enrolling into Cohort 3B will begin luspatercept treatment at a starting dose of 1.33 mg/kg and can have their dose increased to a maximum dose of 1.75 mg/kg (with the total dose not to exceed 168 mg).

If the subject has 2 of the most recent prior treatment cycles assessed at the same dose level **and** if the subject has not met any protocol dose delay and/or reduction criteria in the 2 most prior treatment cycles, they may be eligible for a dose titration. The dose may be increased by 1 dose level if 1 or more of the following criteria are met:

- **For all cohorts**: subject has ≥ 1 RBC transfusion event (for pretransfusion Hgb of ≤ 9.5 g/dL) during the 2 most recent prior treatment cycles (~6 weeks)
- **For all cohorts**: Hemoglobin decrease of ≥ 1 g/dL is observed and this decrease is not preceded by an RBC transfusion (the hemoglobin decrease occurs ≥ 14 days after the last RBC transfusion)
- **For subjects in Cohorts 1 and 3A**: Hemoglobin increase from baseline is < 1.5 g/dL throughout the previous 2 cycles at the same dose level
- **For subjects in Cohorts 1 and 3A**: Hemoglobin increase from baseline is ≥ 1.5 g/dL but not sustained for at least 2 consecutive study measurements during the previous 2 cycles at the same dose level
- **For subjects in Cohorts 2 and 3B**: Hgb value is not exceeding 1 g/dL increase from the baseline mean pretransfusion Hgb value, which will be calculated using the reported RBC transfusions that confirmed the eligibility of the subject

The dose level should be titrated individually for each subject.

7.3.2. Dose Reduction and Dose Delay

Dose delay and/or reduction or discontinuation may be required due to increased hemoglobin or adverse events. Table 5 below provides guidelines for dose modifications and dose delay.

Table 5: Dose Modification: Dose Delay, Dose Reduction, and Discontinuation Guidelines

Event at the Day of Dosing (Assessed prior to each luspatercept administration)	Action
Any suspected related adverse event (AE) ≥ Grade 3[a,b]	Dose delay[c] until resolved to ≤ Grade 1 or baseline, and then reduce dose by 1 dose level
≥ 2 dose reductions suspected related AE[a]	Discontinue treatment
Change in hemoglobin (Hgb) ≥ 2 g/dL compared to predose Hgb of previous treatment cycle	Reduce dose by 1 dose level[d] if change in Hgb not influenced by red blood cell (RBC) transfusions
Predose Hgb ≥ 11.5 g/dL	Dose delay until Hgb ≤ 11 g/dL
Blood myeloblast percentage[e] *(based on either local or central lab hematology sample)*	If the blood myeloblast percentage at the first day of a dosing cycle is ≥ 10% conduct retesting within a week before the next dosing cycle: • If the retest has a myeloblast percentage that is still ≥ 10%, discontinue luspatercept • If the retest has a myeloblast percentage < 10%, the subject may continue luspatercept treatment
Transformation to blast phase *(based on either local or central lab)*	If there is transformation to blast phase confirmed by a bone marrow blast count of ≥ 20% **or** an increase in blood myeloblast percentage of ≥ 20% associated with an absolute blast count ≥ 1 x 10^9/L that lasts for at least 2 weeks, discontinue luspatercept. Refer to Section 6.1
White blood count (WBC) is: • ≥ 120 x 10^9/L **or** • ≥ 3 x baseline and ≥ 30 x 10^9/L[f] *(based on either local or central lab hematology sample)*	Dose delay[c] with weekly WBC monitoring until WBC is: • < 120 x 10^9/L **or** • < 3 x baseline **or** < 30 x 10^9/L If WBC continues to be elevated for 3 consecutive determinations, discontinue luspatercept treatment.

Table 5: Dose Modification: Dose Delay, Dose Reduction, and Discontinuation Guidelines (Continued)

Event at the Day of Dosing (Assessed prior to each luspatercept administration)	Action
Leukopenia, Neutropenia and/or Thrombocytopenia A shift (worsening) by ≥ 2 grades[g] leukopenia, neutropenia or thrombocytopenia to ≥ Grade 3 during treatment with luspatercept not clearly and solely related to an extraneous case such as advancing MPN-associated myelofibrosis or an infectious event. **Worsening of Anemia:** **For Cohorts 2 and 3B:** A ≥ 50% increase from baseline in transfusion burden in combination with an unexplained shift from baseline (worsening) of ≥ 2 grades[g] leukopenia, neutropenia or thrombocytopenia. **For Cohorts 1 and 3A:** A decrease of > 2 g/dL Hgb from baseline [uninfluenced by transfusion] or becomes transfusion dependent in combination with an unexplained shift from baseline (worsening) of ≥ 2 grades[g] leukopenia, neutropenia or thrombocytopenia.	Dose delay[c] and repeat WBC, neutrophils and platelet counts weekly for two weeks • If WBC, neutrophils and platelet counts are resolved to ≤ Grade 1, baseline, or shifts by at least one toxicity grade (improvement) and if cytopenia is not regarded as related to luspatercept and the myeloblast percentage is < 10% (follow the myeloblast percentage rule above), then discuss the dose level for continuation of therapy with the medical monitor. • If WBC, neutrophils and platelet counts are not resolved to ≤ Grade 1, baseline or does not shift by at least one toxicity grade (improvement) and an alternative cause cannot be identified, then consider additional bone marrow assessments and discuss next steps with the medical monitor.

[a] Possibly, probably or definitely related to luspatercept.
[b] Includes systolic blood pressure ≥ 160 mmHg and diastolic blood pressure ≥ 100 mmHg.
[c] If dose delay is > 12 consecutive weeks, treatment should be discontinued.
[d] Predose Hgb value not being influenced by red blood cell (RBC) transfusion (ie, hemoglobin [Hgb] result > 14 days after last RBC transfusion); Hgb should be rechecked weekly during dose delay.
[e] The Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion prior to making decision regarding treatment discontinuation.
[f] Corrected WBC should be used to establish the baseline white blood count (WBC). Baseline = highest WBC between Screening WBC and Cycle 1 Day 1 (C1D1).
[g] Thrombocytopenia, leukopenia, and neutropenia toxicity grades as defined by CTCAE criteria.

7.4. Overdose

Overdose, as defined for this protocol, refers to luspatercept dosing only. On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of luspatercept assigned to a given subject, regardless of any associated adverse events or sequelae:

Subcutaneous 10% over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency. Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the eCRF. See Section 10.1 for the reporting of adverse events associated with overdose.

7.5. Method of Treatment Assignment

The cohort assignment will occur at the end of the Screening Period, once all the required screening procedures have been completed and all required data have been submitted to the Sponsor or its authorized representative. Upon receiving acknowledgment of subject's eligibility review from the Sponsor or its authorized representative, the subject can be assigned treatment using an IRT built for this study.

Designated research personnel at each investigational site will be assigned unique, password-protected user accounts which give them the authorization to utilize the IRT to enroll subjects. For drug assignment, dose reduction or titrations, site staff must contact the IRT to record the new dose level and obtain the new study treatment assignment.

7.6. Packaging and Labeling

The label(s) for luspatercept will include Sponsor name, address and telephone number, the protocol number, luspatercept name, dosage form and strength (where applicable), amount of luspatercept per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

7.7. Investigational Product Accountability and Disposal

Accountability for luspatercept that is administered during the course of the study is the responsibility of the Investigator or designee. Investigational clinical supplies must be received by a designated person at the clinical site and kept in a secure and temperature-controlled location. The investigational site must maintain accurate records demonstrating dates and amounts of luspatercept received, to whom it was administered (subject-by-subject accounting), and accounts of any luspatercept accidentally or deliberately destroyed or returned. Accurate recording of all luspatercept administration will be made in the appropriate section of the subject's eCRF and source documents. Unless otherwise notified, all vials of luspatercept, both used and unused, must be saved for drug accountability. The used vials may be discarded, per the institution's standard practice, after drug accountability has been completed by the monitor. The Investigator must return all unused vials of luspatercept to the Sponsor at the end of the study, or luspatercept may be destroyed at the clinical site with the permission of the Sponsor. For either scenario, the outcome must be documented on the drug accountability log. The Sponsor will provide direction for the outcome of all unused vials.

Celgene (or designee) will review with the Investigator and relevant site personnel the process for investigational product return, disposal, and/or destruction including responsibilities for the site versus Celgene (or designee).

7.8. Investigational Product Compliance

Luspatercept will be administered as a subcutaneous injection at the clinical site by the study staff. Monitoring for subject compliance with the treatment regimen is therefore unnecessary.

Accurate recording of all luspatercept administration will be made in the appropriate section of the subject's eCRF and source documents.

The Investigator or designee is responsible for accounting for all luspatercept that is administered during the course of the study.

8. CONCOMITANT MEDICATIONS AND PROCEDURES

Over the course of this study, additional medications may be required to manage aspects of the disease state of the subjects, including side effects from trial treatments or disease progression. Supportive care, such as anti-emetic medications, may be administered at the discretion of the Investigator.

All prior/concomitant treatments used from 28 days prior to the enrollment date until 42 days after the last dose of luspatercept must be reported on the eCRF. Additionally, any prior/concomitant treatments with a potential effect on the hematopoietic system should be captured from 112 days prior to the enrollment date until 42 days after the last dose of luspatercept and must be reported on the eCRF.

All prior procedures within the 28 days prior to the enrollment date will be recorded on the appropriate eCRF(s).

Prior granulocyte colony-stimulating factor (G-CSF)/ granulocyte macrophage colony-stimulating factor (GM-CSF) and ICT should be recorded on the appropriate eCRF(s) regardless of treatment discontinuation date.

Prior anticancer treatments should be recorded on the appropriate eCRF(s) regardless of treatment discontinuation/procedure date.

If a subject requires treatment with any new medications that are specifically excluded in Section 8.2, the subject will be discontinued from treatment and should complete the End of Treatment Visit and enter the Posttreatment Follow-up Period. The Investigator should consult the medical monitor regarding any questions about whether a new medication or dosage of existing medication would require the subject to discontinue from the study.

For information regarding other drugs that may interact with luspatercept and affect its metabolism, pharmacokinetics, or excretion, please see the Investigator's Brochure and/or local package insert.

8.1. Permitted Concomitant Medications and Procedures

For subjects in Cohort 2 and Cohort 3B, concurrent treatment for anemia with blood transfusions is recommended when Hgb is ≤ 9.0 g/dL or at the discretion of the Investigator if Hgb is ≥ 9.0 g/dL and associated with symptom(s) of anemia (eg, hemodynamic or pulmonary compromise requiring treatment) or comorbidity justifying a threshold of ≥ 9.0 g/dL Hgb.

For any RBC transfusions received during the study, the Hgb value just prior to transfusion should be collected, along with several other parameters (ie, number of units transfused, volume transfused, date of transfusion).

Granulocyte colony stimulating factors (ie, G-CSF, GM-CSF) are allowed only in cases of neutropenic fever or as clinically indicated per product label.

Thrombopoietin and platelet transfusions are permitted.

Treatment with systemic corticosteroids is permitted for nonhematological conditions providing the subject is receiving a stable or decreasing dose for ≥ 84 days immediately prior to enrollment and is receiving a constant dose equivalent to ≤ 10 mg prednisone during the study.

Administration of attenuated vaccines (eg, influenza vaccine) is allowed if clinically indicated per Investigator discretion.

Subjects who are using iron chelation therapies at the time of enrollment should be on a stable dose during the study and is recommended to be used per product label.

8.2. Prohibited Concomitant Medications and Procedures

The following concomitant medications are specifically excluded during the course of the study:

- Cytotoxic, chemotherapeutic, targeted, or investigational agents/therapies
- Azacitidine, decitabine, or other hypomethylating agents
- Lenalidomide, thalidomide, and other immunomodulatory compounds
- Erythropoietin stimulating agents (ESAs) and other RBC hematopoietic growth factors (eg, IL-3)
- Hydroxyurea or other alkylating agents
- Androgens (unless given to treat hypogonadism)
- Oral retinoids (topical retinoids are permitted)
- Arsenic trioxide
- Interferon
- Anagrelide

The following procedures are specifically excluded during the course of the study:

- Splenectomy
- Radiotherapy

For subjects specifically in Cohorts 1 and 2, concomitant treatment with ruxolitinib is prohibited.

Subjects in Cohort 1 and Cohort 3A are not permitted to receive RBC transfusions during the Treatment Period. Should an RBC transfusion be indicated to manage anemia, subjects in these cohorts might not be available for the efficacy evaluable population.

8.3. Required Concomitant Medications and Procedures

Not applicable.

9. STATISTICAL CONSIDERATIONS

9.1. Overview

This is a Phase 2, multicenter, open-label study to evaluate the efficacy and safety of luspatercept in subjects with MPN-associated myelofibrosis and anemia with and without RBC-transfusion dependence.

The design of the study, including the proposed targeted subject population, study endpoints, and statistical plan, is discussed below.

9.2. Study Population Definitions

Subjects will be enrolled to provide approximately 100 ITT subjects in this study, denoted by the following cohorts:

Cohort 1 (anemia only):

Approximately 20 subjects, but no less than 14 efficacy evaluable subjects, with MPN-associated myelofibrosis who are RBC-transfusion independent (no RBC transfusions within at least 84 days immediately up to the C1D1 date) with anemia will be enrolled in Cohort 1 and receive luspatercept at a starting dose level of 1.0 mg/kg (subcutaneous injection on Day 1 of a 21-day treatment cycle) for up to 8 cycles (or up through Day 168 in the event of dose delays). Should subjects meet the clinical benefit definition, they may continue treatment for approximately 2 years or more from the C1D1 date following the Day 169 Disease Response Assessment.

Cohort 2 (RBC-transfusion dependent):

Approximately 20 subjects with MPN-associated myelofibrosis and an average RBC-transfusion burden of 2 to 4 RBC units/28 days (calculated from the 84-day period immediately up to the C1D1 date) will be enrolled in Cohort 2 and receive luspatercept at a starting dose level of 1.0 mg/kg (subcutaneous injection on Day 1 of a 21-day treatment cycle) for up to 8 cycles (or up through Day 168 in the event of dose delays). Should subjects meet the clinical benefit definition, they may continue treatment for approximately 2 years or more, from the C1D1 date following the Day 169 Disease Response Assessment.

Cohort 3 (subjects on ruxolitinib as part of their standard-of-care therapy):

Approximately 60 subjects will be enrolled in Cohort 3 who must be on a stable dose of ruxolitinib for at least 112 days (16 weeks) immediately up to the enrollment date. Effective from Protocol Amendment 3, the additional subjects enrolled into Cohort 3B must also have a minimum prior treatment with ruxolitinib per their local standard-of-care for at least 280 days (40 weeks) without interruptions exceeding 2 consecutive weeks leading up to the date of enrollment. These subjects will receive luspatercept at a starting dose level of 1.0 mg/kg (subcutaneous injection on Day 1 of a 21-day treatment cycle) for up to 8 cycles (or up through Day 168 in the event of dose delays) ***Note for Protocol Amendment 3**: Additional subjects enrolling into Cohort 3B will begin luspatercept treatment at a starting dose of 1.33 mg/kg and can have their dose increased to a maximum dose of 1.75 mg/kg (with the total dose not to exceed 168 mg). Should subjects meet the clinical response definition, they may

continue treatment for approximately 2 years or more, following the Day 169 Disease Response Assessment.

Study populations to be analyzed are defined as follows:

Intent-to-treat (ITT) Population:

The intent-to-treat (ITT) population will consist of all enrolled subjects regardless of whether or not the subject received luspatercept. Efficacy analyses will be conducted primarily on the ITT population.

Efficacy Evaluable (EE) Population:

A subject who meets all the inclusion/exclusion criteria will be considered "efficacy evaluable" upon receiving ≥ 3 cycles of luspatercept and remain in the study for ≥ 21 days following the third dose of luspatercept. Subjects who attain Hgb values > 13 g/dL in < 3 cycles will also be considered efficacy evaluable. Subjects not considered "efficacy evaluable" are in general those that receive < 3 cycles of luspatercept in which luspatercept is held or discontinued or who receive < 3 cycles due to a treatment-emergent adverse event (TEAE) or discontinued treatment for any other reason.

Subjects will become nonefficacy evaluable in certain cases (eg, prohibited concomitant medication/s was/were used during the study). Subjects specifically in Cohort 3 become nonefficacy evaluable in certain cases (eg, the ruxolitinib dose was modified during the study).

The study steering committee will review the allocation of all subjects to the EE population. Efficacy analyses will be conducted based on the ITT and EE populations.

Safety Population:

The Safety Population will consist of all subjects who were enrolled and received at least 1 dose of luspatercept.

Statistical methods to handle missing data will be described in the statistical analysis plan (SAP).

The SAP will describe any predefined rules for including/excluding any subjects with data from any analyses (eg, time windows, visit by visit analysis, endpoint analysis, protocol violation).

9.3. Sample Size and Power Considerations

The Sponsor estimates that out of 20 enrolled subjects in Cohort 1, at least 14 will become efficacy evaluable.

For Cohort 1, the probability of observing no responses among 14 subjects is less than 0.05 if the response probability is greater than 20%. If no responses are observed in the first 14 evaluable subjects, the trial is stopped because it can be concluded that the response rate for the primary endpoint is less than 20% in Cohort 1.

For Cohort 2, the probability of observing no responses among 14 subjects is less than 0.05 if the response probability is greater than 20%. If no responses are observed in the first 14 evaluable subjects, enrollment in this cohort will be stopped because it can be concluded that the response rate for the primary endpoint is less than 20% in Cohort 2.

The sample size of Cohort 3 has been increased to approximately 60 ITT subjects. A total of 14 subjects in Cohort 3A would be sufficient to ensure the probability of observing no responses is less than 0.05 if the true response probability were greater than 20%, while 46 subjects in Cohort 3B would provide for 80% power to detect a 15% increase in response rate for luspatercept over a null response rate of 17%. This assumes a one-sided z test of a binomial proportion (with a 5% significance level).

9.4. Background and Demographic Characteristics

Subjects' age, height, weight, and baseline characteristics will be summarized using descriptive statistics, while gender, race, and other categorical variables will be provided using frequency tabulations by dose cohort. Prior transfusion history will be summarized. Medical history data will be summarized using frequency tabulations by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Myeloproliferative neoplasm (MPN)-associated myelofibrosis diagnoses as well as RBC transfusion dependence will be summarized using frequency tabulations.

9.5. Subject Disposition

Subject disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent for both treatment and follow-up phases. A summary of subjects enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations.

9.6. Efficacy Analysis

Efficacy analyses will be primarily conducted in the ITT population, and confirmatory analyses will be conducted in the EE population. Statistical analyses will be primarily descriptive in nature since the goal of the study is to establish efficacy and safety of luspatercept for further investigation. The results will be presented by cohort that subject is assigned to. Subjects in Cohorts 3A and 3B will be summarized separately.

9.6.1. Primary Efficacy Analysis

The primary efficacy endpoint is the proportion of subjects that achieved anemia response as defined below:

Cohorts 1 (anemia only) and 3A:

Proportion of subjects achieving ≥ 1.5 g/dL hemoglobin increase from baseline over any consecutive 84-day period without an RBC transfusion from Day 1 up through and including Day 168. This 84-day period will begin as soon as the ≥ 1.5 g/dL hemoglobin increase is detected. There must be ≥ 3 determinations of ≥ 1.5 g/dL hemoglobin increase from baseline in this interval with no value showing a < 1.5 g/dL hemoglobin increase from baseline **and** no 2 measurements are ≥ 42 days apart.

Cohorts 2 (RBC-transfusion dependent) and 3B:

Proportion of subjects who become RBC-transfusion free over any consecutive 84-day period from Day 1 up through and including Day 168. This 84-day period will begin from the date of the prior RBC transfusion that is given for a Hgb value ≤ 9.5 g/dL.

Examples of any consecutive 84-day period are from Day 1 to 84, Day 2 to 85, Day 3 to 86, etc. Response rate will be calculated using the number of responders divided by number of subjects in the ITT population (responders plus nonresponders).

Anemia response rate, together with a 95% confidence interval, will be calculated for each cohort.

9.6.2. Secondary Efficacy Analyses

Time to anemia response will be summarized only for subjects who achieved anemia response. It is defined as time from first dose to first onset of anemia response, calculated from Day 1 through and including Day 168.

Duration of anemia response will be summarized only for subjects who achieved anemia response. It is defined as maximum duration of modified anemia response, calculated from Day 1 through end of treatment.

Frequency of RBC transfusions will be assessed for Cohort 2 subjects and RBC-transfusion dependent subjects in Cohort 3B. It is defined as the mean number of RBC units transfused per subject per 28 days. It will be calculated from Day 1 through and including Day 168 and Day 1 through end of treatment.

Frequency of RBC-transfusion dependence will be assessed for Cohort 2 subjects and RBC-transfusion dependent subjects in Cohort 3B. It is defined as the proportion of subjects who reduce their transfusion burden by ≥ 50% from baseline over any consecutive 84-day period. It will be calculated from Day 1 through and including Day 168 and Day 1 through end of treatment.

Symptoms response improvement will be assessed using the proportion of subjects who achieve ≥ 50% reduction in fatigue symptom as measured by the MPN-SAF TSS, calculated from Day 1 through and including Day 168 and Day 1 through end of treatment. The proportion of subjects who achieve ≥ 50% reduction in total symptom score (TSS) will also calculated.

Health-related quality of life (HRQoL) will be assessed via the mean changes in domain scores over the study compared to baseline using the FACT-An and EQ-5D-5L, calculated from Day 1 through and including Day 168 and Day 1 through end of treatment. Various schemes will be assessed for missing data imputation if needed.

Changes in hemoglobin will be assessed for Cohorts 1 and 3A subjects over the study compared to baseline in the absence of RBC transfusions, calculated from Day 1 through and including Day 168 and Day 1 through end of treatment.

Mean hemoglobin increase of ≥ 1.5 g/dL from baseline over any consecutive 84-day period without an RBC transfusion will be assessed for Cohorts 1 and 3A subjects, calculated from Day 1 through and including Day 168 and Day 1 through end of treatment. Duration of anemia response may be estimated using Kaplan-Meier methods. Point estimates and 95% confidence intervals will be provided where appropriate. Additional details of the censoring rules will be specified in the SAP.

Other efficacy endpoints will be primarily summarized by descriptive statistics. There will be no inferential comparison between treatment cohorts.

9.7. Safety Analysis

All safety analyses will be performed on the safety population. Full details will be included in the SAP. Planned data presentations and analyses include the following:

- Adverse events will be coded using MedDRA. Adverse event listings will include the verbatim term and the MedDRA preferred term. Treatment-emergent adverse events will be summarized by system organ class and preferred term. Treatment-emergent adverse events leading to death or to discontinuation from treatment, TEAEs classified as National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (version 4.03) all grades or grade 3/4 TEAEs, related to investigational product, and serious TEAEs will be summarized separately.
- Clinical laboratory results will be summarized descriptively by cohort. Clinically significant hematologic and nonhematologic laboratory abnormalities will be listed and summarized according to the NCI CTCAE (version 4.03). Cross tabulations will be provided to summarize frequencies of abnormalities.
- Physical examination data and vital sign measurements, including body weight, will be listed for each subject at each visit. Descriptive statistics for vital signs, both observed values and changes from baseline, will be summarized by cohort.

Graphical displays will be provided where useful to assist in the interpretation of results.

9.8. Timing of Analyses

9.8.1. Interim Analysis

No formal interim analysis is planned for the study. Once the last subject completes or discontinues the Primary Phase of the Treatment Period, top-line results on efficacy and safety endpoints will be generated.

9.8.2. Final Analysis

The final analysis will be performed when all subjects have completed or discontinued the Treatment Period. Additional follow-up analyses will be performed when subjects complete the Long-term Follow-up Period.

9.9. Other Topics

9.9.1. Pharmacokinetic Analysis

Population PK analysis will be performed for luspatercept using nonlinear mixed effect modeling. Concentration data obtained from this study and other studies may be combined to develop a population PK model that describes the PK exposure data and the associated variability. Subject-specific factors (demographics, baseline characteristics, markers for organ function, antiluspatercept antibodies, etc.) will be explored as covariates for their potential to influence luspatercept PK parameters. Empiric individual Bayesian estimates of PK parameters will be generated using the final population PK model. With these individual parameter estimates, appropriate measures of luspatercept exposure (area under the curve [AUC], maximum plasma concentration of drug [C_{max}], or other exposure metrics of interest) will be

computed for each subject. The relationship between serum luspatercept exposure and selected efficacy endpoints and AEs of interest may be explored as appropriate.

Furthermore, frequency of ADA and effects on efficacy, safety, or PK parameters will also be assessed.

[redacted]

9.9.3. Steering Committee

A SC will be established by charter for this study. The SC will be comprised of study Investigators, Sponsor representatives, and may include additional ad hoc members as appropriate. The SC will have the opportunity to review efficacy and safety data on an ongoing basis. The SC will serve in an advisory capacity to the Sponsor. The SC may advise and recommend to the Sponsor on the following (but not limited to) points:

- Changes to the protocol or conduct of the study based upon emerging clinical or scientific data from this and/or other studies.
- Procedures to ensure the safety of subjects and integrity of study data.
- Procedures to meet the overall goals and objectives of the study.

The SC will review all available safety and efficacy data after:

- approximately 3 subjects in Cohort 3 complete 2 cycles of therapy;
- approximately 6 efficacy-evaluable subjects complete at least 5 cycles of therapy; and
- approximately 14 efficacy-evaluable subjects complete at least 5 cycles of therapy in Cohort 1.

During this time, enrollment will continue without delay in all 3 cohorts.

If a minimum level of response is not seen in Cohort 1 (at least 1 per protocol responder out of the first 14 efficacy evaluable subjects in Cohort 1), the SC may recommend ending the study early due to lack of efficacy.

The SC responsibilities, authorities, and procedures will be detailed in the SC charter, which will be endorsed by the SC prior to the first data review meeting.

Additional details, including operational considerations, for the SC will be detailed in a separate SC charter.

10. ADVERSE EVENTS

10.1. Monitoring, Recording and Reporting of Adverse Events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 10.3), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose eCRF (See Section 7.2 for the definition of overdose). Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE on the AE eCRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE eCRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and eCRF but should not be reported as an SAE itself.

In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for luspatercept overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

All AEs (including serious adverse events [SAEs]), regardless of causal relationship to luspatercept, will be recorded by the Investigator from the time the subject signs informed consent until 42 days after the last dose of luspatercept. After the 42-Day Follow-up Period, only those serious adverse events (SAEs) made known to the Investigator that are suspected of being related to luspatercept will be recorded by the Investigator.

Adverse events (AEs) and SAEs will be recorded on the AE page of the eCRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

10.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

10.2.1. Seriousness

An SAE is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (ie, in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life-threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events **not considered** to be SAEs are hospitalizations for:

- a standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- the administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- a procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- a procedure that is planned (ie, planned prior to start of treatment on study); must be documented in the source document and the eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- an elective treatment of or an elective procedure for a pre-existing condition, unrelated to the studied indication, that has not worsened from baseline.
- emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the eCRF and the SAE Report Form must be completed.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to the luspatercept, action taken regarding the luspatercept, and outcome.

10.2.2. Severity/Intensity

For both AEs and SAEs, the Investigator must assess the severity/intensity of the event.

The severity/intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of the Common Terminology Criteria for Adverse Events (CTCAE, version 4.03);
https://evs.nci.nih.gov/ftp1/CTCAE/About.html

Adverse events (AEs) that are not defined in the CTCAE should be evaluated for severity/intensity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
- Grade 4 = Life-threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death - the event results in death

The term "severe" is often used to describe the intensity 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 severe headache). This criterion is *not* the same as "serious" which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

10.2.3. Causality

The Investigator must determine the relationship between the administration of luspatercept and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected:	a causal relationship of the adverse event to luspatercept administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	there is a **reasonable possibility** that the administration of luspatercept caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the luspatercept and the adverse event.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional luspatercept that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

10.2.4. Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

10.2.5. Action Taken

The Investigator will report the action taken with luspatercept as a result of an AE or SAE, as applicable (eg, discontinuation, interruption, or dose reduction of luspatercept, as appropriate) and report if concomitant and/or additional treatments were given for the event.

10.2.6. Outcome

The Investigator will report the outcome of the event for both AEs and SAEs.

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered (returned to baseline), recovered with sequelae, or death (due to the SAE).

10.3. Adverse Events of Special Interest

The occurrence of a new malignancy or premalignant lesion will be monitored as an event of special interest and should be included as part of the assessment of adverse events throughout the course of the study. Investigators are to report the development of any new malignancy or premalignant lesion as a serious adverse event, regardless of causal relationship to IP, occurring at any time for the duration of the study, from the time of signing the ICF up to and including at least 5 years following the date of first dose of IP or 3 years post last dose of IP of the Posttreatment Follow-up Period, whichever occurs later.

Events of new malignancy and premalignant lesions (excluding benign tumors or benign neoplasia) are to be reported within 24 hours of the Investigator's knowledge of the event by fax, or other appropriate method, using the SAE Report Form, and must be considered an "Important Medical Event" even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the eCRF and subject's source documents. Documentation of the diagnosed malignancy must be provided at the time of reporting as a serious adverse event (eg, any confirmatory histology or cytology results, x-rays, computed tomography [CT] scans, etc.).

Malignancies or cancerous tumors are lesions capable of invading into adjacent tissues and may be capable of spreading to distant tissues. A benign tumor has none of those properties.

Malignancy or cancer is characterized by anaplasia, invasiveness, and metastasis. For MPN-associated myelofibrosis studies, these also include transformation to blast phase, myeloproliferation (eg, clinically significant increases in blasts), etc.

Premalignant or precancerous lesions refer to a state of disordered morphology of cells that is associated with an increased risk of cancer. If left untreated, these conditions may lead to cancer. Such conditions are usually either dysplasia or benign neoplasia (and the dividing line between those is sometimes blurry). Sometimes the term "precancer" is used to describe carcinoma in situ, which is a noninvasive cancer that has not progressed to an aggressive, invasive stage. Not all carcinoma in situ will progress to invasive disease.

Premalignant lesions are morphologically atypical tissue which appears abnormal under microscopic examination and in which cancer is more likely to occur than in its apparently normal counterpart.

10.4. Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of luspatercept dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance, eg, one that indicates a new disease process and/or organ toxicity, or is an exacerbation or worsening of an existing condition.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the eCRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

10.5. Pregnancy

All pregnancies or suspected pregnancies occurring in either a female subject of childbearing potential or partner of childbearing potential of a male subject are immediately reportable events.

10.5.1. Females of Childbearing Potential:

Pregnancies and suspected pregnancies (including elevated β-hCG or positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring while the subject is on luspatercept, or within 12 weeks of the subject's last dose of luspatercept, are considered immediately reportable events. Luspatercept is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by email, phone or facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The female subject may be referred to an obstetrician-gynecologist or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, spontaneous abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the luspatercept should also be reported to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

10.5.2. Male Subjects

If a female partner of a male subject taking luspatercept becomes pregnant, the male subject taking luspatercept should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

Males will be advised to use a latex condom during any sexual contact with FCBP prior to study entry and continue for 12 weeks following the last dose of luspatercept, even if he has undergone a successful vasectomy.

10.6. Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the eCRF. All SAEs must be reported to Celgene Drug Safety and Medical Monitor within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method (eg, via email), using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The Investigator is required to ensure that the data on these forms are accurate and consistent. This requirement applies to all SAEs (regardless of relationship to luspatercept) that occur during the study (from the time the subject signs informed consent until 42 days after the last dose of luspatercept) or any SAE made known to the Investigator at any time thereafter that are suspected of being related to luspatercept. Serious adverse events occurring prior to treatment (after signing the ICF) will be captured.

The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Celgene Drug Safety as soon as these become available. Any follow-up data should be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Celgene Drug Safety.

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board/Ethics Committee (IRB/EC) of the SAE and providing them with all relevant

initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

In addition, any report of transformation to blast phase or AML, regardless of causality, will be reported as an expedited safety report to the regulatory authorities, if requested.

10.6.1. Safety Queries

Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than five (5) business days. Urgent queries (eg, missing causality assessment) may be handled by phone.

10.7. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to luspatercept based on the IB.

In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

For countries within the European Economic Area (EEA), Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, SUSARs in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

Celgene or its authorized representative shall notify the Investigator of the following information:

- Any AE suspected of being related to the use of luspatercept in this study or in other studies that is both serious and unexpected (ie, SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information on file including correspondence with Celgene and the IRB/EC. (See Section 14.3 for record retention information).

Celgene Drug Safety Contact Information:

For Celgene Drug Safety contact information, please refer to the Serious Adverse Event Report Form Completion Guidelines or to the Pregnancy Report Form Completion Guidelines.

10.8. Monitoring of Toxicity and Study Stopping Rules

Adverse events occurring in the study are monitored continuously by Celgene.

When more than three such adverse events of a particular type (preferred term) are reported this will be addressed by the Celgene Safety Management Team and will be brought to the attention of the Study Steering Committee.

Excessive toxicity in the context of this study is defined as a rate of treatment-emergent Grade 3 or above serious adverse events assessed by investigator or Celgene as related to luspatercept of 20% or higher.

If the posterior probability of the toxicity rate exceeding 20% is greater than 0.8, then further subject enrollment will be put on hold and after assessment of the findings by the Celgene Safety Management Team and the Study Steering Committee study treatment for all ongoing subjects receiving luspatercept might be stopped early.

For the subject on ongoing treatment and additional enrollment of subjects into Cohort 3B the following stopping rule will apply, accounting for the subjects already enrolled in the study. This assumes a relatively weak prior distribution of Beta (1/3, 1/3) for toxicity rate, which will allow the accruing data on toxicities to dominate. This prior is also 'neutral' in the sense that the maximum likelihood estimate of toxicity rate is approximately at the posterior median (Kerman, 2011).

Number of Subjects	Number of Subjects with Toxicities Required to Stop Study
1-75	Not applicable
76-79	19
80-84	20
85-88	21
89-93	22
94-98	23
99-102	24
103-107	25
108-111	26
112-116	27
117-120	28

11. DISCONTINUATIONS

11.1. Treatment Discontinuation

Subjects will have an End of Treatment (EOT) Visit at the time of luspatercept discontinuation (refer to Section 6.4 for more information). All subjects who received at least one dose of luspatercept will be followed for at least 3 years post last dose of luspatercept.

The following events are considered sufficient reasons for discontinuing a subject from the investigational product(s):

- Adverse Event
- Withdrawal by subject
- Death
- Lost to follow up
- Pregnancy
- Protocol violation/deviation
- Study terminated by Sponsor
- Disease progression of MPN-associated myelofibrosis according to IWG-MRT criteria, defined as:
  - Appearance of a new splenomegaly that is palpable at least 5 cm below the left costal margin (LCM);
  - A ≥ 100% increase in palpable distance, below LCM, for baseline splenomegaly of 5 to 10 cm;
  - A 50% increase in palpable distance, below LCM, for baseline splenomegaly of > 10 cm;
  - Transformation to blast phase confirmed by a bone marrow blast count of ≥ 20% **or** a blood myeloblast percentage of ≥ 20% associated with a blast count of ≥ 1 x 10^9/L that lasts for at least 2 weeks.
- ≥ 2 dose reductions suspected related AE
- Dose delay lasting > 12 consecutive weeks
- Requiring a medication/procedure on the prohibited medication/procedure list (refer to Section 8.2 for more information
- Other (to be specified on the eCRF and in the protocol)
  - Including treatment discontinuation guidance related to dose modifications (refer to Section 7, Table 5)
  - Clinical benefit criteria (refer to Section 6.2.2 for more information)

The reason for discontinuation of treatment should be recorded in the eCRF and in the source documents.

The decision to discontinue a subject from treatment remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, prior to discontinuing a subject, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

All subjects discontinued from luspatercept for any reason will have EOT evaluations at the time of discontinuation, outlined in Section 6.4. Subsequently, subjects would then move into the Posttreatment Follow-up Period, consisting of a 42-Day Follow-up Period and Long-term Follow-up Period (refer to Section 6.5).

11.2. Study Discontinuation

Subjects who discontinue from treatment for any reason will be followed via telephone contact by the site for collection of data on survival, cause(s) of death, transformation to blast phase, and posttreatment therapies for MPN-associated myelofibrosis during the 42-Day Follow-up Period. During the Long-term Follow-up Period time points, collection of data on posttreatment therapies for MPN-associated myelofibrosis, survival, cause(s) of death, and transformation to blast phase will occur every 3 months after the 42-Day Follow-up Period for at least 3 years after the last dose of luspatercept or until death, lost to follow up, or withdrawal of consent from the study.

Every attempt should be made to contact subjects during follow up unless subjects discontinue from the study. Every attempt should be made to collect all data on discontinued subjects.

The following events are considered sufficient reasons for discontinuing a subject from the study:

- Screen failure
- Adverse events
- Withdrawal by subject
- Death
- Lost to follow up
- Protocol violation/deviation
- Study terminated by Sponsor
- Other (to be specified on the eCRF)

The reason for study discontinuation should be recorded in the eCRF and in the source documents.

12. EMERGENCY PROCEDURES

12.1. Emergency Contact

In emergency situations, the Investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page). Following the phone discussion with the Clinical Research Physician/Medical Monitor, a courtesy email can be sent to the study Medical Monitor Mailbox to alert the full study team and for action on any additional follow-up items.

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page). This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on-call Celgene/contract research organization Medical Monitor, who will then contact you promptly.

Note: The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

12.2. Emergency Identification of Investigational Products

This is an open-label study; therefore, luspatercept will be identified on the package labeling.

13. REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene, its authorized representative, and Investigator abide by Good Clinical Practice (GCP), as described in International Council for Harmonisation (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

13.2. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for GCP and in the local regulations. Celgene staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions, including obligations of confidentiality of Celgene information. The Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an informed consent form (ICF) and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of eCRFs and queries.

The information contained in the protocol and amendments (with the exception of the information provided by Celgene on public registry websites) is considered Celgene confidential information. Only information that is previously disclosed by Celgene on a public registry website may be freely disclosed by the Investigator or its institution, or as outlined in the Clinical Trial Agreement. Celgene protocol, amendment and IB information is not to be made publicly available (for example on the Investigator's or their institution's website) without express written approval from Celgene. Information proposed for posting on the Investigator's or their institution's website must be submitted to Celgene for review and approval, providing at least 5 business days for review.

At the time results of this study are made available to the public, Celgene will provide Investigators with a summary of the results that is written for the lay person. The Investigator is responsible for sharing these results with the subject and/or their caregiver as agreed by the subject.

13.3. Subject Information and Informed Consent

The Investigator must obtain informed consent of a subject and/or a subject's legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original ICF signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the ICF must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the ICF. The revised ICF signed and dated by the study subject and by the person consenting the study subject must be maintained in the Investigator's study files and a copy given to the study subject.

13.4. Confidentiality

Celgene affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Celgene requires the Investigator to permit Celgene's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed ICF, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

13.5. Protocol Amendments

Any amendment to this protocol must be initiated only by Celgene and approved by the Celgene Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

13.6. Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, ICF, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

Luspatercept can only be supplied to an Investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received

by Celgene or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the ICF should also be revised.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by Celgene and the IRB/EC prior to use.

13.7. Ongoing Information for Institutional Review Board/ Ethics Committee

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected adverse events as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

13.8. Termination of the Study

Celgene reserves the right to terminate this study prematurely at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities, etc.).

The Sponsor may consider closing this trial when data supporting key endpoints and objectives of the study have been analyzed. In the case where there are subjects still being administered luspatercept, and it is the opinion of the Investigator(s) that these subjects continue to receive benefit from treatment, the Sponsor may choose to initiate a roll-over or extension study under a separate protocol, if applicable, to allow these subjects continued access to luspatercept following their participation in the ACE-536-MF-001 study.

In addition, the Investigator or Celgene has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;

- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

14. DATA HANDLING AND RECORDKEEPING

14.1. Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; subject questionnaires; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of eCRFs or CD-ROM.

14.2. Data Management

Data will be collected via eCRF and entered into the clinical database per Celgene standard operating procedures (SOPs). This data will be electronically verified through the use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team and investigational site personnel as necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

14.3. Record Retention

Essential documents must be retained by the Investigator according to the period of time outlined in the clinical trial agreement. The Investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed ICFs for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, Celgene, and their authorized representative(s);
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of eCRFs and of documentation of corrections for all subjects;
- Luspatercept accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);

- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from Celgene prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator or institution should take measures to prevent accidental or premature destruction of these documents.

15. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by Celgene or its authorized representative for compliance with applicable government regulations with respect to current GCP and SOPs.

15.1. Study Monitoring and Source Data Verification

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the Investigator and the staff at a study initiation visit and/or at an Investigators' Meeting. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, eCRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, investigational product storage area, eCRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative in accordance with the Study Monitoring Plan.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the eCRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the eCRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

15.2. Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene. Representatives of this unit will conduct audits of clinical research activities in accordance with Celgene SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The Investigator is required to permit direct access to the facilities where the study took place, source documents, eCRFs and applicable supporting records of study subject participation for audits and inspections by IRB/ECs, regulatory authorities (eg, FDA, EMA, Health Canada) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

15.3. Product Quality Complaint

A Product Quality Complaint (PQC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, purity, or performance of any drug product manufactured by or on behalf of Celgene Corporation after it is released for distribution. PQCs may reduce the usability of the product for its intended function or affect performance of the product and therefore pose a significant risk to the subject. Examples of PQCs include (but are not limited to): mixed product, mislabeling, lack of effect, seal/packaging breach, product missing/short/overage, contamination, suspected falsified,

tampered, diverted or stolen material, and general product/packaging damage. If you become aware of a suspected PQC, you are obligated to report the issue immediately. You can do so by emailing [redacted] or by contacting the Celgene Customer Care Center [redacted]

16. PUBLICATIONS

As described in Section 13.2, all protocol- and amendment-related information, with the exception of the information provided by Celgene on public registry websites, is considered Celgene confidential information and is not to be used in any publications. Celgene protocol-related information proposed for use in a publication must be submitted to Celgene for review and approval, and should not be utilized in a publication without express written approval from Celgene, or as described in the Clinical Trial Agreement.

Celgene will ensure Celgene-sponsored studies are considered for publication in the scientific literature in a peer-reviewed journal, irrespective of the results. At a minimum, this applies to results from all Phase 3 clinical studies, and any other study results of significant medical importance. This also includes results relating to investigational medicines whose development programs have been discontinued.

Study results may also be presented at one or more medical congresses, and may be used for scientific exchange and teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations.

Eligibility for external authorship, as well as selection of first authorship, will be based on several considerations, including, but not limited to, contribution to protocol development, study recruitment, data quality, participation in data analysis, participation in study steering committee (when applicable) and contribution to abstract, presentation and/or publication development.

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[redacted]

18. APPENDICES

Appendix A: Table of Abbreviations

Abbreviation or Specialist Term	Explanation
ActRIIB	Activin receptor type IIB
ADA	Antidrug antibodies
AE	Adverse event
ALT	Alanine transaminase (SGPT)
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the curve
β-hCG	β-subunit of human chorionic gonadotropin
BMP6, BMP9	Bone morphogenetic protein 6, bone morphogenetic protein 9
CALR	Calreticulin
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
ECG	Electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
FACT-An	Functional Assessment of Cancer Therapy – Anemia
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
GDF11	Growth differentiation factor 11
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte macrophage colony-stimulating factor
HepB	Hepatitis B
HepC	Hepatitis C
Hgb	Hemoglobin
HI-E	Hematologic improvement – erythroid response
HIV	Human immunodeficiency virus

Abbreviation or Specialist Term	Explanation
HRQoL	Health-related quality of life
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICT	Iron chelation therapy
Ig	Immunoglobulin
IL	Interleukin
IRB	Institutional Review Board
IRT	Integrated Response Technology
ITT	Intent-to-treat
IWG	International Working Group
IWG-MRT	International Working Group – Myeloproliferative Neoplasms Research and Treatment
JAK	Janus kinase
JAK2	Janus kinase 2 gene
LCM	Left costal margin
LTFU	Long-term follow-up
MDRD	Modification of diet in renal disease
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MPL	Thrombopoietin receptor
MPN	Myeloproliferative neoplasm
MPN-SAF TSS	Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score
NCI	National Cancer Institute
NTD	Non-transfusion dependent
Post-ET MF	Post-essential thrombocythemia myelofibrosis
Post-PV MF	Post-polycythemia vera myelofibrosis
PV	Polycythemia vera
[redacted]	[redacted]
RBC	Red blood cell
RBC-TI	Red blood cell – transfusion independence

Abbreviation or Specialist Term	Explanation
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Steering committee
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
TD	Transfusion-dependent
TGF-β	Transforming growth factor-beta
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
TSS	Total symptom score
ULN	Upper limit of normal
WBC	White blood count

Appendix B: Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

The ECOG scale (Oken, 1982) is used to assess a subject's quality of life in an evaluation by a health professional of the daily activities and how the activities are affected by the disease of the subject.

Eastern Cooperative Oncology Group (ECOG) Performance Status	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead.

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J. Clin Oncol 1982; 5(6):649-55.

Appendix C: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03

Currently active minor version of NCI CTCAE, version 4.03:

https://evs.nci.nih.gov/ftp1/CTCAE/About.html

Celgene Signing Page

This is a representation of an electronic record that was signed electronically in Livelink. This page is the manifestation of the electronic signature(s) used in compliance with the organizations electronic signature policies and procedures.

UserName: [redacted]
Title: [redacted]
Date: Sunday, 23 February 2020, 04:03 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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1. JUSTIFICATION FOR AMENDMENT

The following change was made to the protocol as subjects on luspatercept therapy continue to demonstrate clinical benefit while on study treatment in the absence of any significant safety signals. To enable long-term access to luspatercept therapy (provided subjects continue to demonstrate clinical benefit as assessed by the Investigator and do not meet any protocol treatment discontinuation criteria), the Extension Phase has been extended beyond 2 years.

Significant changes included in this amendment are summarized below:

- **Prolongation of Extension Phase of the Treatment Period**The primary purpose of this protocol amendment is to amend the 2-year study treatment limit for subjects in the Extension Phase of the Treatment Period to extend beyond 2 years for those that continue to receive benefit according to investigator assessment (eg, ≥ 50% reduction of transfusion burden from baseline).Revised sections: Protocol Summary, Section 3.1, Section 3.2, Section 6.2.2, Section 6.2.3, and Section 9.2 **The amendment also includes several other minor clarifications and corrections:Correction of Column Header and diagram text for Figure 2 in Section 3.1**: wording added to indicate Treatment Period may extend past 2 years from C1D1 date. **Clarification made to Section 9.2**: text that mentioned that subjects who are not efficacy evaluable will be scored as nonresponders was removed. **Clarification made to Section 10**: Removed and consolidated Section 10.6 “Other Malignancies/Premalignancies” with Section 10.3 “Adverse Events of Special Interest” as these sections contained duplicate information pertaining to “Other Malignancies/Premalignancies.”**Added Section 15.3**: provided contact information for product quality complaints for drug products manufactured by Celgene CorporationOther additional administrative changes (ie, spelling, grammatical error corrections, etc.) were also made throughout the document.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in the amendment are summarized below. The following changes were made to provide a more accurate estimate of the luspatercept treatment effect to enable effective planning of a future potential Phase 3 study.

- **Expansion of Cohort 3 enrollment**
  - Expand total enrollment of Cohort 3B by approximately 27 subjects for an approximate total of 46 subjects. This would result in an approximate total of 60 subjects in Cohort 3 and an approximate total study enrollment of 100 subjects.
  - Revised sections: Protocol Summary, Section 3.1, Section 4.1, Section 9.2, Section 9.3
- **Modifying Cohorts 2 and 3B inclusion criterion**
  - Update inclusion criterion to enable subjects with a transfusion burden defined as 4 to 12 RBC units/84 days, with no interval > 56 days between RBC transfusions to collect additional data on subjects with a lower transfusion burden.
  - Revised section: Section 1.4.2, Section 4.2
- **Statistical considerations supporting Cohort 3 expansion**
  - Sample size and power calculations have been incorporated to justify expansion of Cohort 3B.
  - Revised section: Protocol Summary, Section 9.3
- **Addition of secondary endpoint to assess mean hemoglobin increase**
  - Update to protocol to include an additional secondary endpoint to analyze the mean hemoglobin increase of ≥ 1.5 g/dL from baseline over any consecutive 84-day period without an RBC transfusion that will be assessed for Cohort 1 and 3A subjects, calculated from Day 1 through and including Day 168 and Day 1 through end of treatment. [redacted]
  - Revised sections: Protocol Summary, Section 2 (Tables 1 and 2), Section 9.6.2

Additional significant changes made to the protocol are described below. [redacted]

Furthermore, language has been incorporated that reflects implementation of an approved roll-over study that subjects in the parent protocol may transition over to if eligible.

- **Modifying dose titration criteria**
  - For subjects in any cohort who may start to demonstrate a loss of response as defined as a Hgb decrease of ≥ 1 g/dL (not influenced by an RBC transfusion), the dose level may be increased by 1 dose level.

  - For subjects in Cohorts 2 and 3B whose Hgb is not exceeding 1 g/dL increase from the baseline mean pretransfusion Hgb value (calculated using the reported RBC transfusions that confirmed the eligibility of the subject), the dose level may be increased by 1 dose level
  - Revised section: Section 7.3.1

- **Adapting clinical benefit criteria to allow subjects to continue in the Extension Phase**
  - Added additional wording that would allow subjects to continue receiving luspatercept therapy if, in the assessment of the Investigator, the subject is benefiting from treatment not necessarily reflected by the protocol's clinical benefit criteria (eg, clinically significant reduction of the transfusion burden or clinically significant improvement of a subject's symptom burden) and that these cases would be discussed with the Medical Monitor.
  - Revised sections: Section 3.1, Section 6.2.2

- **Addition of language supporting the ACE-536-LTFU-001 roll-over study**
  - As the ACE-536-LTFU-001 roll-over study has been implemented, language has been added that when applicable, any subject remaining on the ACE-536-MF-001 study may be consented and transition over to the new roll-over study to continue to receive access to luspatercept and/or complete posttreatment follow up requirements.
  - Revised section: Figure 2, Section 3.3

Another significant change made to the protocol includes a starting dose of 1.33 mg/kg and can dose titrate up to a maximum dose of 1.75 mg/kg, with a total dose not to exceed 168 mg) for the additional Cohort 3B subjects that are enrolled. [redacted]

- **New starting dose level of 1.33 mg/kg**
  - Additional language has been provided that denotes subjects enrolling into Cohort 3B due to Protocol Amendment 3 will start a luspatercept dose of 1.33 mg/kg and can have their dose increased to a maximum dose of 1.75 mg/kg (with the total dose not to exceed 168 mg).
  - Revised sections: Protocol Summary, [redacted], Section 3.1, Section 7.2, Section 7.3, Section 7.3.1, Section 9.2

The following changes were made in response to a regulatory agency request received from the FDA for IND 112,562 on 04 Jun 2019.

- **Amended Exclusion Criterion #3 for ruxolitinib dosing in Cohort 3**
  - In addition to the original Exclusion Criterion #3 requiring subjects to be on a stable daily dose of ruxolitinib for at least 112 days (16 weeks), Exclusion criterion #3 was amended to signify that Cohort 3 subjects are also required to have at least 280 days (40 weeks) of ruxolitinib dosing without interruptions exceeding 2 weeks consecutively leading up to the date of enrollment also.

  - Revised sections: Protocol Summary, Section 3.1, Section 4.3, Section 9.2
- **Added Section 10.9 Monitoring of Toxicity and Study Stopping Rules**

This amendment also includes additional minor clarifications and corrections:

- **Inclusion of updated luspatercept Phase 3 results to Section 1.3.2 and Section 17**: data from the Phase 3 MEDALIST and BELIEVE studies have been incorporated along with their applicable references.
- **Clarification of capturing RBC transfusion information in Table 3, Section 6.1, 6.2.1, Section 6.2.2, Section 6.2.3, Section 6.4, and Section 6.5.1**: when applicable, additional language has been incorporated to ensure all subjects (regardless if local procedures are in place) will receive a transfusion diary to collect pertinent information regarding transfusions given outside the study site. Furthermore, appropriate source documentation for historical transfusions or transfusions given while subject is on study must be available for source document verification.
- **Modification and clarification of the length of study duration in the Protocol Summary section**: enrollment timelines reflecting Cohort 3 expansion have been implemented in the overall study duration timelines, as well as clarifying expected time on study for an individual subject and the expected total study duration.
- **Updated references in Section 17**: several references were updated/modified with more recent publication information available; one reference was removed due to the referenced text being deleted from the protocol.
- Other additional administrative changes (ie, spelling, grammatical error corrections, etc.) were also made throughout the document.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in the amendment are summarized below. [redacted] additional criteria for dose adjustments has been introduced:

- Dose delay for worsening by ≥ 2 grades for leukopenia, neutropenia, or thrombocytopenia to ≥ Grade 3 that is not clearly and solely related to an extraneous case such as advancing myeloproliferative neoplasm-associated myelofibrosis or an infectious event
- Dose delay for worsening of anemia in presence of unexplained shift (worsening) from baseline of ≥ 2 grades for leukopenia, neutropenia, or thrombocytopenia

Revised section: Section 7.3.2 (Table 5)

This amendment also includes additional minor clarifications and corrections:

- [redacted]

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in the amendment following the recommendation from the study's Steering Committee from a 12 Jan 2018 meeting are summarized below. [redacted]

- **Addition of exclusion criterion for a white blood count threshold**
  - Update to the protocol to exclude subjects in screening with a white blood count $> 100 \times 10^9$/L.
  - Revised section: Section 4.3
- **Addition of exclusion criterion for a platelet count threshold**
  - Update to the protocol to exclude subjects in screening with a platelet count $> 1000 \times 10^9$/L.
  - Revised section: Section 4.3

Additional significant changes agreed upon by the Steering Committee Chair on 31 Jan 2018 included in the amendment are described below. [redacted]

- **Addition of exclusion criterion for subjects on anticoagulant therapy who are not under appropriate control or not on a stable dose of anticoagulant therapy for ≥ 8 weeks up to the enrollment date**
  - Update to the protocol to exclude subjects on anticoagulant therapy who may not be under appropriate control or subjects not on a stable dose of anticoagulant therapy for ≥ 8 weeks up to the enrollment date.
  - Revised section: Section 4.3
- **Addition of exclusion criterion for subjects on anagrelide within 28 days immediately up to the enrollment date**
  - Update to the protocol to exclude subjects on anagrelide within 28 days prior to the enrollment date.
  - Revised sections: Section 4.3, Section 8.2
- **Addition of exclusion criterion for subjects with a major bleeding event in the last 6 months prior to enrollment**
  - Update to the protocol to exclude subjects with a major bleeding event (defined as symptomatic bleeding in a critical area or organ and/or bleeding causing a fall in hemoglobin of ≥ 2 g/dL or leading to transfusion of ≥ 2 units of packed red cells) within the last 6 months prior to enrollment.
  - Revised section: Section 4.3

Additional significant changes that were included in the amendment:

- **Addition of secondary endpoint to capture changes in hemoglobin over the study compared to baseline in the absence of red blood cell (RBC) transfusions**
    - Update to the protocol to include an additional secondary endpoint to analyze in Cohorts 1 and 3A subjects the changes in hemoglobin over the course of the study compared to baseline in the absence of RBC transfusions starting from Day 1 through and including Day 168 and Day 1 through end of treatment.
    - Revised sections: Protocol Summary, Section 2 (Table 2), Section 9.6.2
- **Addition of minimum number of days between hemoglobin assessments as outlined within Inclusion Criterion 3A**
    - Update to the protocol to include a minimum number of 14 days between hemoglobin assessments within the 84-day period immediately up to the Cycle 1 Day 1 date when evaluating the hemoglobin baseline to ensure that subjects with persistent anemia are enrolled.
    - Revised section: Section 4.2
- **Modified protocol criteria related to dose modification (dose delay, dose reductions, and discontinuation) measures to account for elevated white blood counts at the day of dosing**
    - Update to the protocol to include additional white blood count parameters at the day of dosing to guide dosing decisions. In addition to the ≥ 3 x baseline and $\geq 30 \times 10^9$/L white blood count parameters, a white blood count of $\geq 120 \times 10^9$/L would also result in a dose delay to account for subjects with an elevated white blood count at baseline.
    - Revised section: Section 7.3.2 (Table 5)

This amendment also includes several other minor clarifications and corrections:

- **Administrative change in the Celgene Therapeutic Area Head signature**: required signature has been updated from [redacted] to [redacted].
- **Administrative change to Section 1.3.2:** number of patients and affiliated percentages have been provided for the response rates for the luspatercept Phase 2 clinical studies.
- **Administrative change to Section 4.2**: most recent local bone marrow biopsy report should confirm diagnosis of myeloproliferative neoplasm-associated myelofibrosis according to the World Health Organization 2016 criteria (Arber, 2016).
- [redacted]
- **Clarification regarding implementation of MPN-SAF TSS questionnaire**: as the MPN-SAF TSS questionnaire has been confirmed over the MPN-SAF v4, language in the protocol has been updated to reflect this.

- **Removal of posttransfusion hemoglobin collection**: as we are no longer collecting this information for the study, all references to posttransfusion hemoglobin collection in the protocol have been removed.
- **Clarification to assessments required prior to luspatercept administration**: white blood counts and blood myeloblast percentage, in addition to hemoglobin and blood pressure, must be assessed prior to luspatercept dosing. This change has been reflected in the protocol.
- **Clarification to secondary endpoint (frequency of RBC transfusions)**: time duration has been updated from 4 weeks to 28 days to remain consistent with eligibility average of RBC transfusions.
- Other additional administrative changes (ie, spelling, grammatical error corrections, etc.) were also made throughout the document.