DISCLOSURE

REDACTED PROTOCOL AMENDMENT 2

ACE-536-MDS-001

A PHASE 3, DOUBLE-BLIND, RANDOMIZED STUDY TO COMPARE THE EFFICACY AND SAFETY OF LUSPATERCEPT (ACE-536) VERSUS PLACEBO FOR THE TREATMENT OF ANEMIA DUE TO IPSS-R VERY LOW, LOW, OR INTERMEDIATE RISK MYELODYSPLASTIC SYNDROMES IN SUBJECTS WITH RING SIDEROBLASTS WHO REQUIRE RED BLOOD CELL TRANSFUSIONS

The "MEDALIST" Trial

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A PHASE 3, DOUBLE-BLIND, RANDOMIZED STUDY TO COMPARE THE EFFICACY AND SAFETY OF LUSPATERCEPT (ACE-536) VERSUS PLACEBO FOR THE TREATMENT OF ANEMIA DUE TO IPSS-R VERY LOW, LOW, OR INTERMEDIATE RISK MYELODYSPLASTIC SYNDROMES IN SUBJECTS WITH RING SIDEROBLASTS WHO REQUIRE RED BLOOD CELL TRANSFUSIONS

The "MEDALIST" Trial

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PROTOCOL SUMMARY

Study Title

A Phase 3, Double-blind, Randomized Study to Compare the Efficacy and Safety of Luspatercept (ACE-536) Versus Placebo for the Treatment of Anemia Due to IPSS-R Very Low, Low, or Intermediate Risk Myelodysplastic Syndromes in Subjects with Ring Sideroblasts Who Require Red Blood Cell Transfusions

Indication

Treatment of anemia due to very low, low, or intermediate risk myelodysplastic syndromes (MDS) according to the revised International Prognostic Scoring System (IPSS-R) in subjects with ring sideroblasts who require red blood cell (RBC) transfusions

Objectives

The primary objective is:

- To evaluate RBC transfusion independence (RBC-TI) of luspatercept compared with placebo for the treatment of anemia due to IPSS-R very low, low, or intermediate risk MDS in subjects with ring sideroblasts who require RBC transfusions

The secondary objectives are:

- To assess the safety and tolerability of luspatercept compared with placebo
- To evaluate the effect of luspatercept on reduction in RBC transfusions, increase in hemoglobin, duration of RBC-TI, improvement in health-related quality of life (HRQoL) (ie, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire [EORTC QLQ-C30]), increase in neutrophils, increase in platelets, decrease in serum ferritin, decrease in iron chelation therapy use, and time to RBC-TI compared with placebo
- To evaluate population pharmacokinetics and exposure-response relationships for luspatercept in MDS subjects

Study Design

This is a Phase 3, double-blind, randomized, placebo-controlled, multicenter study to determine the efficacy and safety of luspatercept (ACE-536) versus placebo for the treatment of anemia due to IPSS-R very low, low, or intermediate risk MDS in subjects with ring sideroblasts who require RBC transfusions.

The study is divided into the Screening Period, a double-blind Treatment Period (Primary Phase and Extension Phase) and a Posttreatment Follow-up Period.

The study design is described in detail in Section 3.

The study will be conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practices (GCPs).

Study Treatments

Eligible subjects will be randomized at a 2:1 ratio to either:

- Experimental Arm - Luspatercept (ACE-536): Starting dose of 1.0 mg/kg subcutaneous injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle)

OR

- Control Arm: Placebo (volume equivalent to experimental arm) subcutaneous injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle).

After randomization, no crossover between the treatment arms will be permitted at any point during the study.

Best supportive care may be used in combination with study treatment in both arms when clinically indicated per investigator discretion. See Section 8 for more details.

Stratification will be based on the following factors:

1. RBC Transfusion burden at baseline
   - ≥ 6 RBC units/8 weeks (mean of the two consecutive 8-week periods immediately prior to randomization)
   - < 6 RBC units/8 weeks (mean of the two consecutive 8-week periods immediately prior to randomization)
2. IPSS-R at baseline
   - Very low, low
   - Intermediate

Primary Phase of the Treatment Period: Weeks 1-24

Subjects should receive investigational product (IP) through at least the first 24 calendar weeks unless the subject experiences unacceptable toxicities, withdraws consent, or meets any other discontinuation criteria (Section 11).

Refer to Section 6.2.1 for additional details related to study procedures and assessments during the Primary Phase of the Treatment Period.

MDS Disease Assessment: Week 25 Visit

The Week 25 Visit should be completed 24 calendar weeks after the date of first dose, regardless of dose delays. Because central laboratory results from bone marrow and peripheral blood samples are required as part of the MDS Disease Assessment, a 14-day window is allowed for the Week 25 Visit. Please refer to Section 6.2.2 for details.

In order for subjects to remain on double-blind treatment beyond the first 24 calendar weeks, the following criteria must be confirmed upon the completion of the MDS Disease Assessment by the investigator at the Week 25 Visit:

- Evidence of clinical benefit (eg, decrease in RBC transfusion requirement compared to baseline requirement or hemoglobin increase compared to baseline)

AND

- Absence of disease progression per IWG criteria for altering natural history of MDS (Cheson, 2006; Appendix E).

Based on the outcome of the Week 25 Visit MDS Disease Assessment, subjects will either be discontinued from treatment with IP and enter the Posttreatment Follow-up Period or continue double-blind treatment with IP in the Extension Phase of the Treatment Period.

Refer to Section 6.2.2 for additional details related to procedures/assessments.

Extension Phase of the Treatment Period: After Week 25 Visit

Subjects who meet the criteria for remaining on double-blind treatment with IP in the Extension Phase may continue dosing on Day 1 of each 21-day treatment cycle until the subject experiences unacceptable toxicities, disease progression per IWG criteria for altering natural history of MDS (Cheson, 2006; Appendix E) or withdraws consent, or meets any other discontinuation criteria (Section 11).

MDS Disease Assessment will be repeated by the investigator at Extension Cycle 8, Day 1 and Day 1 of every eighth Extension cycle thereafter (ie, Extension Cycle 8, 16, 24+, or every 24 weeks in the event of dose delays) until the subject is discontinued from IP.

Refer to Section 6.2.3 for additional details related to procedures/assessments.

Posttreatment Follow-up Period:

All subjects discontinued from protocol-prescribed therapy for any reason will be followed for adverse event (AE)/serious adverse event (SAE) reporting for a period of 42 days after the last dose of IP, as well as for SAEs made known to the Investigator at any time thereafter that are suspected of being related to IP, as described in Section 10.

For subjects who do not complete the Primary Treatment Phase or do not participate in the Extension Phase or subjects who terminate the Extension Phase with less than 1-year of ADA monitoring, ADA and PK samples will be collected at End of Treatment (EOT) and then every 12 weeks for up to 1 year from the first dose in the Primary Treatment Phase (please refer to Section 6.4 and Section 6.5).

Transfusion data collection will continue up until 16 weeks from the date of last dose of IP or the EOT Visit (whichever is later).

Continuation of monitoring for progression to AML and other malignancies/pre-malignancies (please refer to Section 10.5 for details) will occur in the Posttreatment Follow-up Period along with collection of information related to subsequent MDS therapies, and overall survival for at least 3 years from the date of last dose of IP unless the subject withdraws consent from the study, dies, or is lost to follow-up.

Refer to Section 6.8 for additional details.

Study Population

The study will enroll approximately 210 subjects with IPSS-R (Greenberg, 2012; Appendix D) very low, low, or intermediate MDS with ring sideroblasts who require RBC transfusions.

Length of Study

The expected duration of the study is approximately 5 years which consists of approximately 2 years of enrollment, approximately 1 additional year of blinded luspatercept or placebo treatment

after the last subject is randomized, and at least an additional 3 years to complete the posttreatment follow-up period.

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary CCI [redacted] analysis, as prespecified in the protocol and/or SAP, whichever is the later date.

The Sponsor may end the trial when all key endpoints and objectives of the study have been analyzed and the availability of a roll-over protocol exists into which any subjects remaining on study may be consented and continue to receive access to luspatercept and/or complete long-term follow-up. Such a protocol would be written for a compound that would not yet be commercially available.

Overview of Key Efficacy Assessments

Efficacy assessments include:

- Transfusions (eg, RBC);
- Hematology (eg, hemoglobin, platelet count, neutrophils);
- Bone marrow aspirate (or biopsy) for assessment of MDS disease (eg, cytomorphology, cytogenetics)

Refer to Section 6 for full list.

Overview of Key Safety Assessments

Safety assessments will include:

- Adverse event reporting;
- Concomitant medication/procedures;
- MDS disease assessment (eg, cytomorphology, cytogenetics) via bone marrow aspirate (or biopsy)
- Hematology (eg, hemoglobin, hematocrit, complete blood count [CBC] with differential);
- Serum Chemistry;
- Urinalysis;
- Electrocardiogram (ECG);
- Vital signs and body weight;
- Physical examinations;
- Eastern Cooperative Oncology Group (ECOG) performance status;

Refer to Section 6 for full list.

Statistical Methods

A total sample size of 210 (140 in experimental arm [luspatercept (ACE-536)], 70 in control arm [placebo]) will have 90% power to detect the difference between a response rate of 0.30 in the

experimental arm (luspatercept [ACE-536]) and a response rate of 0.10 in the control arm (placebo). The sample size calculation is based on one-sided alpha of 0.025, test statistics on difference of proportions using pooled estimate of variance and 10% dropout rate.

The primary efficacy analysis will be the comparison of the response rates in the two treatment arms in the intent-to-treat (ITT) population. The primary efficacy endpoint of transfusion independent response is defined as the absence of any RBC transfusion during any consecutive 56 day period during the Primary Phase of the Treatment Period.

The Cochran–Mantel–Haenszel (CMH) test will be used to compare the response rates from treatment group and control group with randomization factors as strata. Kaplan–Meier methods will be used to characterize the duration of response and survival.

The primary efficacy endpoint will be tested first at the one-sided 0.025 significance level. If superiority of luspatercept is demonstrated for the primary efficacy endpoint, then the key secondary endpoint will be tested at a one-sided 0.025 significance level. The key secondary endpoint, proportion of subjects achieving RBC-TI with duration ≥ 12 weeks, will be tested in the same manner as primary efficacy endpoint using the CMH test.

The analyses for the key secondary endpoint will be based on the ITT population. In order to perform hypothesis testing on multiple endpoints while controlling the overall Type I error rate, a sequential testing approach will be employed where the order of the endpoints to be tested are prespecified.

An interim analysis to assess futility will be performed when approximately 105 subjects have completed the Primary Phase of the Treatment Period (first 24 weeks of double-blind treatment) or discontinued before reaching 24 weeks of double-blind treatment (50% information for primary endpoint).

Conditional power for the primary endpoint will be calculated assuming the observed trend continues for the rest of the data. If it is 10% or less, with confirmative data for secondary and other efficacy endpoints, the Data Monitoring Committee (DMC) may recommend stopping the study for futility.

There is no plan to claim luspatercept superiority based on interim analysis efficacy results, thus the type one error rate remains at 0.025 one-sided for the final analysis.

The final analysis will be performed when all 210 subjects have completed 48 weeks of treatment or discontinued before 48 weeks.

Additional follow-up analysis for efficacy and safety will be performed when all subjects have been followed for at least 3 years from the last dose of IP.

Refer to Section 9 for additional details.

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1. INTRODUCTION

1.1. Disease Background

Anemia is the predominant cytopenia observed in adult myelodysplastic syndrome (MDS) and is present in approximately 85% of MDS patients at the time of diagnosis (Noel, 1992). Anemia in MDS can range in severity from mild (asymptomatic) to severe, requiring regular RBC transfusion support. Of the approximately 80% to 90% of patients with MDS who develop anemia, 40% become transfusion dependent (TD) (Zeidan, 2013).

Lower hemoglobin (Hgb) levels and red blood cell (RBC) transfusion-dependence have been associated with inferior cardiovascular outcomes and increased mortality in patients with MDS, representing a strong rationale for aggressive management of anemia in MDS (Zeidan, 2013). In addition, long-term RBC transfusion dependence has other clinical and economic consequences, including a potentially negative impact on health-related quality of life (HRQoL), iron overload, and its associated complications, immune-related disorders, and increased risk of infections (Hellstrom-Lindberg, 2003; Jansen, 2003; Thomas, 2007). Therefore, a therapeutic option that would achieve transfusion independence in patients with International Prognostic Scoring System-Revised (IPSS-R) lower-risk MDS for a sustained period of time is an important unmet medical need.

Myelodysplastic syndromes are a heterogeneous group of clonal disorders of hematopoietic stem cells characterized by ineffective hematopoiesis that manifest clinically as anemia, neutropenia, and/or thrombocytopenia of variable severity; these often result in RBC- transfusion dependent (TD) anemia, increased risk of infection, and/or hemorrhage, as well as a potential to progress to acute myeloid leukemia (AML) (Adès, 2014; Visconte, 2014; Zeidan, 2013; Brunning, 2008; Fenaux, 2009; Steensma, 2013; Catenacci, 2005).

For most patients with MDS, anemia and associated transfusion dependency are the most prominent clinical problems and the main determinants of quality-of-life (QoL) (Balducci, 2010; Chan, 2014; Kao, 2008; Malcovati, 2005; Platzbecker, 2012; Hellström-Lindberg, 2013).

1.1.1. Staging and Prognostic Factors

1.1.1.1. Revised International Prognostic Scoring System (IPSS-R) for MDS

Patients with MDS can be categorized into 1 of 4 risk groups according to the IPSS (low, intermediate [Int]-1, Int-2, and high) based on cytogenetics, number of peripheral blood cell lineages affected by cytopenia, and bone marrow (BM) blast percentages obtained at diagnosis. The 4 risk groups showed significantly different risk of progression to AML and overall survival (OS) (Greenberg, 1997). The median survival rate is 5.7 years for patients with low risk MDS is as short as 0.4 years for high-risk MDS.

While providing insight into the prognostic significance of baseline variables such as percent bone marrow blasts and cytogenetics, one of the limitations of the International Prognostic Scoring System (IPSS) (Greenberg, 1997) is that it underestimates the impact of cytopenias on prognosis for patients with lower-risk disease. The IPSS also underestimates the impact that RBC transfusion dependency has on overall survival and does not adequately assess the impact of cytogenetic changes (Germing, 2012).

A recent revision of the IPSS (the IPSS-R) provides more discriminatory risk factor assessment than the original IPSS for evaluating clinical outcomes (survival duration and time to AML evolution) for MDS patients (Greenberg, 2012). Bone marrow cytogenetics, bone marrow blast percentage, and cytopenias remain the basis of the IPSS-R, but with further refinement of these categories (Table 1). Cytogenetic prognostic subgroups were split into 5 rather than 3 categories with the addition of new and specific classifications of a number of less common cytogenetic subsets. Low bone marrow blast percentage was split into 2 categories (ie, ≤ 2% versus > 2% to < 5%), and the depth of cytopenias was defined using precise cutpoints. The application of additional refinements and prognostic variables in IPSS-R were intended to provide more meaningful classifications upon which to assess clinical outcome in MDS patients.

Table 1: Revised International Prognostic Scoring System for Myelodysplastic Syndromes (IPSS-R): Prognostic Score Values

Prognostic Variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	--	Good	--	Intermediate	Poor	Very poor
BM blast %	≤ 2	--	> 2% to < 5%	--	5% to 10%	> 10%	--
Hemoglobin	≥10	--	8 to <10	<8	--	--	--
Platelets	≥100	50 to <100	<50	--	--	--	--
ANC	≥0.8	<0.8	--	--	--	--	--

Source: Greenberg, 2012.

1.1.1.2. Ring Sideroblasts

Early investigators defined ring sideroblasts as having iron granules in a perinuclear distribution surrounding the entire nucleus. The definition of a ring sideroblast proposed by the International Working Group on Morphology of Myelodysplastic Syndromes (IWGMDS) (an erythroblast with at least 5 siderotic granules covering at least a third of the circumference of the nucleus) has been incorporated into the 2008 World Health Organization (WHO) classification of Tumors of Hematopoietic and Lymphoid Tissues and for the definition of refractory anemia with ring sideroblasts (RARS), the required number of ring sideroblasts is ≥ 15% (Mufti, 2008). The 2016 update to the WHO criteria further expanded on this definition of ring sideroblastic disease by also including cases with ring sideroblasts ≥ 5% if *SF3B1* mutation is present (Arber, 2016).

It is estimated that approximately 30% of all MDS patients have > 15% of bone marrow erythroid precursors being ring sideroblasts. Recently, spliceosome mutations were shown to be prevalent in MDS with ring sideroblasts, particularly mutations involving splicing factor 3B subunit 1 (SF3B1). RNA splicing is the most commonly mutated pathway in MDS, and there is strong evidence that mutations in splicing factors occur early in disease evolution. These mutations play a major role in determining the clinical features of the disease, with differences in morphological features seen on bone marrow biopsy and in leukemia-free survival (Papaemmanuil, 2013).

Subjects with RS with splicing factor mutations have been shown to have ineffective erythropoiesis, possibly related to defects in iron utilization (Conte, 2015; del Rey, 2015; Dolatshad, 2015). Recently, a heterozygous conditional knock-in mouse model has been developed with the most frequent K700E mutation of SF3B1 (Obeng, 2014). Ineffective

erythropoiesis developed in these mice, with a block in the maturation of late-stage erythroid precursors.

1.1.2. Current Treatment Options for Lower Risk MDS

In lower risk MDS, the risk of AML progression is less and survival is longer, with approximately one-half of these elderly patients dying from a cause other than the consequences of MDS or AML (Greenberg, 2012). In those patients, the main priority is generally the treatment of cytopenias, primarily anemia (usually the predominant cytopenia), and the improvement in quality of life (Fenaux, 2013). A clinically prominent challenge in patients with lower-risk MDS is the management of preexisting conditions aggravated by anemia, such as cardiovascular diseases.

The standard of care for cytopenias remains supportive treatment with erythropoiesis-stimulating agents (ESAs) such as epoetin alfa or darbepoetin, administration of RBC and/or platelet transfusions, infection prophylaxis and/or treatment and use of hematopoietic growth factors such as granulocyte colony-stimulating factor (G-CSF) and nutritional supplements when needed (Greenberg, 1997; Casadevall, 2004).

1.1.2.1. Revlimid

Revlimid® (lenalidomide) is approved in the United States (US) for the treatment of patients with transfusion-dependent anemia due to low- or Int-1-risk MDS associated with a del (5q) abnormality with or without additional cytogenetic abnormalities. This is the standard of care (in those countries where it is approved) for the small proportion of patients with lower risk del-5q MDS. In this population, lenalidomide led to transfusion independence for 67% of the patient population and a median duration of transfusion independence of 44 weeks.

1.1.2.2. Erythropoiesis Stimulating Agents (ESAs) Therapy

Erythropoiesis stimulating agents (ie, recombinant erythropoietin [EPO] or darbepoetin [DAR]), although not currently approved in most countries, are commonly used for the treatment of anemia in lower-risk MDS without del(5q) cytogenetic abnormality. Major favorable prognostic factors for response to ESAs are low or no RBC transfusion requirement (< 2 U per month) and baseline serum EPO level < 500 U/L. (Fenaux, 2013) Responses to ESAs are best in subjects with low endogenous levels (eg < 500 U/L) of erythropoietin (EPO), normal blast counts and lower IPSS/WHO Prognostic Scoring System (WPSS) scores (Hellström-Lindberg, 2003; Santini, 2011).

More recently, the European ESA Scoring System was developed, using a serum EPO level of ≤ 200 U/L as a prognostic factor for ESA responsiveness (Santini, 2013). Approximately 70% of the relapses of anemia after initial response to ESAs are not associated with progression to higher-risk MDS but simply to loss of sensitivity of erythroid progenitors to ESAs. Second-line treatments in those patients may be different from those required in patients showing concomitant progression to higher-risk MDS (Fenaux, 2013).

1.1.2.3. Red Blood Cell Transfusions

In many patients with lower-risk MDS, anemia will eventually become resistant to all available drug treatments, even in the absence of evolution to higher-risk MDS, and will require repeated

RBC transfusions. Frequent RBC transfusions are associated with chronic anemia (ie, average hemoglobin levels < 10g/dL) which can lead to increased morbidity, especially as a result of cardiac failure, falls, fatigue and lower quality of life (Fenaux, 2013). The development of transfusion dependency significantly worsens the survival of patients with MDS (Malcovati, 2005). Long-term RBC transfusion dependence has several detrimental clinical effects including iron overload, economic consequences, and a negative impact on patients' QoL (Hellström-Lindberg, 2003; Jansen, 2003; Thomas, 2007).

1.1.2.3.1. Iron Chelation Therapy (ICT)

Clinically significant iron overload associated with decreased cardiac function is often observed in patients who have received 100 or more RBC units (Adès, 2014). Therefore, iron chelation may be required in patients receiving frequent transfusions in order to avoid iron-related cardiac, hepatic and endocrine toxicities. Deferoxamine (intramuscular/subcutaneous/intravenous) or deferasirox (oral) have been used in MDS patients as a treatment for iron overload (Messa, 2010). However, deferasirox is frequently associated with gastrointestinal side effects and cannot be used in patients with renal function impairment (Fenaux, 2013).

Retrospective studies suggest that when serum ferritin levels exceed 1000 µg/L, in the absence of inflammatory or other causes for ferritin elevation, transfusion burden often exceeds the body's capacity to maintain iron bound to transferrin (Dreyfus, 2008). Patients with lower-risk World Health Organization (WHO) morphologic categories of refractory anemia (RA) or refractory anemia and with ringed sideroblasts (RARS) who had ferritin levels above 1,000 µg/L experienced more cardiac complications and had a reduced overall survival (hazard ratio [HR] = 1.51; $p < 0.001$) (List, 2010).

Sanz, et al reported that transfusion dependence and iron overload are independent risk factors for overall survival and leukemic progression (Sanz, 2008). In their review of 2241 patients whose complete transfusion history was available, 835 were transfusion dependent at the time of diagnosis, 526 became transfusion dependent during follow-up, and 880 remained transfusion independent (Sanz, 2008). Median survival was significantly shorter in patients who were transfusion dependent at diagnosis (19 months) compared with 60 months for those who later became transfusion dependent and 96 months for those who remained transfusion free ($p < 0.0001$). Independent prognostic factors associated with OS in a multivariate analysis included iron overload (HR = 52.4; $p < 0.0001$) and transfusion dependency (HR = 8.8; $p < 0.0001$) (Sanz, 2008).

Hence, therapeutic options that would achieve transfusion independence (TI) or reduce transfusion intensity in patients with lower-risk MDS for a significant amount of time would be highly desirable in terms of reduced requirements for iron chelation therapy.

1.1.2.4. Hypomethylating Agents

There are 2 hypomethylating agents currently approved for the treatment of various subtypes of MDS, azacitidine and decitabine.

Vidaza® (azacitidine for injection) is indicated for treatment of patients with the following French-American-British (FAB) classification subtypes of MDS (Appendix C) in the US: RA or RARS (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in

transformation (RAEB-T), and chronic myelomonocytic leukemia (CMML), but it is not routinely utilized in the lower risk disease setting.

Azacitidine is approved in the European Union (EU) for the treatment of adult patients who are not eligible for hematopoietic stem cell transplantation with IPSS Int-2 or High risk MDS, CMML with 10% to 29% marrow blasts without myeloproliferative disorder and AML with 20% to 30% blasts and multi-lineage dysplasia, according to WHO classification. In addition to the US and EU, azacitidine is currently approved in 30 other countries, including Canada, Switzerland, Australia and Japan, for the treatment of MDS (approvals for specific subtypes vary by country).

Dacogen® (decitabine for injection), another hypomethylating agent, is approved in the US for treatment of patients with MDS, including previously treated and untreated, de novo and secondary MDS of all FAB subtypes (RA, RARS, RAEB, RAEB-T, and CMML) and Int-1, Int-2, and high-risk IPSS groups.

While azacitidine and decitabine are approved for treatment of various subtypes of MDS including Int-1 risk MDS in some countries, these agents are not uniformly administered as standard of care. This is partly because clinicians are reluctant to treat asymptomatic or minimally symptomatic lower-risk MDS patients, especially those who are not yet transfusion-dependent. In addition, extensive data for these agents in the lower-risk MDS patient population are not currently available.

1.2. Compound Background

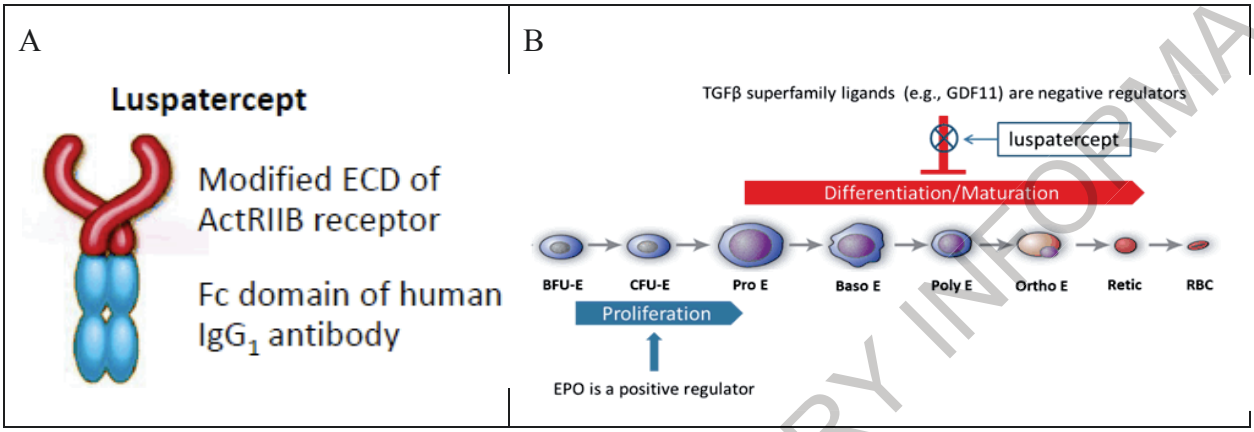
Luspatercept (ACE-536) is a recombinant fusion protein consisting of a modified form of the extracellular domain (ECD) of the human activin receptor type IIB (ActRIIB) linked to the human IgG1 Fc domain. The ActRIIB receptor and its ligands are members of the transforming growth factor (TGF)-β superfamily, a group of proteins involved in the development, differentiation, and/or maturation of various organ systems. 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 (Massagué, 1998). Thus, observations from pharmacology studies of luspatercept or its murine analog RAP-536 in animal models provide significant insight into the potential of luspatercept to treat human disease.

Members of the TGF-β family have been shown to play a role as negative regulators of red blood cell (RBC) development (erythropoiesis). In nonclinical experiments, luspatercept has been shown to bind with high affinity to some TGF-β ligands (eg, growth differentiation factor [GDF]8, GDF11, bone morphogenetic protein [BMP]6 and activin B) [redacted]. The emerging body of evidence on luspatercept suggests that its mechanism of action is completely independent from that of EPO, and involves stimulation of the later, maturation phase of erythroblast differentiation and maturation in the bone marrow (Figure 1).

Across the Phase 2 program, responses to luspatercept treatment were observed in the majority of subjects at expected pharmacologic dose levels of approximately 0.75 up to 1.75 mg/kg, administered once every 3 weeks. In particular, as described in more detail in the following sections, luspatercept treatment led to hematologic improvement in erythroid response (HI-E) in a substantial proportion of MDS subjects within the initial 3 months of treatment.

The preliminary Phase 2 data suggest luspatercept is likely to attenuate ineffective erythropoiesis and correct the anemia that characterizes MDS and could provide significant clinical benefit to patients by improving hemoglobin levels and reducing the need for regular RBC transfusions. The impact on these endpoints, as supported by the preliminary clinical evidence presented here, suggest that luspatercept may provide a sustained clinical benefit (eg, RBC transfusion independence) for the treatment of anemia in patients with IPSS lower risk MDS with ≥15% ring sideroblasts.

Figure 1: Luspatercept Schematic Representation and Mechanism of Action



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

1.2.1. 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 the investigational product (IP). The most recent version of the luspatercept IB should be reviewed prior to initiating the study.

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CCI

[redacted]

1.2.2. Summary of Clinical Experience

One Phase 1 trial with healthy postmenopausal women has been completed. Two Phase 2 studies with MDS patients are ongoing:

- Study A536-03: A Phase 2, Open-label, Ascending Dose Study of ACE-536 for the Treatment of Anemia in Patients with Low or Intermediate-1 Risk Myelodysplastic Syndromes (MDS)
- Study A536-05: An Open-label Extension Study to Evaluate the Long-Term Effects of ACE-536 for the Treatment of Anemia in Patients with Low or Intermediate-1 Risk Myelodysplastic Syndromes (MDS)

Preliminary results from ongoing Phase 2 studies of luspatercept in patients with MDS indicate that the dose levels up to 1.75 mg/kg have been generally safe and well-tolerated to date, with no dose-limiting toxicities observed as of 07 July 2015 in either study. Efficacy parameters are still under evaluation.

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

1.2.2.1. Potential Risks of Human Use

Increases in hematologic parameters (RBC, hemoglobin, 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 considered probably or possibly related to study drug that were reported in at least 5% of subjects in the Phase 1 study in healthy volunteers included injection site hemorrhage and injection site macule. Adverse events reported in at least 10% of patients regardless of causality in the ongoing Phase 2 studies in MDS and β-thalassemia included bone pain, headache, asthenia, myalgia, arthralgia, pyrexia, musculoskeletal pain, oropharyngeal pain, diarrhea, nasopharyngitis, and cough. As with all biologics, there is the potential for antidrug antibodies (ADA) that can be associated with increased drug clearance and hypersensitivity reactions. CCI [redacted]

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 use effective methods of contraception during the Treatment Period and up to 12 weeks from the last dose of IP. Females of childbearing potential (FCBP) must agree to pregnancy testing prior to enrollment and prior to each treatment cycle for the duration of the Treatment Period.

CCI [redacted] The occurrence of new malignancies, pre-malignant or precancerous lesions will be monitored as events of interest and will be included as part of the assessment of adverse events regardless of causality, throughout the course of the study. In addition, participating subjects should be followed long term as specified in the protocol for evidence of tumor formation. CCI [redacted] Safety effects will be monitored closely through adverse event (AE) reporting, clinical laboratory tests, vital signs, physical examinations, and ongoing review of unblinded data by an external Data Monitoring Committee (DMC).

Please refer to the most current version of the Investigator's Brochure and subsequent safety correspondence for additional information regarding findings from toxicology and clinical studies.

The most recent version of the luspatercept IB should be reviewed prior to initiating the study.

1.2.2.2. Overall Benefit Risk Assessment

Current available information continues to support an acceptable benefit-risk profile for luspatercept when used in accordance with the precautions, dosing, and safety monitoring outlined in the study protocol and the routine pharmacovigilance practices.

1.3. Rationale

1.3.1. Study Rationale and Purpose

IPSS-R classification of MDS (very low, low, or intermediate risk)

The IPSS-R classification has been chosen to define the Phase 3 patient population because as discussed in Section 1.1.1.1, the IPSS-R classification provides a more discriminatory risk factor assessment than the original IPSS (Greenberg, 1997) for evaluating clinical outcomes (survival duration and time to progression of AML) for MDS subjects (Greenberg, 2012). The Phase 3 patient population has been defined as having IPSS-R very low, low or, intermediate risk MDS.

This patient population represents a subset of subjects with IPSS-R lower-risk MDS who have anemia and have limited treatment options in managing the anemia. Subjects in the lower risk groups often become dependent on frequent RBC transfusions, which leads to decreased health-related quality of life (HRQoL) and increased morbidity and mortality (Hellström-Lindberg, 2003; Malcovati, 2005). Therefore, the clinically prominent challenge in subjects with lower risk MDS is the management and treatment of cytopenias, mainly anemia (the predominant cytopenia), and the improvement in QoL. The recent IPSS-R classified 39% of subjects with RARS as very low risk, 56% as low risk, and 5% as intermediate risk. The IPSS-R assigns 34% of subjects with refractory cytopenia with multilineage dysplasia with ringed sideroblasts (RCMD-RS) to the very low risk, 50% to the low, and 16% to the intermediate risk groups respectively (Malcovati, 2013).

Ring sideroblasts ≥ 15% of erythroid precursors in bone marrow (or ≥ 5%, if SF3B1 mutation is present)

According to WHO criteria, refractory anemia with ring sideroblasts (RARS) is characterized by isolated anemia, erythroid dysplasia only, less than 5% blasts and ≥ 15% ring sideroblasts in the bone marrow. The 2016 update to the WHO criteria further expanded on this definition of ring sideroblastic disease by also including cases with ring sideroblasts ≥ 5% if *SF3B1* mutation is present (Arber, 2016). Anemia is macrocytic in the large majority of these subjects, while reticulocyte count is in the normal range, reflecting an inappropriately low RBC production leading to anemia. The natural history of RARS is characterized by an initial phase of erythroid hyperplasia and ineffective erythropoiesis (Malcovati, 2013).

Two recent phase 3 randomized controlled studies evaluated the use of erythropoiesis-stimulating agents (ESAs) versus placebo. In these studies, subjects with lower-risk MDS without ring sideroblasts had a higher probability of response, compared to those with ring sideroblasts. In subjects with RARS, responses were less frequent and not significantly different between ESAs and placebo (Hellström-Lindberg, 2013). The mode of action of ESAs on early erythroid progenitors would not be expected to benefit subjects with defects in the later stages of erythropoiesis when erythropoietin receptors are absent (Hattangadi, 2011; Broudy, 1991).

Study A536-03 is a Phase 2, open-label, ascending dose study of luspatercept for the treatment of anemia in patients with low or intermediate-1 risk MDS.

In patients (n = 49) receiving 0.75 to 1.75 mg/kg, 51% of patients responded per International Working Group (IWG) hematologic improvement, erythroid response (HI-E) hemoglobin increase ≥ 1.5 g/dL for low transfusion burden patients or reduction of ≥ 4 RBC units or ≥ 50%

of units of RBCs transfused/8 weeks for high transfusion burden patients). Higher response rates were observed in ring sideroblast positive patients. Patients with splicing factor mutations present (primarily SF3B1) had a 58% response rate. Of the patients in the higher-dose group who received RBC transfusions prior to luspatercept treatment (range 2 to 18 units/8 weeks), 14 out of 40 (35%) patients were transfusion-free for ≥ 8 weeks during the 12-week treatment period. Additional information is summarized in the current version of the luspatercept IB.

Refractory, intolerant, or ineligible (endogenous serum erythropoietin level > 200 U/L) for ESAs.

Erythropoiesis-stimulating agents (ESAs) are often used in many newly diagnosed IPSS-R lower to intermediate (very low, low, intermediate) risk MDS subjects with early onset anemia, as many subjects respond well to ESAs. To be eligible for the ACE-536-MDS-001 Phase 3 study, subjects must be refractory to, intolerant, or ineligible for ESAs.

Treatment guidelines vary in regards to defining an adequate course of ESA treatment. The National Comprehensive Cancer Network (NCCN) guidelines (NCCN 2015 guidelines) recommends dose levels starting at 40,000 IU administered 1-3 times weekly for a duration 6-8 weeks prior to assessment of hematological improvement. The European Society for Medical Oncology (ESMO) guidelines recommend dose levels starting at 30,000 IU weekly (Fenaux, 2014). However, a significant proportion of these subjects will be resistant to ESAs as monotherapy or experience short-lasting responses. (Hellström-Lindberg, 2013). Studies have shown that elevated endogenous serum erythropoietin levels and RBC transfusion requirements are negatively correlated with response to ESAs. (Hellström-Lindberg, 2013).

Meta-analyses of clinical trials with thousands of treated subjects have led to the following conclusions:

- RARS subjects with or without a need for transfusion but with a serum EPO level > 200 U/L had a response rate of 0% to ESAs (Hellström-Lindberg, 1995; Santini, 2011).
- MDS subjects without a need for transfusion, with a serum EPO level < 200 U/L, and a diagnosis other than RCMD-RS have a higher response rate to ESAs (Santini, 2011).

In study A536-03, high response rates were also seen in subjects in the higher-dose group with EPO levels < 200U/L (68%) and 200-500 U/L (36%).

1.3.2. Rationale for the Study Design

ACE-536-MDS-001 is a phase-3 multicenter randomized double-blind placebo controlled study. The primary objective is to evaluate RBC transfusion independence (RBC-TI) in 2 treatment arms (luspatercept versus placebo) for treatment of anemia due to very low, low, or intermediate risk (IPSS-R) MDS in subjects with ring sideroblasts who require RBC transfusions. Secondary objectives include evaluation of efficacy (eg, hematological improvement, HRQoL, changes in serum ferritin and iron chelation therapy use) as well as safety and tolerability.

The multicenter nature of the study provides assurance that the results are likely to have general applicability. The design of this study (ie, randomized, double-blinded, placebo-controlled, and parallel-group) will eliminate bias in assignment of the IP or in data interpretation.

A 2:1 randomization will be used as this is an orphan disease with a limited number of subjects available. Subjects will be randomized to receive luspatercept or placebo at a 2:1 ratio. A 2:1

randomization scheme would enrich the number of participants exposed to the active treatment group (Dumville, 2006).

In order to mitigate the potential bias should subjects in the control arm drop out early due to the lack of a quick response, the primary efficacy analysis will be the proportion of subjects achieving RBC-TI with a duration ≥ 8 weeks measured at 24 weeks.

After completion of the MDS Disease Assessment by the investigator at the Week 25 Visit, subjects who exhibit clinical benefit with no evidence of disease progression per IWG criteria for altering natural history of MDS (Cheson, 2006; Appendix E) will continue double-blind treatment. The proportion of subjects achieving RBC-TI with a duration ≥ 8 weeks at 48 weeks will be assessed as a secondary endpoint to capture potential late responders. In addition, the proportion of subjects achieving RBC-TI with a duration ≥ 12 weeks will be assessed as a secondary endpoint, representing extended duration of benefit achieved with therapy.

The study will be stratified by RBC transfusion burden and IPSS-R risk category (Greenberg, 2012) at baseline. These factors are discussed below.

RBC transfusion burden at baseline

The primary endpoint for the study is the proportion of subjects who are RBC transfusion free over any consecutive 56-day period. In the phase 2 studies, achieving transfusion independence (TI) was shown to be dependent on baseline transfusion burden, Subjects who receive an average of ≥ 6 RBC units during each of two consecutive 8-week periods prior to randomization will be less likely to become transfusion independent than those subjects who receive < 6 RBC units/8 weeks. Thus, stratification by RBC transfusion burden is considered useful due to its likely effect on the primary endpoint.

IPSS-R classification at baseline: Very low and low versus intermediate

Among the lower risk categories for IPSS-R, mortality risk is distinctively worse for intermediate risk than for very low and low risk. The intermediate classification may also be indicative of higher risk of progression to AML (Greenberg, 2012). Thus in consideration of the long-term safety analyses, stratification for IPSS-R will be used.

1.3.3. Rationale for Dose, Schedule and Regimen Selection

The starting dose level of 1.0 mg/kg and the maximum dose level of 1.75 mg/kg are based on clinical data from the ongoing Phase 2 A536-03 and A536-05 studies in MDS. Preliminary results indicate that the dose levels up to 1.75 mg/kg have been generally safe and well-tolerated to date. A higher response rate, including HI-E and RBC-TI, was observed in the higher dose groups (0.75-to 1.75 mg/kg subcutaneous every 3 weeks [Q3W]) compared to the lower dose groups (0.125-0.5 mg/kg subcutaneous Q3W).

Selection of the dosing schedule (every 3 weeks, Q3W) was based on the duration of the luspatercept responses as well as pharmacokinetic parameters for luspatercept in MDS patients. The transfusion-reducing effect of luspatercept relies on its ability to increase hemoglobin; in the Phase 2 studies, the increase in hemoglobin was well maintained with the Q3W dosing schedule.

Additional information regarding these clinical studies is summarized in the current version of the luspatercept IB.

1.3.4. Rationale for Choice of Placebo Comparator

Treatment algorithms such as those issued by NCCN (NCCN 2015 guidelines) suggest that lower risk MDS patients with symptomatic anemia be treated with ESAs ± G-CSF if the serum EPO level is ≤ 500 U/L. Those without a response or who have a higher EPO level and either have a poor probability to respond to immune suppressive therapy, or who are intolerant to or fail immune suppressive therapy, have three options proposed: hypomethylating agents (HMAs), lenalidomide, or entry on a clinical trial.

Entry into a clinical trial of luspatercept rather than use of HMAs or lenalidomide may be preferred in order to avoid the risk of Grade 3-4 cytopenias, which occur with both azacitidine and decitabine. Since lower risk MDS patients with ring sideroblasts and low blast counts (< 5%) are unlikely to progress to AML, the predominant therapeutic objective is the management of anemia and the prevention of transfusion related complications. Since this might mean 5 or more years of primarily chronic anemia management before disease progression, the benefit/risk of early intervention with HMAs is questionable. Subjects who fail to benefit from study drug in this clinical trial may subsequently receive HMAs or lenalidomide.

The primary endpoint for this study, RBC-TI, is better assessed against the natural history of the disease (ie, in subjects previously untreated with disease modifying agents). Based on these considerations, placebo is the appropriate comparator for the proposed Phase 3 study. Standard of care for the management of acute anemia (ie, RBC transfusions) will be applied to both treatment groups.

CCI [redacted]

CCI [redacted]

SF3B1 and other genes involved in RNA splicing such as SRSF2, U2AF1 and ZRSR2 have been observed in MDS patients (Pellagatti, 2015). SF3B1 mutations were found in greater than 70% of RS+ patients (Papaemmanuil, 2011; Malcovati, 2011) and thought to be causally related to chromosome stability, DNA repair and gene regulation that may result in anemia and thrombocytopenia (Visconte, 2014; and Pellagatti, 2015).

CCI [redacted]

2. STUDY OBJECTIVES AND ENDPOINTS

Table 2: Study Objectives

Primary Objective
The primary objective of the study is to evaluate RBC transfusion independence (RBC-TI) of luspatercept compared with placebo for the treatment of anemia due to IPSS-R very low, low, or intermediate risk MDS in subjects with ring sideroblasts who require red blood cell (RBC) transfusions.
Secondary Objectives
The secondary objectives are: • To assess the safety and tolerability of luspatercept compared with placebo • To evaluate the effect of luspatercept on reduction in RBC transfusions, increase in hemoglobin, duration of RBC-TI, improvement in health-related quality of life (HRQoL) (ie, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire [EORTC QLQ-C30]), increase in neutrophils, increase in platelets, decrease in serum ferritin, decrease in iron chelation therapy use, and time to RBC-TI compared with placebo • To evaluate population pharmacokinetics and exposure-response relationships for luspatercept in MDS subjects
CCI [redacted]
[redacted]

Table 3: Study Endpoints

Endpoint	Name	Description	Timeframe
Primary	Red Blood Cell Transfusion Independence (RBC-TI) ≥ 8 weeks	Proportion of subjects who are RBC transfusion free over any consecutive 56-day period	Week 1 through Week 24
Secondary	RBC-TI ≥ 12 weeks	Proportion of subjects who are RBC transfusion free over any consecutive 84-day period	Week 1 through Week 24; Week 1 through Week 48
	RBC-TI ≥ 8 weeks	Proportion of subjects who are RBC transfusion free over any consecutive 56-day period	Week 1 through Week 48
	Reduction in RBC units transfused over 16 weeks	Mean change in total RBC units transfused over a fixed 16-week period	Week 9 through 24; Week 33 through 48
	Modified hematologic improvement - erythroid (mHI-E) per IWG (Cheson, 2006)	Proportion of subjects achieving modified HI-E over any consecutive 56-day period	Week 1 through Week 24; Week 1 through Week 48
	Mean hemoglobin increase ≥ 1.0 g/dL	Proportion of subjects achieving hemoglobin (Hgb) increase from baseline ≥ 1.0 g/dL over any consecutive 56-day period in absence of RBC transfusions	Week 1 through Week 24; Week 1 through Week 48
	Duration of RBC-TI	Maximum duration of RBC transfusion independence for subjects who achieve RBC TI ≥ 8 weeks	Week 1 through Week 24; Week 1 through end of treatment
	Health-related quality of life (HRQoL)	Change in EORTC QLQ-C30 score	Week 1 through Week 48; baseline through end of treatment
	Hematologic improvement - neutrophils (HI-N) per IWG (Cheson, 2006)	Proportion of subjects achieving HI-N over any consecutive 56-day period	Week 1 through Week 24; Week 1 through Week 48
	Hematologic improvement - platelets (HI-P) per IWG (Cheson, 2006)	Proportion of subjects achieving HI-P over any consecutive 56-day period	Week 1 through Week 24; Week 1 through Week 48
	Mean decrease in serum ferritin	Change in serum ferritin.	Week 9 through 24; Week 33 through 48

Table 3: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
	Mean decrease in iron chelation therapy (ICT) use	Change in mean daily dose of ICT	Week 9 through 24; Week 33 through 48
	Time to RBC-TI	Time from first dose to first onset of transfusion independence ≥ 8 weeks	Week 1 through Week 24; Week 1 through Week 48
	Progression to AML	Number and percentage of subjects progressing to AML; time to AML progression	Randomization through at least 3 years post last dose; Week 1 through Week 48
	Overall survival	Time from date of randomization to death due to any cause	Randomization through at least 3 years post last dose; Week 1 through Week 48
	Safety	Type, frequency, severity of AEs and relationship of AEs to luspatercept/placebo	Screening through 42 days post last dose; Week 1 through Week 48
	A population PK model. Exposure-response relationship.	A Population PK model that describes the PK exposure data of luspatercept and associated variability. Exposure-response relationship for the primary efficacy endpoint, AEs of interest, and selected secondary endpoints.	Randomization through 1-year post first dose.
	Anti-drug antibodies (ADA)	Frequency of anti-drug antibodies and effects on efficacy, or safety, or PK	Randomization through 1-year post first dose.

Table 3: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
CCI [redacted]	[redacted]	[redacted]	[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 on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

This is a Phase 3, double-blind, randomized, placebo-controlled, multicenter study to determine the efficacy and safety of luspatercept (ACE-536) versus placebo in subjects with anemia due to IPSS-R very low, low, or intermediate MDS with ring sideroblasts who require RBC transfusions.

The study is divided into the Screening Period, a double-blind Treatment Period (Primary Phase and Extension Phase), and a Posttreatment Follow-up Period. See Figure 2 for more details and refer to Section 6 for full list of study procedures/assessments.

Screening Period

Upon giving written informed consent, subjects enter the Screening Period to determine eligibility. Subject screening procedures are to take place within 5 weeks prior to randomization. During the Screening Period, the subject will undergo safety and other assessments to determine eligibility for the randomized study.

Central review of bone marrow aspirate smear and biopsy, peripheral blood smear, cytogenetics, will be used to confirm MDS diagnosis and WHO classification (Appendix B) and/or FAB classification (Appendix C) and to determine the baseline IPSS-R risk classification (Greenberg, 2012; Appendix D).

Transfusion history must be available for at least the 16 weeks immediately preceding and including the date of randomization. Transfusion data should include the type of transfusion (eg, RBC, platelets), number of units, and date of transfusion. Red blood cell (RBC) cell transfusion data should include the hemoglobin (Hgb) value for which the transfusion was administered (ie, pretransfusion Hgb value).

Refer to Section 6 for full list of study procedures/assessments.

Randomization

Randomization will occur by a central randomization procedure using integrated response technology (IRT). Eligible subjects will be randomized at a 2:1 ratio to either:

- Experimental Arm: Luspatercept (ACE-536): Starting dose of 1.0 mg/kg subcutaneous injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle)

OR

- Control Arm: Placebo (Volume equivalent to experimental arm) subcutaneous injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle)

After randomization, no crossover between the treatment arms will be permitted at any point during the study.

Stratification will be based on the following factors:

- RBC Transfusion burden at baseline
  - ≥ 6 RBC units/8 weeks (mean of the two consecutive 8 weeks periods immediately prior to randomization)
  - < 6 RBC units/8 weeks (mean of the two consecutive 8 weeks periods immediately prior to randomization)
- IPSS-R at baseline
  - Very low, low
  - Intermediate

Refer to Section 6 for additional details.

Primary Phase of the Treatment Period: Weeks 1-24

The first dose of investigational product (IP) should be administered after, but within 3 days of randomization and can be on the same day as randomization. Refer to the IRT manual for additional information on randomization utilizing IRT.

Subjects will receive IP (either luspatercept or matching placebo) on Day 1 of each 21-day treatment cycle.

In both treatment arms, 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, treatment with transfusions, 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.

Subjects should receive IP through at least the first 24 calendar weeks after the date of first dose unless the subject experiences unacceptable toxicities, withdraws consent, or meets any other treatment discontinuation criteria (Section 11.1).

Week 25 Visit: MDS Disease Assessment

The Week 25 Visit should be completed 24 calendar weeks after the date of first dose, regardless of dose delays. As central laboratory results from bone marrow and peripheral blood samples are required as part of the MDS Disease Assessment, a 14 day window is allowed for the Week 25 Visit. Please refer to Section 6.2.2 for more details related to assessments/procedures.

In order for subjects to remain on double-blind treatment beyond the first 24 calendar weeks, the following criteria must be confirmed upon the completion of the MDS Disease Assessment by the investigator at the Week 25 Visit:

- Evidence of clinical benefit (eg, decrease in RBC transfusion requirement compared to baseline requirement or hemoglobin increase compared to baseline)

AND

- Absence of disease progression per IWG criteria for altering natural history of MDS (Cheson, 2006; Appendix E).

Based on the outcome of the Week 25 Visit MDS Disease Assessment, subjects will either be discontinued from treatment with IP and enter the Posttreatment Follow-up Period or continue double-blind treatment with IP in the Extension Phase of the Treatment Period.

Extension Phase of the Treatment Period: After Week 25 Visit

Subjects who meet criteria to remain on double-blind treatment after completion of the Week 25 Visit MDS Disease Assessment may continue dosing on Day 1 of each 21-day treatment cycle in the Extension Phase of the Treatment Period until the subject experiences unacceptable toxicities, disease progression per IWG criteria for altering natural history of MDS (Cheson, 2006; Appendix E), withdraws consent, or meets any other discontinuation criteria (Section 11).

MDS Disease Assessment will be repeated by the investigator at Extension Cycle 8, Day 1 and Day 1 of every eighth Extension Cycle thereafter (ie, Extension Cycle 8, 16, 24+, etc. or every 24 weeks in the event of dose delays) until the subject is discontinued from treatment.

For subjects to continue double-blind treatment in the Extension Phase of the Treatment Period, each MDS Disease Assessment (criteria detailed in Section 6.2.2) should confirm continued clinical benefit and absence of disease progression per IWG criteria for altering natural history of MDS (Cheson, 2006; Appendix E).

Serial measurements of safety and efficacy will continue on scheduled study visits (Day 1 of every treatment cycle) in the Extension Phase of the Treatment Period. Refer to Section 6 for full list of study procedures/assessments.

Best supportive care (BSC) may continue to be used in combination with study treatment when clinically indicated per investigator. See Section 8 for more information on best supportive care/concomitant medications.

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 7.2.1 for dose modification rules and Section 11.2 for discontinuation criteria.

All subjects who have received at least one dose of study treatment should undergo end of treatment (EOT) evaluations when IP is discontinued. The reason for discontinuation will be recorded in the electronic case report form (eCRF) pages and in the source document.

Posttreatment Follow-up Period

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

Transfusion data collection will continue up until 16 weeks from the date of last dose of IP or the End of Treatment Visit (whichever is later).

Females of childbearing potential (FCBPs) will be advised to avoid becoming pregnant during study and for 12 weeks after the last dose of IP. Males will be advised to use a latex condom during any sexual contact with FCBP prior to starting investigational product and continue for 12 weeks following the last dose of IP, even if he has undergone a successful vasectomy. Refer to Section 10.

For subjects who do not complete the Primary Treatment Phase or do not participate in the Extension Phase or subjects who terminate the Extension Phase with less than 1-year of ADA monitoring, ADA and PK samples will be collected at EOT and then every 12 weeks for up to one year from the first dose in the Primary Treatment Phase (please refer to Section 6.4 and Section 6.5).

Long-Term Follow-up: Progression to AML, Other Malignancies/Pre-malignancies, Subsequent MDS Therapies, Overall Survival

For all subjects who receive at least one dose of IP, continuation of monitoring for progression to AML and other malignancies/pre-malignancies (please refer to Section 10.5 for details) will occur in the Posttreatment Follow-up Period along with data collection of subsequent MDS therapies, and overall survival for at least 3 years from the date of last dose of IP unless the subject withdraws consent from the study, dies or is lost to follow-up. Refer to Section 6.1 for additional details.

Data Monitoring Committee (DMC)

An external, independent DMC will be comprised of experts in MDS not involved in the ACE-536-MDS-001 study, an independent Geriatrician/Hypertension Expert, and an independent Statistician, and may include additional ad hoc members. Representatives of the Sponsor may attend the blinded part of the DMC meetings. The Sponsor will not have access to unblinded data during DMC meetings.

Operational details for the DMC will be detailed in the DMC charter. Refer to Section 9.11.2 for additional details.

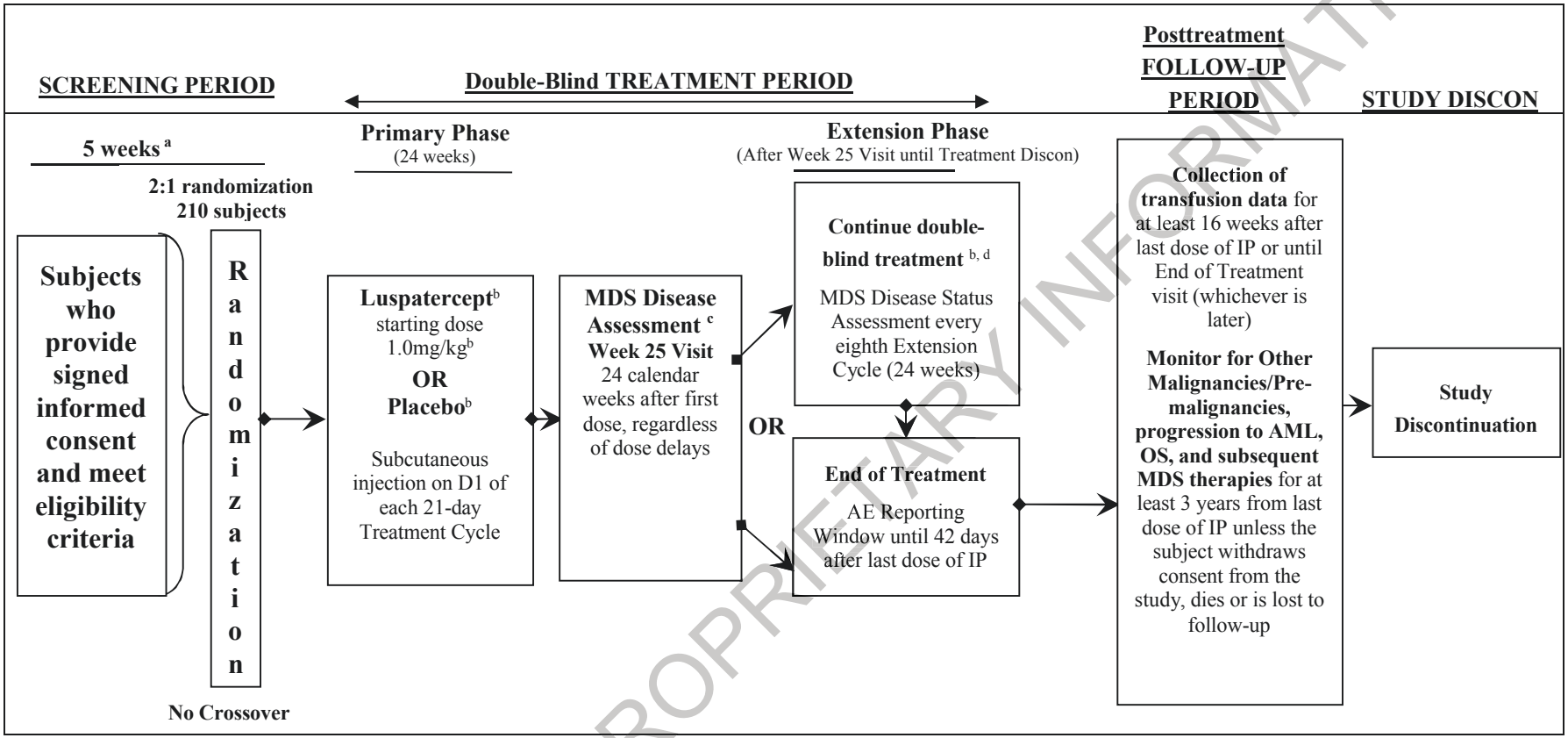
Steering Committee

A Steering Committee (SC) will be established by charter for this study. The Steering Committee will be comprised of Study Investigators and Sponsor representatives, and may include additional ad hoc members. The Steering Committee will review blinded data. The SC will serve in an advisory capacity to the Sponsor.

Operational details for the SC will be detailed in a separate SC charter. Refer to Section 9.11.3 for additional details.

Note: The SC is separate from the DMC.

Figure 2: Overall Study Design



[a] Historical documentation of RBC transfusion dependence should be available (RBC units transfused and pre-transfusion Hgb values) for at least 16 weeks prior to randomization. Refer to Section 6 for additional details.

[b] Dose may be titrated up to a maximum of 1.75 mg/kg. Refer to Section 7.2.1.1 for additional details.

[c] After completion of the Week 25 Visit MDS Disease Assessment by the investigator, subjects experiencing clinical benefit and have not experienced disease progression per IWG criteria for altering natural history of MDS (Cheson, 2006; Appendix E), may continue double-blind treatment with IP beyond the Week 25 Visit in the Extension Phase of the Treatment Period until meeting protocol discontinuation criteria. Refer to Section 6 and Section 11 for additional details.

[d] MDS Disease Assessment will be repeated by the investigator at Extension Cycle 8, Day 1 and Day 1 of every eighth Extension Cycle thereafter (ie, Extension Cycle 8, 16, 24+, etc. or every 24 weeks in the event of dose delays) until the subject is discontinued from treatment. For subjects to continue double-blind treatment in the Extension Phase of the Treatment Period, each MDS Disease Assessment (criteria detailed in Section 6.2.2) should confirm continued clinical benefit and absence of disease progression per IWG criteria for altering natural history of MDS (Cheson, 2006; Appendix E). Refer to Section 6 for additional details.

3.2. Study Duration for Subjects

After a Screening Period of up to 5 weeks, eligible subjects who are randomized to receive IP (either placebo or luspatercept) should continue double-blind treatment through at least the first 24 calendar weeks of the study unless the subject experiences unacceptable toxicities, disease progression per IWG criteria for altering natural history of MDS (Cheson, 2006; Appendix E), withdraws consent, or meets any other discontinuation criteria (Section 11).

Subjects who experience clinical benefit as determined by the Week 25 Visit MDS Disease Status Assessment (Section 6.2.2) may continue double-blind treatment beyond the Week 25 Visit (ie, in the Extension Phase of the Treatment Period) until the subject experiences unacceptable toxicities, disease progression per IWG criteria for altering natural history of MDS (Cheson, 2006; Appendix E), withdraws consent, or meets any other discontinuation criteria (Section 11).

For all subjects who receive at least one dose of IP, continuation of monitoring for progression to AML and other malignancies/pre-malignancies (please refer to Section 10.5 for details) will occur in the Posttreatment Follow-up Period, along with subsequent MDS therapies, and overall survival for at least 3 years from the date of last dose of IP unless the subject withdraws consent from the study, dies or is lost to follow-up.

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 post-treatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary [CCI] analysis, as prespecified in the protocol and/or SAP, whichever is the later date.

The Sponsor may end the trial when all key endpoints and objectives of the study have been analyzed, and the availability of a roll-over protocol exists into which any subjects remaining on study may be consented and continue to receive access to luspatercept and/or complete post-treatment follow-up. Such a protocol would be written for a compound that would not yet be commercially available.

4. STUDY POPULATION

4.1. Number of Subjects

Approximately 210 subjects with anemia due to IPSS-R very low, low, or intermediate MDS with ring sideroblasts who require RBC transfusions will be randomized worldwide.

4.2. Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study:

1. Subject is ≥ 18 years of age the time of signing the informed consent form (ICF).
2. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.
3. Documented diagnosis of MDS according to WHO/FAB classification that meets IPSS-R classification (Greenberg, 2012; Appendix D) of very low, low, or intermediate risk disease, and:
   - Ring sideroblast ≥ 15% of erythroid precursors in bone marrow or ≥ 5% (but < 15%) if SF3B1 mutation is present.
   - < 5% blasts in bone marrow
   - Peripheral blood WBC count < 13,000/μL
4. Refractory or intolerant to, or ineligible for, prior ESA treatment, as defined by any one of the following:
   - Refractory to prior ESA treatment - documentation of non-response or response that is no longer maintained to prior ESA-containing regimen, either as single agent or combination (eg, with G-CSF); ESA regimen must have been either:
     – recombinant human erythropoietin (rHu EPO) ≥ 40,000 IU/wk for at least 8 doses or equivalent;

     OR

     – darbepoetin alpha ≥ 500 μg Q3W for at least 4 doses or equivalent;
   - Intolerant to prior ESA treatment - documentation of discontinuation of prior ESA-containing regimen, either as single agent or combination (eg, with G-CSF), at any time after introduction due to intolerance or an adverse event
   - ESA ineligible - Low chance of response to ESA based on endogenous serum erythropoietin level > 200 U/L for subjects not previously treated with ESAs
5. If previously treated with ESAs or granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), both agents must have been discontinued ≥ 4 weeks prior to date of randomization.
6. Requires RBC transfusions, as documented by the following criteria:

- average transfusion requirement of ≥ 2 units/8 weeks of pRBCs confirmed for a minimum of 16 weeks immediately preceding randomization.
- Hemoglobin levels at the time of or within 7 days prior to administration of a RBC transfusion must have been ≤ 10.0 g/dL in order for the transfusion to be counted towards meeting eligibility criteria. Red blood cell transfusions administered when Hgb levels were > 10.0 g/dL and/or RBC transfusions administered for elective surgery will not qualify as a required transfusion for the purpose of meeting eligibility criteria. Refer to Section 8.1.2 for guidance on transfusions during the course of the study.
- no consecutive 56-day period that was RBC transfusion-free during the 16 weeks immediately preceding randomization

7. Eastern Cooperative Oncology Group (ECOG) score of 0, 1, or 2 (Appendix G)
8. Females of childbearing potential (FCBP), defined as a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) 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), must:
   - Have two negative pregnancy tests as verified by the Investigator prior to starting study therapy (unless the screening pregnancy test was done within 72 hours of C1D1). Refer to Section 6.1 for additional details. She must agree to ongoing pregnancy testing during the course of the study, and after end of study treatment.
   - If sexually active, agree to use, and be able to comply with, highly effective contraception** without interruption, 5 weeks prior to starting investigational product, during the study therapy (including dose interruptions), and for 12 weeks after discontinuation of study therapy.

   *** Highly effective contraception is defined in this protocol as the following (information will also appear in the ICF): Hormonal contraception (for example, birth control pills, injection, implant, transdermal patch, vaginal ring); intrauterine device (IUD); tubal ligation (tying your tubes); or a partner with a vasectomy*
9. Male subjects must:
   - Agree to use a condom, defined as a male latex condom or nonlatex condom NOT made out of natural (animal) membrane (for example, polyurethane), 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 following investigational product discontinuation, even if he has undergone a successful vasectomy.
10. 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:

1. Prior therapy with disease modifying agents for underlying MDS disease (eg, immune-modulatory drug [IMiDs such as lenalidomide], hypomethylating agents, or immunosuppressive therapy [IST]).
   - subjects who previously received hypomethylating agents (HMA) or lenalidomide may be enrolled at the investigator's discretion contingent that the subject received no more than 2 doses of HMA or no more than 1 calendar week of treatment with lenalidomide. The last dose must be ≥ 5 weeks from the date of randomization.
2. Previously treated with either luspatercept (ACE-536) or sotatercept (ACE-011)
3. MDS associated with del 5q cytogenetic abnormality
4. Secondary MDS, ie, MDS that is known to have arisen as the result of chemical injury or treatment with chemotherapy and/or radiation for other diseases.
5. Known clinically significant anemia due to iron, vitamin B12, or folate deficiencies, or autoimmune or hereditary hemolytic anemia, or gastrointestinal bleeding
   - iron deficiency to be determined by serum ferritin ≤ 15 µg/L and additional testing if clinically indicated (eg, calculated transferrin saturation [iron/total iron binding capacity ≤ 20%] or bone marrow aspirate stain for iron).
6. Prior allogeneic or autologous stem cell transplant
7. Known history of diagnosis of AML
8. Use of any of the following within 5 weeks prior to randomization:
   - anticancer cytotoxic chemotherapeutic agent or treatment
   - corticosteroid, except for subjects on a stable or decreasing dose for ≥ 1 week prior to randomization for medical conditions other than MDS
   - iron-chelating agents, except for subjects on a stable or decreasing dose for at least 8 weeks prior to randomization
   - other RBC hematopoietic growth factors (eg, Interleukin-3)
   - investigational drug or device, or approved therapy for investigational use. If the half-life of the previous investigational product is known, use within 5 times the half-life prior to randomization or within 5 weeks, whichever is longer is excluded.
9. Uncontrolled hypertension, defined as repeated elevations of diastolic blood pressure (DBP) ≥ 100 mmHg despite adequate treatment.
10. Absolute neutrophil count (ANC) < 500/µL (0.5×10^9/L)
11. Platelet count < 50,000/µL (50×10^9/L)
12. Estimated glomerular filtration rate (eGFR) or creatinine clearance < 40 mL/min.

13. Serum aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT) or alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT) ≥ 3.0 x upper limit of normal (ULN)
14. Total bilirubin ≥ 2.0 x ULN.
    - higher levels are acceptable if these can be attributed to active red blood cell precursor destruction within the bone marrow (ie, ineffective erythropoiesis) or in the presence of known history of Gilbert Syndrome.
    - subjects are excluded if there is evidence of autoimmune hemolytic anemia manifested as a corrected reticulocyte count of > 2% with either a positive Coombs' test or over 50% indirect bilirubin
15. Prior history of malignancies, other than MDS, unless the subject has been free of the disease (including completion of any active or adjuvant treatment for prior malignancy) for ≥ 5 years. However, subjects with the following history/concurrent conditions are 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)
16. Major surgery within 8 weeks prior to randomization. Subjects must have completely recovered from any previous surgery prior to randomization
17. History of stroke, deep venous thrombosis (DVT), pulmonary or arterial embolism within 6 months prior to randomization
18. Pregnant or breastfeeding females
19. Myocardial infarction, uncontrolled angina, uncontrolled heart failure, or uncontrolled cardiac arrhythmia as determined by the investigator within 6 months prior to randomization. Subjects with a known ejection fraction < 35%, confirmed by a local ECHO or MUGA performed within 6 months prior to randomization are excluded.
20. 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), known Human Immunodeficiency Virus (HIV), known evidence of active infectious Hepatitis B, and/or known evidence of active Hepatitis C. Local testing confirming HIV, Hepatitis B, and Hepatitis C status should not have been performed earlier than 4 weeks from the date of ICF signature.
21. History of severe allergic or anaphylactic reactions or hypersensitivity to recombinant proteins or excipients in the investigational product (see Investigator Brochure).
22. Subject has 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.

23. Subject has any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study.
24. Subject has any condition or concomitant medication that confounds the ability to interpret data from the study.

5. TABLE OF EVENTS

Table 4: Table of Events

	Screening	Treatment Period[1]								Posttreatment Follow-up • 42 Day Follow-up = Occurs 42 days after last dose of IP • 12 Week Follow-up = Occurs 12 Weeks after last dose of IP • Long Term Follow-up = Occurs every 3 months after 12 Week Follow-Up until at least 3 years post last dose of IP			
		Primary Phase *First 24 weeks of double-blind treatment Up to maximum of 8 Treatment Cycles (if no dose delays)*				Week 25[1,2] Visit *24 calendar weeks after first dose regardless of dose delays.*	Extension Phase *Continuation of double-blind treatment beyond Week 25 Visit*			EOT Visit[2]				
	Day -35 to -1	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 Ext Cycle 1[2],2,3 + Day 1	Ext Cycle 4, 8, 12+ Day 1	Ext Cycle 8, 16, 24+ Day 1		42 Day Follow-up[2]	12, 24, 48 Week Follow-up	Long Term Follow-up	End of Study
STUDY ENTRY AND GENERAL ASSESSMENTS														
Informed Consent	X	--	--	--	--	--	--	--	--	--	--	--	--	--
Inclusion/Exclusion evaluations	X	--	--	--	--	--	--	--	--	--	--	--	--	--
Physical Examination	X	X				X	X			X				
Randomization[3]	X	--	--	--	--	--	--	--	--	--	--	--	--	--
Demographics	X	--	--	--	--	--	--	--	--	--	--	--	--	--
Medical History	X	--	--	--	--	--	--	--	--	--	--	--	--	--
Prior ESA Therapies	X	--	--	--	--	--	--	--	--	--	--	--	--	--
Prior RBC and Platelet Transfusions[4]	X	--	--	--	--	--	--	--	--	--	--	--	--	--
INVESTIGATIONAL PRODUCT (IP)														
IP Administration and Accountability[15]	--	X[3]	--	--	--	--	X	--	--	--	--	--	--	--

Table 4: Table of Events (Continued)

	Screening	Treatment Period[1]									Posttreatment Follow-up • 42 Day Follow-up = Occurs 42 days after last dose of IP • 12 Week Follow-up = Occurs 12 Weeks after last dose of IP • Long Term Follow-up = Occurs every 3 months after 12 Week Follow-Up until at least 3 years post last dose of IP			
		Primary Phase *First 24 weeks of double-blind treatment* *Up to maximum of 8 Treatment Cycles* *(if no dose delays)*				Week 25[1,2] Visit *24 calendar weeks after first dose regardless of dose delays.*	Extension Phase *Continuation of double-blind treatment beyond Week 25 Visit*			EOT Visit[2]				
	Day -35 to -1	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 Ext Cycle 1[2],2,3 + Day 1	Ext Cycle 4, 8, 12+ Day 1	Ext Cycle 8, 16, 24+ Day 1		42 Day Follow-up[2]	12, 24, 48 Week Follow-up	Long Term Follow-up	End of Study
SAFETY ASSESSMENTS														
ECOG Performance Status	X	X	--	--	--	X	X	--	--	X	--	--	--	--
Urinalysis[5]	X	C1D1 and D1 of every fourth cycle in Primary Phase (eg, C1, C4, C8)				X	Ext C1D1, then D1 of every fourth Extension cycle until treatment discontinuation			X	--	--	--	--
Coombs' test[6]	X	--	--	--	--	--	--	--	--	--	--	--	--	--
Assessment of HIV/HepB/HepC status[6]	X	--	--	--	--	--	--	--	--	--	--	--	--	--
ECG (12-lead)	X	--	--	C5D8 only	--	--	--	--	--	X	--	--	--	--
Pregnancy Test and Counseling[7]	X	X	--	--	--	X	X	--	--	X	--	--	--	--
Adverse events	Continuous, after signing informed consent until 42 days after last IP administration											--	--	--
Prior and Concomitant medications/procedures	X	Continuous, until 42 days after last IP administration or until the EOT visit, whichever occurs later										--	--	--

Table 4: Table of Events (Continued)

	Screening	Treatment Period[1]								Posttreatment Follow-up • 42 Day Follow-up = Occurs 42 days after last dose of IP • 12 Week Follow-up = Occurs 12 Weeks after last dose of IP • Long Term Follow-up = Occurs every 3 months after 12 Week Follow-Up until at least 3 years post last dose of IP			
		Primary Phase *First 24 weeks of double-blind treatment* *Up to maximum of 8 Treatment Cycles* *(if no dose delays)*				Week 25[1,2] Visit *24 calendar weeks after first dose regardless of dose delays.*	Extension Phase *Continuation of double-blind treatment beyond Week 25 Visit*			EOT Visit[2]				
	Day -35 to -1	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 Ext Cycle 1[2],2,3+ Day 1	Ext Cycle 4, 8, 12+ Day 1	Ext Cycle 8, 16, 24+ Day 1		42 Day Follow-up[2]	12, 24, 48 Week Follow-up	Long Term Follow-up	End of Study
Vital Signs (Height to be measured only at screening; Weight to be measured only at screening and prior to each IP administration)	X	X	--	X	X	X	X	--	--	X	--	--	--	--
Serum Chemistry[8]	X	X	--	--	--	X	X	--	--	X	--	--	--	--
EFFICACY ASSESSMENTS														
Hematology[9, 15]	X	X	--	X	X	X	X	--	--	X	--	--	--	--
Serum EPO	X[10]	--	X	--	--	X	--	--	--	X	--	--	--	--
Serum Ferritin	X[11]	X[11]	--	--	--	X	--	X	--	X	--	--	--	--
Transfusion Data Collection and Assessment	Assess and record on ongoing basis (prior to each dose of IP) until 16 weeks after last dose of IP or the End of Treatment Visit, whichever occurs later. Clinical site staff should confirm if any transfusions were received by the subject (including any at outside local institutions in between study visits) prior to each IP administration via use of patient diary or other local procedure in place at the investigational site.													--
MDS Disease Assessment[12]	--	--	--	--	--	X	--	--	X	X	--	--	--	--

Table 4: Table of Events (Continued)

	Screening	Treatment Period[1]								Posttreatment Follow-up • 42 Day Follow-up = Occurs 42 days after last dose of IP • 12 Week Follow-up = Occurs 12 Weeks after last dose of IP • Long Term Follow-up = Occurs every 3 months after 12 Week Follow-Up until at least 3 years post last dose of IP			
		Primary Phase *First 24 weeks of double-blind treatment* *Up to maximum of 8 Treatment Cycles* *(if no dose delays)*				Week 25[1,2] Visit *24 calendar weeks after first dose regardless of dose delays.*	Extension Phase *Continuation of double-blind treatment beyond Week 25 Visit*			EOT Visit[2]				
	Day -35 to -1	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 Ext Cycle 1[2],2,3 + Day 1	Ext Cycle 4, 8, 12+ Day 1	Ext Cycle 8, 16, 24+ Day 1		42 Day Follow-up[2]	12, 24, 48 Week Follow-up	Long Term Follow-up	End of Study
Bone Marrow Aspirate (BMA) and Peripheral Blood for cytomorphology and cytogenetic testing[13]	BM Biopsy and Aspirate Required	--	--	--	--	X	--	--	X	X	--	--	--	--
CCI [redacted]														

Table 4: Table of Events (Continued)

	Screening	Treatment Period[1]								EOT Visit[2]	Posttreatment Follow-up • 42 Day Follow-up = Occurs 42 days after last dose of IP • 12 Week Follow-up = Occurs 12 Weeks after last dose of IP • Long Term Follow-up = Occurs every 3 months after 12 Week Follow-Up until at least 3 years post last dose of IP			
		Primary Phase *First 24 weeks of double-blind treatment* *Up to maximum of 8 Treatment Cycles* *(if no dose delays)*				Week 25[1,2] Visit *24 calendar weeks after first dose regardless of dose delays.*	Extension Phase *Continuation of double-blind treatment beyond Week 25 Visit*							
	Day -35 to -1	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 Ext Cycle 1[2],2,3 + Day 1	Ext Cycle 4, 8, 12+ Day 1	Ext Cycle 8, 16, 24+ Day 1		42 Day Follow-up[2]	12, 24, 48 Week Follow-up	Long Term Follow-up	End of Study
PK and ADA														
PK Sample Collection Refer to Section 6.4	--	C1,2,4, 6,8 Only	--	X	X	X	Extension C4D1 and D1 of every 4th Extension Cycle thereafter (eg, Ext. C4, C8, etc.) for up to one year from the first dose in the Primary Treatment Phase.			X[18]	--	X[18]	--	--
ADA Sample Collection Refer to Section 6.5	--	C1,2,4, 6,8 Only	--	--	--	X	Extension C4D1 and D1 of every 4th Extension Cycle thereafter (eg, Ext. C4, C8, C12 C16+, etc.) for up to one year from the first dose in the Primary Treatment Phase.			X[18]	--	X[18]		
QUALITY OF LIFE														
EORTC QLQ-C30 CCI [redacted] Questionnaire Completion	X	--	X[16]	--	--	X	Day 1 of Every Other Ext. Cycle (Ext. C1,C3, C5+, etc.)			X	--	--	--	--
CCI [redacted]														

Table 4: Table of Events (Continued)

	Screening	Treatment Period[1]									Posttreatment Follow-up • 42 Day Follow-up = Occurs 42 days after last dose of IP • 12 Week Follow-up = Occurs 12 Weeks after last dose of IP • Long Term Follow-up = Occurs every 3 months after 12 Week Follow-Up until at least 3 years post last dose of IP			
		Primary Phase *First 24 weeks of double-blind treatment* *Up to maximum of 8 Treatment Cycles* *(if no dose delays)*				Week 25[1,2] Visit *24 calendar weeks after first dose regardless of dose delays.*	Extension Phase *Continuation of double-blind treatment beyond Week 25 Visit*			EOT Visit[2]				
	Day -35 to -1	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 Ext Cycle 1[2],2,3 + Day 1	Ext Cycle 4, 8, 12+ Day 1	Ext Cycle 8, 16, 24+ Day 1		42 Day Follow-up[2]	12, 24, 48 Week Follow-up	Long Term Follow-up	End of Study
FOLLOW UP														
Monitoring for progression to AML and other malignancies/pre-malignancies [17] (Refer to Section 10.5 for details)	After signing ICF and until at least 3 years post last dose of IP or until death, lost to follow-up, withdrawal of consent for further data collection.													
Posttreatment MDS therapies[17]	--	--	--	--	--	--	--	--	--	--	X	X	X	X
Survival Follow-up[17]	--	--	--	--	--	--	--	--	--	--	X	X	X	X

[1] Window of +/- 3 days is allowed during Treatment Period. A window of +/- 14 days is allowed for the Week 25 Visit (Section 6.2.2). A window of +/- 14 days is allowed for Posttreatment Long-term Follow-up Assessments (ie, OS, Progression to AML, other malignancies/pre-malignancies (please refer to Section 10.5 for details), subsequent MDS therapies).

[2] Week 25 Visit and Extension Cycle 1 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 may not need to be repeated if previously performed within +/-7 days of EOT visit. If a subject is discontinued during a regular scheduled visit, all EOT procedures should be completed at that visit. End of Treatment (EOT) Visit procedures/assessments may occur at 42 Day Follow-up assessment if subject is discontinued within +/- 7 days of 42 Day Follow-up assessment.

[3] Randomization via IRT. The first dose of IP should be administered after, but within 3 days of randomization and can be on the same day as randomization. Refer to the IRT manual for additional information on randomization utilizing IRT. Documentation must be complete to confirm an average RBC transfusion requirement of at least 2 units of packed red blood cells (pRBCs) per 8 weeks during the 16 weeks immediately preceding randomization. Hemoglobin levels at the time of or within 7 days prior to administration of a RBC transfusion must have been ≤ 10.0 g/dL in order for the transfusion to be counted towards meeting eligibility criteria. Red blood cell transfusions administered when Hgb levels were > 10.0 g/dL and/or RBC transfusions administered for elective surgery will not qualify as a required transfusion for the purpose of meeting

eligibility criteria. There must also not be any consecutive 56-day period that was RBC transfusion free during the 16 weeks immediately preceding randomization. Refer to Section 4.2.

[4] Subjects must have at least 16 weeks documented transfusion history prior to randomization. This transfusion data includes hemoglobin measured prior to transfusion (pretransfusion Hgb). Refer to Section 6.1.

[5] Urinalysis assessed centrally and to include microscopic, quantitative analysis of urine. (eg, microalbumin/albumin, protein, creatinine, microalbumin/creatinine ratio).

[6] A local Coomb's test is only performed if total bilirubin > 2 x ULN (see Section 4.3). If positive, a local reticulocyte count may be requested. Local test results confirming known Human Immunodeficiency Virus (HIV), Hepatitis B, Hepatitis C status should not have been performed earlier than 4 weeks from the date of ICF signature. If beyond this window, additional local testing may be requested (see Section 4.3).

[7] Pregnancy test is required for all female subjects of childbearing potential. Serum beta human chorionic gonadotropin (β-hCG) will be performed at screening. A urine (or serum) pregnancy test will be repeated prior to the first administration of IP on C1D1, unless the screening pregnancy test was done within 72 hours of C1D1. During the Treatment Period, urine or serum pregnancy test is allowed. For males and FCBP, counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted prior to each IP administration or on a monthly basis (eg, in the event of dose delays). Refer to Section 6.1 for additional details.

[8] Serum chemistry (eg, sodium, potassium, chloride, bicarbonate [if available], calcium, magnesium, phosphorus, blood urea nitrogen [BUN], creatinine, creatinine clearance and/or estimated glomerular filtration rate, glucose, albumin, total protein, alkaline phosphatase, direct/indirect total bilirubin, AST/SGOT or ALT/SGPT, lactate dehydrogenase [LDH], uric acid) will be analyzed by the central laboratory. Refer to Section 6.1.

[9] Hematology assessment (eg, red blood cell [RBC] count, complete blood count [CBC], white blood cell [WBC] with differential, hemoglobin, hematocrit, nucleated red blood cells [nRBC], absolute reticulocyte count, platelet count, mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], and red blood cell distribution width [RDW]) will be tested by the central laboratory. Refer to Section 6.1.

[10] EPO will be assessed centrally. During the Screening Period, the serum EPO level 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.

[11] Serum ferritin will be assessed centrally. Sample should be collected within 5 weeks prior to randomization. Sample should be collected prior to administration of IP. Additional serum ferritin results from previous local laboratory assessments (ie, within the 16 week window immediately prior to randomization date) should be collected, if available in the medical records, and entered into the eCRF.

[12] During the Treatment Period, MDS Disease Assessment (which includes investigator assessment of clinical benefit and MDS disease status) should be completed by the investigator in conjunction with bone marrow/peripheral blood sample collection for cytomorphology and cytogenetics collected at the Week 25 Visit. For details related to the allowed time window related to procedures and assessments refer to Section 6.2.2. Based on the outcome of the MDS Disease Assessment, subjects will either be discontinued from treatment with IP and enter the Posttreatment Follow-Up Period or continue double-blind treatment with IP in the Extension Phase of the Treatment Period. Refer to Section 6.2.3 for additional details.

[13] During the Screening Period, bone marrow biopsy AND bone marrow aspirate are required. The screening BMB should be performed within 5 weeks prior to randomization. The screening BMA should be collected within the protocol screening window. After randomization, a bone marrow biopsy is collected only when adequate aspirate is not attainable. During the Extension Phase of the Treatment Period: Bone marrow and peripheral blood samples to be collected at Extension Cycle 8, Day 1 and Day 1 of every eighth Extension Cycle thereafter (ie, Extension Cycle 8, 16, 24+, etc. or approximately every 24 weeks in the event of dose delays). Bone marrow samples at End of Treatment Visit: Perform only if visit is > 90 days from prior bone marrow procedure. Refer to central laboratory manual for additional information related to sample collection

CCI [redacted].

[15] On dosing days, local laboratory sample should be collected and Hgb levels assessed prior to each IP administration to ensure dose modification rules are followed as outlined in Section 7.2.1.1, Table 6. In these circumstances, a split sample should also be collected and sent to the central laboratory for analysis. Subjects must have blood pressure assessed (as detailed in Section 6.1) prior to each IP administration.

[16] If subject completed Screening EORTC QLQ-C30 CCI [redacted] questionnaires within 14 days prior to C1D1, it does not have to be repeated at C1D1. If performed on C1D1, both EORTC QLQ-C30 CCI [redacted] questionnaires should be completed by the subject prior to IP administration.

[17] Long-Term Posttreatment Follow-up for Overall Survival (OS), Progression to AML, other malignancies/pre-malignancies (please refer to Section 10.5 for details), and data collection for subsequent MDS 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.

[18] Post-treatment Follow-up: For subjects who do not complete the Primary Treatment Phase or do not participate in the Extension Phase or subjects who terminate the Extension Phase with less than 1-year of ADA monitoring, ADA and PK samples will be collected at EOT and then every 12 weeks for up to one year from the first dose in the Primary Treatment Phase (please refer to Section 6.4 and Section 6.5 for details).

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 4, 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 Week 25 Visit, 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 Week 25 Visit (refer to Section 6.2.2 for details). Week 25 Visit and Extension Cycle 1 Visit procedures/assessments may not need to be repeated if previously performed within ±7 days of the scheduled visit.

End of Treatment Visit procedures/assessments may not need to be repeated if previously performed within ±7 days of EOT visit. If a subject is discontinued during a regular scheduled visit, all EOT procedures should be completed at that visit. End of Treatment Visit procedures/assessments may occur at 42 Day Follow-up assessment if subject is discontinued within ± 7 days of 42 Day Follow-up assessment.

A window of ± 14 days is allowed for Posttreatment Long-Term Follow-up assessments (ie, OS, progression to AML, other malignancies/pre-malignancies, subsequent MDS therapies). Procedures are described in detail below.

Subjects must have hemoglobin and blood pressure assessed prior to each IP administration. Blood pressure values should be confirmed by a mean of two readings obtained approximately 5 minutes apart with the subject seated for approximately 10 minutes prior to initial reading.

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

Local laboratories are allowed in cases when timely results are needed (eg, randomization, study treatment dosing decisions, hematology assessments between clinic visits, adverse event). In these circumstances, a split sample should still be collected and sent to the central laboratory for analysis. With prior sponsor consultation, local laboratories may also be used to determine study eligibility if central laboratory results are not available (eg, hemolyzed sample, etc.) or if there is a discrepancy between local and central laboratory results impacting study eligibility. Local laboratory data should be collected in the eCRF if relevant to study eligibility determination, dose administration, dose modification, or an AE, significant discrepancy between local and central laboratory results (from samples collected at the same study time point), 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

- **Signing of the ICF**

- **Assessment of Inclusion/Exclusion Criteria For Study Eligibility**

Screening evaluations will be performed for all subjects to determine study eligibility. These evaluations must be completed within 5 weeks of randomization (refer to Table of Events, Section 5, Table 4 for further information). Screening laboratory values must demonstrate subject eligibility, but may be repeated within the screening window, if necessary.

Waivers to the protocol will not be granted during the conduct of this trial, under any circumstances.

The following assessments/procedures will be performed during the Screening Period as specified in the Table of Events, Table 4:

- **Bone Marrow and Peripheral Blood Samples**

Screening MDS diagnosis confirmation requires both bone marrow biopsy (BMB), bone marrow aspirate (BMA), and peripheral blood samples. Samples may be reviewed locally, but must also be sent to the central laboratory for analysis.

The screening BMB, BMA, and peripheral blood samples should be collected within the protocol screening window or 5 weeks prior to randomization. If a subject is rescreened (eg, due to retesting of another lab), repeat bone marrow samples do not need to be collected contingent that initial samples were adequate for cytomorphology/cytogenetic assessment by the central laboratory. During the course of the study, whenever a bone marrow sample is collected, a peripheral blood smear is to be prepared.

Sample collection, processing, storage, and shipment procedures will be provided in the study's Central Laboratory Manual.

- Cytomorphology Assessment

  Bone marrow and peripheral blood samples will be prepared locally and sent to the central laboratory for analysis to confirm MDS diagnosis and baseline WHO (Appendix B) and/or FAB classification (Appendix C) prior to randomization.

  If the central reviewer and local pathologist disagree on the diagnosis of a subject, a third reviewer at the central laboratory may be consulted to provide an adjudication assessment. The central laboratory may also request the site to send in samples reviewed by the local pathologist for further assessment.

- Cytogenetics Analysis

  The central laboratory will conduct cytogenetic analysis throughout the study. The central laboratory will provide standardized analysis and reporting for all subjects. Bone marrow samples will be sent to the central laboratory for processing and cytogenetic analysis prior to randomization.

In the event that cytomorphology/cytogenetic analysis cannot be performed by the central laboratory prior to randomization, local cytomorphology/cytogenetic analysis may suffice for randomization purposes after consultation with the Sponsor. Every attempt should be made to send bone marrow and peripheral blood samples to the central laboratory for processing and analysis prior to the first dose of investigational product. If this does not occur, a central "over

read" of the cytomorphology/cytogenetics report and photographs will be performed (at a later date) by the central laboratory.

Results from central laboratory analysis should be used to determine baseline IPSS-R category (Greenberg, 2012; Appendix D).

The central laboratory will also assess bone marrow and peripheral blood samples during the Treatment Period of the study.

CCI [redacted]

Refer to Section 6.11 for additional information and Table 4 for timing of sample collection during the study.

- **Prior Transfusion History**

Transfusion history must be available for at least the 16 weeks immediately preceding and including the date of randomization. Transfusion data should include the type of transfusion (eg, RBC, platelets), number of units, reason and date of transfusion.

Transfusion data should also include the pretransfusion Hgb levels that triggered the RBC transfusions.

These Hgb levels can be from local or central laboratory measurements. For platelet transfusions, data should include the platelet value for which the platelet transfusion was administered. These platelet values can be from the central or a local laboratory.

Documentation of the following criteria is required to meet protocol inclusion criteria and must be confirmed prior to randomization:

- Average transfusion requirement of at least 2 units of packed red blood cells (pRBCs) per 8 weeks during the 16 weeks immediately preceding randomization. Only RBC transfusions administered due to a pre-transfusion Hgb of ≤ 10 g/dL will counted to determine eligibility.
- There must also not be any consecutive 56-day period that was RBC transfusion free during the 16 weeks immediately preceding randomization.

All RBC transfusion records for at least 16 weeks immediately preceding and including the date of randomization should be collected (including any transfusions at outside local institutions). Red blood cell (RBC) transfusions administered for elective surgery will not count towards meeting RBC transfusion inclusion criteria requirements, but should still be recorded in the eCRF.

The RBC transfusion data during the 16 weeks immediately preceding randomization will be used to determine the baseline RBC transfusion requirement for an individual study subject. Thus, this information must be collected during the Screening window (prior to randomization).

- **Prior Erythropoiesis-stimulating agent (ESA) Therapies**

Type of ESA, dose, frequency, duration, best response, and reason for discontinuation should be collected and entered into the eCRF regardless of date of discontinuation.

Eligible subjects must also be refractory or intolerant to prior ESA treatment, or ineligible for, ESA treatment. See Section 4.2 for additional details.

- **Demographics and Medical History**

The subject's date of birth, sex, race and ethnicity will be recorded on the appropriate eCRF. Relevant medical history (including recent surgical history) and current medical conditions, including those symptoms related to MDS, must also be recorded on the appropriate eCRF at screening.

History of MDS disease and other prior malignancies will also be recorded on the appropriate eCRF. This may include relevant information related to original MDS diagnosis (eg, date of original diagnosis, WHO and/or FAB classification at original diagnosis, prior treatments administered) and/or other past malignancies.

Historic serum ferritin results from previous local laboratory reports (ie, within the 16 week window immediately prior to randomization date) will be also collected, if available in the medical records, and entered on the appropriate eCRF.

- **Concomitant Medications and Procedures**

All prior/concomitant medications taken in the 5 weeks prior to randomization will be recorded on the appropriate eCRF(s).

All prior/concomitant procedures within the 8 weeks prior to randomization will be recorded on the appropriate eCRF(s).

Prior G-CSF/GM-CSF and iron chelation therapy should be recorded on the appropriate eCRF(s) regardless of treatment discontinuation date.

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

Record concomitant medications/procedures on ongoing basis until 42 days post last dose of IP or End of Treatment (EOT), whichever occurs later. Refer to Section 8 for additional details.

- **Physical Examination**

Information about the physical examination must be present in the subject's source documentation. Significant findings must be included on the appropriate eCRF.

Refer to Table 4 for timing of physical examinations during the study.

- **Eastern Cooperative Oncology Group Performance Status**

Performance status will be assessed by the investigator during Screening and at other timepoints indicated on Table 4 using ECOG criteria provided in Appendix G.

- **Electrocardiogram**

Electrocardiogram (ECG) at screening is performed locally at the study site. ECG will be performed using the internationally recognized 12-leads. If available, the following ECG parameters will be recorded on the respective eCRF(s): eg, 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.

Refer to Table 4 for timing of ECGs during the Treatment Period of the study.

- **Urinalysis**

Urinalysis to include microscopic, quantitative analysis of urine. (eg, microalbumin/albumin, protein, creatinine, microalbumin/creatinine ratio).

Microscopic urinalysis will be tested by the central laboratory.

Refer to Table 4 for timing of urinalysis sample collection during the Treatment Period of the study.

- **Coombs' Test**

A direct or indirect Coombs' test at screening is performed at the local laboratory if screening total bilirubin is ≥ 2.0 x ULN. Refer to Section 4.3. If positive, a local reticulocyte count may be requested.

- **Assessment of HIV/Hepatitis B/Hepatitis C status**

If known, local test results confirming HIV, Hepatitis B, Hepatitis C status should not have been performed earlier than 4 weeks from the date of ICF signature. If beyond this window, additional local testing may be requested (see Section 4.3).

- **Serum Ferritin**

Sample should be collected within 5 weeks prior to randomization.

Serum ferritin analysis is to be performed by the central laboratory.

Additional serum ferritin results from previous local laboratory assessments (ie, within the 16 week window immediately prior to randomization date) should be collected, if available in the medical records, and entered into the eCRF.

Refer to Table 4 for timing of serum ferritin testing during the study.

- **Serum EPO Level**

During the Screening Period, the serum EPO level 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 analysis is to be performed by the central laboratory.

Refer to Table 4 for timing of serum EPO level testing during the study.

- **Hematology Panel**

Hematology assessment (eg, red blood cell [RBC] count, complete blood count [CBC], white blood cell [WBC] with differential, hemoglobin, hematocrit, nucleated red blood cells [nRBC], absolute reticulocyte count, platelet count, mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], and red blood cell distribution width [RDW]) will be tested by the central laboratory.

On dosing days, local laboratory sample should be collected and Hgb levels assessed prior to each IP administration to ensure dose modification rules are followed as outlined in Section 7.2.1.1, Table 6. In these circumstances, a split sample should also be collected and sent to the central laboratory for analysis.

Refer to Table 4 for timing of hematology assessments during the study.

- **Serum Chemistry Panel**

Serum chemistry (eg, sodium, potassium, chloride, bicarbonate [if available], calcium, magnesium, phosphorus, blood urea nitrogen [BUN], creatinine, creatinine clearance and/or estimated glomerular filtration rate, glucose, albumin, total protein, alkaline phosphatase, direct/indirect total bilirubin, AST/SGOT or ALT/SGPT, lactate dehydrogenase [LDH], uric acid) will be analyzed by the central laboratory.

Refer to Table 4 for timing of serum chemistry assessments during the study.

- **Pregnancy Testing and Counseling**

This protocol defines a FCBP as a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) 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).

A medically supervised serum pregnancy test (conducted at the central laboratory or locally) is to be obtained and verified negative in all female subjects of childbearing potential at screening. The investigator will appraise a female subject as a FCBP according to this definition. Justification must be recorded in the eCRF and the source document. Pregnancy testing is not required for non-FCBP subjects.

Serum beta human chorionic gonadotropin (β-hCG) pregnancy test (which must be negative) with a minimum sensitivity of 25 mIU/mL will be performed within 5 weeks prior to Dose 1 Day 1. Urine (or serum) pregnancy test will be performed to assess subject eligibility within 72 hours prior to the first administration of IP, if the initial serum pregnancy test did not already occur with 72 hours of dosing (negative results required for IP administration).

During the Treatment Period urine or serum pregnancy test is allowed.

For males and FCBP, counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted prior to each IP administration or monthly (eg, in the event of dose delays). Refer to Section 10.4 for additional details.

Refer to Table 4 for timing of pregnancy testing and counseling during the study.

- **Vital Signs, Height, and Weight**

Vital signs, including height (measured at Screening only), weight (at Screening and on study drug dosing days only), seated blood pressure, temperature, heart rate, and respiratory rate.

On study drug dosing days, blood pressure must be assessed prior to each IP administration. Blood pressure values should be confirmed by mean of two readings obtained approximately 5 minutes apart with the subject seated for approximately 10 minutes prior to initial reading.

Refer to Table 4 for timing of vital signs during the study.

- **Adverse Event Assessment -** record on ongoing basis

Refer to Section 10.1.

- **Subject Reported Outcomes or Quality of Life or Health Economics (EORTC QLQ-C30** CCI [redacted]

Refer to Section 6.12.

- CCI [redacted]

[redacted]

- **Randomization in Integrated Response Technology (IRT)**

In addition to demographic information, the following information should be readily available prior to performing the randomization transaction in the IRT system:

- Baseline IPSS-R risk category (Greenberg, 2012; Appendix D)
- Average 8-week baseline RBC transfusion requirement.

The first dose of IP should be administered after, but within 3 days of randomization and can be on the same day as randomization. Refer to the IRT manual for additional information on randomization utilizing IRT.

- **Monitoring for Progression to AML and Other Malignancies/Pre-malignancies**

Progression to AML as per WHO classification (Vardiman, 2009) will be monitored and will be included as part of the safety assessment throughout the course of the study. Progression to AML should be monitored from time of signing of informed consent through at least 3 years after last dose of IP or until death, lost to follow-up or withdrawal of consent from the study.

The occurrence of a new malignancy or pre-malignant 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 (please refer to Section 10.5 for details). Investigators are to report the development of any new malignancy or pre-malignant lesion as a serious adverse event, regardless of causal relationship to IP (study drug[s] or control), 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 progression to AML and other malignancies/pre-malignancies (eg, confirmatory histology or cytology results, etc.) may be requested. Appropriate information related diagnosis of AML and other malignancies/pre-malignancies should be captured on the eCRF and in the subject's source documents.

Refer to Section 10.5 and Section 10.6 for more information regarding reporting requirements.

6.2. Treatment Period

The subject will begin treatment upon confirmation of eligibility. The subject must start treatment within 5 weeks of signing the informed consent form (ICF). If screening assessments are performed within 72 hours of Cycle 1 Day 1 (C1D1), safety laboratory and physical examinations need not be repeated at C1D1 with the exception of blood pressure measurement, hematology, serum ferritin, and serum EPO sample collection.

If subject completed the Screening EORTC QLQ-C30 [redacted] questionnaires within 2 weeks of C1D1, it does not have to be repeated at C1D1. If performed on C1D1, both EORTC QLQ-C30 [redacted] questionnaires should be completed by the subject prior to IP administration.

On dosing days, local laboratory hgb levels should be assessed prior to each IP administration to ensure 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 should confirm with the subject if any transfusions were received at outside local centers in between study visits, prior to each IP administration.

6.2.1. Primary Phase of the Treatment Period: Weeks 1-24

Subjects will receive IP (either luspatercept or matching placebo) on Day 1 of each 21-day treatment cycle.

Treatment cycles are 21 days in duration, and will occur as described in Section 7.2.

The following procedures/evaluations will be performed at the frequency specified in the Table of Events (Table 4) during the Primary Phase of the Treatment Period. The procedures/evaluations should be performed prior to dosing on the visit day, unless otherwise specified:

- IP administration and accountability
- Eastern Cooperative Oncology Group Performance Status (as detailed in Section 6.1)
- Pregnancy Testing and Counseling (as detailed in Section 6.1)
- PK and ADA sample collection (as detailed in Section 6.4 and Section 6.5)
- ECG (as detailed in Section 6.1)
- Physical Examination (as detailed in Section 6.1)
- Vital Signs (as detailed in Section 6.1)
- Hematology Panel (as detailed in Section 6.1)
- Serum Chemistry Panel (as detailed in Section 6.1)
- Urinalysis (as detailed in Section 6.1)
- Serum EPO Level (as detailed in Section 6.1)
- Serum Ferritin (as detailed in Section 6.1)
- Transfusion Data Collection and Assessment

During the study, the following will be recorded for all transfusions (including any transfusions received at outside institutions in between study visits) the subject received within 16 weeks prior to randomization, until 16 weeks after the last dose of IP or the End of Treatment (EOT) visit, whichever occurs later:

  – type of transfusion (eg, pRBC or platelet)

  - number of units
  - reason for transfusion
  - date of transfusion
  - hemoglobin value for which any RBC transfusion is given (ie, pretransfusion hgb)
  - platelet value for which any platelet transfusion is given
- Clinical site staff should confirm if any transfusions were received by the subject (including any at outside local institutions in between study visits) prior to each IP administration via use of patient diary or other local procedure in place at the investigational site.
- Adverse Event Assessment to be assessed on an ongoing basis. Refer to Section 10.1.
- Monitoring for Progression to AML and other malignancies/pre-malignancies on an ongoing basis. Refer to Section 6.1.
- Concomitant Medications and Procedures - record on ongoing basis. Refer to Section 8.
- Subject Reported Outcomes or Quality of Life (EORTC QLQ-C30 CCI [redacted]). (as detailed in Section 6.12)
- CCI [redacted]

6.2.2. MDS Disease Assessment: Week 25 Visit

Assessment of Transfusions, Bone Marrow, and Peripheral Blood

The MDS Disease Assessment consists of the investigator's assessment of clinical benefit from study drug and status of underlying disease.

The first **MDS Disease Assessment** should be completed 24 calendar weeks after the date of first dose, regardless of dose delays. The calculated due date for the first MDS Disease Assessment is defined as C1D1 + 168 days (ie, 24 weeks). The MDS Disease Assessment by the investigator should be completed no sooner than 24 calendar weeks (ie, 168 days) after the day of C1D1 and requires a minimum of 24-weeks of transfusion information for the assessment of clinical benefit. Up to date information related to all transfusions received during the Treatment Period (including those received at outside institutions) must be available prior to completion of the clinical benefit component of the MDS Disease Assessment.

As central laboratory results from bone marrow and peripheral blood samples (eg, cytomorphology, cytogenetics analysis) are required as part of the MDS Disease Assessment, a 14-day window is allowed for the Week 25 Visit in order to account for sample collection and turnaround time of results.

In order for subjects to remain on double-blind treatment beyond the first 24 calendar weeks, the following criteria must be confirmed upon the completion of the **MDS Disease Assessment** by the investigator:

- Evidence of clinical benefit (eg, decrease in RBC transfusion requirement compared to baseline requirement or hemoglobin increase compared to baseline)

AND

- Absence of disease progression per IWG criteria for altering natural history of MDS (Cheson, 2006; Appendix E).

Based on the outcome of the MDS Disease Assessment, subjects will either be discontinued from treatment with IP and enter the Posttreatment Follow-up Period or continue double-blind treatment with IP in the Extension Phase of the Treatment Period.

For subjects that meet criteria to continue double-blind treatment in the Extension Phase, the duration between the last dose of IP in the Primary Phase and first Extension Phase dose should not be delayed beyond 21 days solely due to awaiting cytomorphology/cytogenetics results contingent that the investigator has confirmed absence of signs of disease progression based on review of peripheral blood parameters.

In circumstances where the subject does receive the first Extension Phase dose prior to cytomorphology/cytogenetics results being available, the investigator must complete assessment of cytomorphology/cytogenetics results prior to the next IP administration.

A bone marrow biopsy is to be collected only when adequate aspirate is not attainable. Whenever a bone marrow sample is collected, a peripheral blood smear is to be prepared. Refer to the Central Laboratory Manual for additional information.

The following procedures/evaluations will also be performed at the Week 25 Visit:

- CCI [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- Subject Reported Outcomes or Quality of Life (EORTC QLQ30 CCI [redacted]) (as detailed in Section 6.12)
- CCI [redacted]
- Transfusion Data Collection and Assessment (as detailed in Section 6.1)
- Adverse Event Assessment - record on ongoing basis. Refer to Section 10.1.
- Monitoring for Progression to AML and other malignancies/pre-malignancies on an ongoing basis. Refer to Section 10.5.
- Concomitant Medications and Procedures - record on ongoing basis. Refer to Section 8.
- Eastern Cooperative Oncology Group Performance Status (as detailed in Section 6.1)
- Pregnancy Testing and Counseling (as detailed in Section 6.1)
- PK and ADA Sample Collection (as detailed in Section 6.4 and Section 6.5)

- Physical Examination (as detailed in Section 6.1)
- Vital Signs (as detailed in Section 6.1)
- Hematology Panel (as detailed in Section 6.1)
- Serum Chemistry Panel (as detailed in Section 6.1)
- Urinalysis (as detailed in Section 6.1)
- Serum EPO Level (as detailed in Section 6.1)
- Serum Ferritin (as detailed in Section 6.1)

6.2.3. Extension Phase of the Treatment Period: After Week 25 Visit

Subjects who meet criteria to remain on double-blind treatment after completion of the Week 25 Visit MDS Disease Assessment may continue dosing on Day 1 of each 21-day treatment cycle in the Extension Phase of Treatment Period until the subject experiences unacceptable toxicities, disease progression per IWG criteria for altering natural history of MDS (Cheson, 2006; Appendix E), withdraws consent, or meets any other discontinuation criteria (Section 11).

Bone marrow aspirate and peripheral blood samples will be collected (eg, cytomorphology, cytogenetics analysis) and the MDS Disease Assessment will be repeated by the investigator at Extension Cycle 8, Day 1 and Day 1 of every eighth Extension Cycle thereafter (ie, Extension Cycle 8, 16, 24+, etc. or approximately every 24 weeks in the event of dose delays) until the subject is discontinued from treatment.

A bone marrow biopsy is to be collected only when adequate aspirate is not attainable. Whenever a bone marrow sample is collected, a peripheral blood smear is to be prepared. Refer to the Central Laboratory Manual for additional information.

In addition, information related to all transfusions received during the Treatment Period (including those received at outside institutions) should be available prior to completion of each MDS Disease Assessment. Clinical site staff should continue to confirm if any transfusions were received by the subject (including any at outside local institutions in between study visits) prior to each IP administration via use of patient diary or other local procedure in place at the investigational site.

For subjects to continue double-blind treatment in the Extension Phase of the Treatment Period, each MDS Disease Assessment (criteria detailed in Section 6.2.2) should confirm continued clinical benefit and absence of disease progression per IWG criteria for altering natural history of MDS (Cheson, 2006; Appendix E).

Additional procedures/assessments as outlined in Section 6.2.1 will also continue in the Extension Phase. The frequency of procedures/assessments in the Extension Phase may differ than the Primary Phase. Refer to Table 4 for additional information related to required assessments/procedures and frequency in the Extension Phase.

6.3. Dose Delays

On days when subjects return to the investigational site for IP administration, but IP is not administered (eg, due to protocol dose modification, delay rules (Section 7.2.1), all required

assessments and procedures should be performed, regardless if IP 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 weekly basis.
- If dose delay is due to increased hemoglobin level, perform hematology at least weekly.
- If dose delay is due to an AE, perform hematology, serum chemistry, and serum ferritin at least every 3 weeks thereafter and before next dose administration.
- Pharmacokinetic (PK)/ADA samples should be collected on first day of dose delay and prior to IP administration on day dosing resumes.
- For males and FCBP, pregnancy counseling as detailed in Section 6.1.

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

6.4. Pharmacokinetics

Blood samples will be collected to analyze luspatercept concentrations in serum in all subjects. At each 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 (also see Table 4):

- Primary Phase of Treatment Period: C1D1 (must be collected before the first dose), C1D8, C1D15, C2D1, C4D1, C5D8 and then Day 1 of every other treatment cycle thereafter in the Primary Phase (ie, C6D1 and C8D1, if no dose delays)
- Week 25 Visit (Collect sample only if > 14 days from prior sample collection.)
- Extension Phase of Treatment Period (if applicable): Extension Phase Cycle 4, Day 1 and Day 1 of every fourth Extension Phase treatment cycle thereafter (eg, Extension Phase Cycles 4, 8, etc.) for up to one year from the first dose in the Primary Treatment Phase.
- Posttreatment Follow-up: For subjects who do not complete Primary Treatment Phase or do not participate in Extension Phase or subjects who terminate the Extension Phase with less than 1-year ADA of monitoring, PK samples will be collected at EOT and then every 12 weeks for up to one year from the first dose in the Primary Treatment Phase.

After the study is unblinded, PK samples may no longer be collected from subjects in the placebo arm. In addition, upon unblinding of the study, PK sampling at all Post-Treatment Follow-up visits may continue only if subjects' last available ADA is positive and they have not reached the maximum of 1-year ADA monitoring. Pharmacokinetic (PK) sampling per investigator's or sponsor's discretion is allowed and should be recorded as an unscheduled visit.

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

6.5. Anti-Drug Antibody (ADA)

Blood samples will be collected for assessment of anti-drug antibodies (ADA) against luspatercept in serum in all subjects. The maximum ADA monitoring period will be 1 year from

the first dose of the Primary Treatment Phase unless justified by safety reasons. At each ADA time point, approximately 3 mL 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 is not needed for the ADA test, as the ADA test will 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 4):

- Primary Phase of Treatment Period: C1D1 (must be collected before the first dose), C2D1, and then Day 1 of every other treatment cycle thereafter in the Primary Phase (ie, C4D1, C6D1, and C8D1 if no dose delays).
- Week 25 Visit (Collect sample only if > 14 days from prior sample collection)
- Extension Phase of Treatment Period (if applicable): Extension Phase Cycle 4, Day 1 and Day 1 of every fourth Extension Phase treatment cycle thereafter (eg, Extension Phase Cycles 4, 8, 12, 16+, etc.) for up to 1 year from the first dose in the Primary Treatment Phase.
- Post-treatment Follow-up: For subjects who do not complete the Primary Treatment Phase or do not participate in the Extension Phase or subjects who terminate the Extension Phase with less than 1-year of ADA monitoring, ADA samples will be collected at EOT and then every 12 weeks for up to one year from the first dose in the Primary Treatment Phase.

After the study is unblinded, ADA samples may no longer be collected from subjects in the placebo arm. In addition, upon unblinding of the study, ADA sampling at all Post-Treatment Follow-up visits may continue only if the subject's last available ADA sample is positive and the subject has not reached the maximum of 1-year ADA monitoring. 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.

6.6. Unscheduled Visits

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. End of Treatment Visit

An end of treatment (EOT) evaluation will be performed for subjects who are withdrawn from treatment for any reason as soon as possible after the decision to permanently discontinue treatment has been made. Evaluations will be performed as specified in the Table 4.

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).

Bone marrow procedure should only be performed at EOT visit if > 90 days from prior bone marrow procedure. End of Treatment (EOT) Visit procedures/assessments may occur at 42 Day Follow-up assessment if subject is discontinued within +/- 7 days of 42 Day Follow-up assessment.

The reason for discontinuation will be recorded in the eCRF and in the source document for all randomized subjects, regardless of whether they are dosed or not. Reasons for treatment discontinuation are provided in Section 11.1.

6.8. Posttreatment Follow-up Period

6.8.1. Safety Follow-up

All subjects discontinued from protocol-prescribed therapy for any reason will be followed for a period of 42 days after the last dose of IP for AE reporting, as well as SAEs made known to the Investigator at any time thereafter that are suspected of being related to IP.

Females of childbearing potential should avoid becoming pregnant for 12 weeks after the last dose of IP and male subjects should avoid fathering a child for 12 weeks after the last dose of IP. Refer to Section 10 for additional details.

6.8.2. Long-Term Follow-up

Transfusion data collection will continue up until 16 weeks from the date of last dose of IP or 16 weeks after the End of Treatment Visit (whichever is later).

For subjects who do not complete the Primary Treatment Phase or do not participate in the Extension Phase or subjects who terminate the Extension Phase with less than 1-year of ADA monitoring, ADA and PK samples will be collected at EOT and then every 12 weeks for up to one year from the first dose in the Primary Treatment Phase (please refer to Section 6.4 and Section 6.5).

All subjects discontinued from protocol-prescribed therapy for any reason should be followed for progression to AML, other malignancies/pre-malignancies, survival and subsequent MDS therapies.

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, progression to AML, other malignancies/pre-malignancies (please refer to Section 10.5 for details), post-treatment therapy (ies) for MDS at the 42-Day and 12-Week Follow-up assessments and then every 3 months after the 12 Week Follow-up assessment for at least 3 years after last dose of IP or until death, lost to follow-up or withdrawal of consent from the study. Refer to Table of Events, Section 5, Table 4.

Data regarding subsequent MDS therapies, determination of AML progression and other malignancies/pre-malignancies, (refer to Section 6.1 and Section 10.5 for additional details), and date and cause of death will be recorded in the eCRF. The investigator must make every effort to obtain information regarding the subject's survival status before determining the subject is lost to follow-up. If the subject is discontinued from Long-Term Follow-up, the reason for discontinuation should be recorded on the End of Study eCRF.

Long-term follow-up 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.

6.9. Efficacy Assessments

Treatment response will be assessed locally by the investigator in accordance with IWG 2006 criteria for MDS (Cheson, 2006; Appendix E) with modifications for the erythroid response criteria through transfusion assessments, hematology laboratory parameters, peripheral blood smear, bone marrow aspirates and/or biopsies, and cytogenetics.

Other efficacy assessments will include serum ferritin, concomitant iron chelation therapy use, health-related quality of life, CCI [redacted].

Efficacy data will also be reviewed by an external unblinded DMC and/or external blinded Steering Committee as specified time points detailed in each committees' respective charters.

Bone marrow aspirate (or biopsy, if adequate aspirate is not attainable) samples for assessing treatment response will be collected at the frequency specified in the Table of Events, Section 5, Table 4. Whenever a bone marrow sample is collected, a stained peripheral blood smear is to be prepared.

Cytogenetic testing is to be completed whenever a bone marrow aspirate is obtained for assessment of cytogenetic response in accordance with IWG 2006 criteria for MDS (Cheson, 2006; Appendix E). Bone marrow biopsy can be used for cytogenetics testing if adequate aspirate is not attainable (note that specific handling of the biopsy is required for cytogenetics testing).

6.10. Safety Assessments

The safety measures assessed are routinely used in clinical studies evaluating the safety of investigational product for hematologic malignancies. Safety assessments, including (but not limited to) physical examination, vital signs, ECG, urinalysis, hematology, serum chemistry, pregnancy testing (for FCBP subjects only), AEs, concomitant medications and procedures, and transfusion data collection and assessment, will be performed at the frequency specified in Table 4 or more frequently if clinically indicated.

CCI [redacted]

CCI [redacted]

6.12. Subject Reported Outcomes or Quality of Life Measurements

The European Organization for Research and Treatment of Cancer Quality-of-Life questionnaire (EORTC QLQ-C30) (Aaronson, 1993; Appendix F) is a validated health-related quality of life (HRQoL) measure applicable to subjects with any cancer diagnosis. It is composed of 30 items that address general physical symptoms, physical functioning, fatigue and malaise, and social and emotional functioning. Subscale scores are transformed to a 0 to 100 scale, with higher scores on functional scales indicating better function and higher score on symptom scales indicating worse symptoms. The EORTC QLQ-C30 is available in many languages. This instrument takes 10 to 15 minutes to administer.

CCI [redacted] All eligible subjects will complete the EORTC QLQ-C30 CCI [redacted] at the frequency noted in the Table of Events, Section 5, Table 4.

For the C1D1 visit, if the subject completed the Screening Visit EORTC QLQ-C30 CCI [redacted] questionnaires within 14 days prior to C1D1, they do not have to be repeated at C1D1. If performed on C1D1, both EORTC QLQ-C30 CCI [redacted] questionnaires should be completed by the subject prior to IP administration.

It is important that every subject complete all of the EORTC QLQ-C30 CCI [redacted] assessments at every specified time point to minimize the amount of missing data.

CCI [redacted]

6.14. 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 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 Products

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 2 fill sizes, and when reconstituted, each consists of 50 mg/mL luspatercept in a 10 mM citrate buffer-based solution (10 mM citrate, pH 6.5, 9% sucrose, 0.02% polysorbate 80). The drug product is packaged in a 3 mL glass vial in the following fill sizes:

- 25 mg/vial: The 25 mg/vial presentation contains 37.5 mg of luspatercept protein. After reconstitution with 0.68 mL water for injection (WFI), each single-use vial will deliver at least 0.5 mL of 50 mg/mL luspatercept (25 mg)
- 75 mg/vial: The 75 mg/vial presentation contains 87.5 mg of luspatercept protein. After reconstitution with 1.6 mL WFI, each single-use vial will deliver at least 1.5 mL of 50 mg/mL luspatercept (75 mg)

The recommended storage condition for Luspatercept for Injection (25 mg/vial and 75 mg/vial; lyophilized powder formulation) is 2°C to 8°C. It is recommended that the reconstituted luspatercept for injection, at room temperature, be administered immediately. However, it may be held for up to 10 hours at 2°C to 8°C. 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.

Placebo to be used in the study will be sterile normal saline (0.9% sodium chloride for injection) subcutaneous. Sterile, normal saline should be supplied by the site. The investigational site's designated individuals will prepare the placebo syringes to match the active syringes. The investigator and subject will be blinded. The manufacturer's directions for storage and handling are to be followed, as are standard clinical practices for ensuring sterility of the placebo.

7.2. Treatment Administration and Schedule

There will be unblinded designated site personnel at each site responsible for preparing the investigational product. Luspatercept or placebo 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 Hgb, blood pressure and weight assessed prior to each IP administration. Clinical site staff should also confirm if any transfusions were received by the subject (including any at outside local institutions in between study visits) prior to each IP administration via use of patient diary or other local procedure in place at the investigational site.

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 separate sites using the same anatomical location but on opposite sides of the body (example left thigh and right thigh). The maximum volume per SC injection should

not exceed 1.2 mL. The maximum total dose per administration should not exceed 168 mg, which results in 3.36 mL maximum total volume after reconstitution.

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.

Eligible subjects will be randomized at a 2:1 ratio to either:

- Experimental Arm: Luspatercept (ACE-536): Starting dose 1.0 mg/kg subcutaneously injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle). Luspatercept clinical drug product will be provided by the Sponsor as a lyophilized powder. Luspatercept will be administered after reconstitution as a subcutaneous injection to subjects by the study staff at the clinical site.

OR

- Control Arm: Placebo (Volume equivalent to experimental arm) subcutaneously injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle). Placebo (normal saline) product will be provided by the local investigational site.

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

7.2.1.1. Dose Titration Increase

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 of 1.0 mg/kg to 1.33 mg/kg, and up to a maximum of 1.75 mg/kg, but the maximum total dose should not exceed 168 mg, during both the Primary and Extension Phases of the Treatment Period if all the following criteria are met:

- Subject has ≥ 1 RBC transfusion event (for pretransfusion Hgb of ≤ 9.0 g/dL) during the 2 most recent prior treatment cycles (~6-weeks).
- The two most recent prior treatment cycles assessed must be at the same dose level.
- Subject must not have met protocol dose delay and/or reduction criteria in the two most recent treatment cycles (exception of dose delay required due to influence of RBC transfusions). Refer to Table 6, footnote b.

If all criteria above are met, the dose may be increased by 1 dose level.

The dose level should be titrated individually for each subject and must not exceed 1.75 mg/kg.

Starting dose with dose increases and reductions are presented below for reference (Table 5).

Table 5: Starting Dose Level with Dose Reductions and Dose Titration

3rd Dose Reduction (~25% reduction)	2nd Dose Reduction (~25% reduction)	1st Dose Reduction (~25% reduction)	Starting Dose Level	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

7.2.1.2. Dose Delay and Dose Reduction

Dose delay and/or reduction or discontinuation may be required due to increased hemoglobin or adverse events in either treatment arm (luspatercept or placebo). Table 6 below provides guidelines for dose modifications and dose delay.

Celgene or its authorized representative should be notified of dose modification or interruption within 24 hours. Dose reduction and dose delays guidelines are detailed in Table 6 below.

Table 6: Dose Modification: Dose Delay, Dose Reduction, and Discontinuation Guidelines

Event at the Day of Dosing (Assessed prior to each IP administration)	Action
Any suspected related AE ≥ Grade 3[a,d]	Dose delay[c] until resolved to ≤ Grade 1 or baseline, and then reduce dose by 25%
≥ 2 dose reductions suspected related AE [a]	Discontinue treatment
ΔHgb ≥ 2.0 g/dL compared to pre-dose Hgb of previous treatment cycle	Reduce dose by 25%[b] if ΔHgb not influenced by RBC transfusions
Predose Hgb ≥11.5 g/dL	Dose delay until Hgb ≤ 11.0 g/dL
≥ 50% increase in white blood cell count (WBC) compared to pre-dose WBC of previous treatment cycle and above upper limit of normal in the absence of an associated condition (eg, infection or concomitant corticosteroid use)	Dose delay; recheck CBC, including WBC, at least weekly during dose delay. Treatment may be resumed if: WBC values below upper limit of normal[e] within 2 weeks If WBC remains above upper limit of normal[e] for ≥ 2 consecutive weeks in absence of an associated condition (eg, infection or concomitant corticosteroid use); continue dose delay and collect bone marrow/peripheral blood samples to assess MDS disease status. Treatment may be resumed if: Absence of disease progression per IWG response criteria for altering natural history of MDS (Cheson, 2006) AND WBC values return below upper limit of normal[e] Discontinue treatment[f] if: Disease progression per IWG response criteria for altering natural history of MDS (Cheson, 2006) OR WBC remain above upper limit of normal[e]

Table 6: Dose Modification: Dose Delay, Dose Reduction, and Discontinuation Guidelines (Continued)

Event at the Day of Dosing (Assessed prior to each IP administration)	Action
Presence of ≥ 1% blasts in peripheral blood (based on either local or central laboratory hematology sample)	Dose interruption; immediately prepare peripheral blood smear[f,g] for cytomorphology assessment by central pathology laboratory. • If central pathology laboratory cytomorphology assessment confirms ≥ 1% blasts in the peripheral blood; discontinue treatment[h] • If central pathology laboratory cytomorphology assessment determines < 1% peripheral blasts are present, repeat hematology assessment. – If presence of < 1% blasts in peripheral blood, treatment can be resumed at next scheduled dosing cycle. – If presence of ≥ 1% blasts in peripheral blood; discontinue treatment[h]

[a] Possibly, probably or definitely related to IP.
[b] Predose Hgb value not being influenced by RBC transfusion (ie, Hgb result > 14 days after last RBC transfusion or within 3 days from next RBC transfusion); Hgb should be rechecked weekly during dose delay.
[c] If dose delay is > 12 consecutive weeks, treatment should be discontinued.
[d] Includes systolic blood pressure ≥160 mmHg and diastolic blood pressure ≥100 mmHg.
[e] Upper limit of normal >10,000 total WBC/μL or as defined by institutional standards
[f] Peripheral blood smear should be prepared for central pathology lab assessment.
[g] At the investigator's discretion, bone marrow samples may also be collected and analyzed centrally to assess MDS disease status (eg, cytomorphology) prior to making decision regarding treatment discontinuation. The central laboratory must also confirm <5% bone marrow blasts prior to resumption of treatment.
[h] The investigator may contact the Medical Monitor prior to making decision regarding treatment discontinuation.

7.2.1.3. 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.

7.3. Method of Treatment Assignment

The treatment assignment (randomization) will occur at the end of the Screening Period, once all the required screening procedures have been completed and subject is deemed eligible to participate in the study based on assessment of all protocol inclusion and exclusion criteria. This study will utilize the IRT for enrollment.

Designated research personnel at each investigational site will be assigned password protected, coded identification numbers which gives them the authorization to call into IRT to enroll subjects. For drug assignment at each dose start and in the event of any dose reduction, dose titration site staff must contact IRT to record the new dose level and obtain the new study treatment assignment.

The relationship of the randomization number to the subject identification (ID) number will be described by a randomization algorithm. The randomization algorithm will be employed by the IRT system to assign a subject to a treatment based on the prespecified rules, such us double blind study, stratified randomization with randomization ratio active versus placebo on a 2:1; subjects will be placed into the appropriate stratum per the responses/data entered/collected for questions collecting stratification and based on the combination of these data points, the IRT will place the subject in the next available slot within the appropriate stratum for that subject. The IRT will be utilized to ensure an equal weight central randomization based on randomization method according to stratification factors defined in Section 3.1, Study Design. The randomization number corresponds to a particular treatment arm within a stratum. The randomization number, by itself, will not unblind a user to the subject's treatment. The randomization number should be coupled with all the unblinded code information, in order the subject to become unblinded.

7.4. Packaging and Labeling

The IP will be labeled per local requirements.

7.4.1. Blinding

For this trial, all subjects, study site staff and Celgene Corporation representatives with the exception of designated individuals (eg, the pharmacist at the investigational site, the bioanalytical laboratory), will remain blinded to all treatment assignments until all subjects have completed the study, or at the time the study is unblinded (per DMC recommendation) and the database is locked.

Placebo will not be supplied for luspatercept. The designated site individual (for example the pharmacist) at the investigational site will use a syringe (that exactly matches the syringe used for reconstituted luspatercept) and sterile normal saline (0.9% sodium chloride for injection) to prepare a matching placebo. Thus, the designated site individual at the Investigational site will be unblinded and will give Investigators and their staff luspatercept and placebo in a blinded manner.

Randomization, drug dispensing, dose reduction/titration, and drug discontinuation will be accomplished by an IRT system. Authorized site personnel must contact the IRT for randomization, study drug assignment at the beginning of each cycle, to register dose reductions

or titrations, and treatment discontinuation. Confirmation of each call will be sent to the investigational site and Celgene.

For emergency unblinding refer to Section 12.2.

If applicable, include information in this section regarding the physical aspect of blinding related to the packaging and labeling.

7.5. Investigational Product Accountability and Disposal

Accountability for study drug that is administrated 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 study drug 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 IP administration will be made in the appropriate section of the subject's eCRF and source documents. Unless otherwise notified, all vials of study drug, 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 study drug to the Sponsor at the end of the study, or the study drug 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).

7.6. Investigational Product Compliance

Study drug 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 IP 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 IP 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, including but not limited to anti-emetic medications, may be administered at the discretion of the Investigator.

All prior/concomitant treatments used from 5 weeks prior to first dose of IP until 42 days after the last dose of IP (or the End of Treatment (EOT) Visit, whichever occurs later) must be reported on the eCRF.

All prior procedures within the 8 weeks prior to randomization will be recorded on the appropriate eCRF(s).

Prior G-CSF/GM-CSF and iron chelation therapy should be recorded on the appropriate eCRF(s) regardless of treatment discontinuation date.

Prior anti-cancer 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 of the study. 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 IP and affect its metabolism, pharmacokinetics, or excretion, please see the Investigators Brochure and/or local package insert.

8.1. Permitted Concomitant Medications and Procedures

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

Concurrent corticosteroids used for medical conditions other than MDS is allowed provided subject is on a stable or decreasing dose for ≥ 1 week prior to randomization.

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

8.1.1. Iron Chelation Therapy

Subjects who are using iron-chelating therapies at time of randomization should be on a stable or decreasing dose for at least 8 weeks.

Concurrent treatment with iron chelation therapies during the Treatment Period is allowed at the discretion of the investigator and is recommended to be used per product label.

8.1.2. RBC Transfusions

Concurrent treatment for anemia with blood transfusions is allowed, at the discretion of the Investigator, for low hemoglobin levels, symptoms associated with anemia (eg, hemodynamic or pulmonary compromise requiring treatment) or comorbidity.

For any RBC transfusions received during the study, collect hemoglobin value just prior to transfusion.

Each subject will have a "pre-transfusion hemoglobin threshold" for requiring transfusion during the study which will be determined based on transfusion history. Baseline pre-transfusion hemoglobin threshold will be the mean of all documented pre-transfusion hemoglobin values during the 16 weeks prior to Dose 1 Day 1. During treatment, if the pre-transfusion hemoglobin level is increased by ≥ 1 g/dL (at the time of a next anticipated transfusion event) compared to the pre-transfusion hemoglobin threshold for that subject, transfusion should be delayed by a minimum of 7 days and/or the number of units transfused should be reduced by 1 or more RBC units. Subjects may be transfused at the Investigator's discretion for symptoms related to anemia or other requirements (eg, infection).

8.2. Prohibited Concomitant Medications and Procedures

Best supportive care for this study specifically excludes cancer surgery, immunotherapy, biologic therapy, radiotherapy, and systemic chemotherapy where the goal is to eradicate or slow the progression of the disease.

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 immunomodulating drugs (IMiDs)
- Erythropoietin stimulating agents (ESAs) and other RBC hematopoietic growth factors (eg, Interleukin-3).
- Granulocyte colony stimulating factors (ie, G-CSF, GM-CSF), except in cases of neutropenic fever in cases of neutropenic fever or as clinically indicated per product label.
- Hydroxyurea
- Androgens, unless to treat hypogonadism
- Oral retinoids (topical retinoids are permitted)
- Arsenic trioxide
- Interferon

8.3. Required Concomitant Medications and Procedures

Not applicable.

9. STATISTICAL CONSIDERATIONS

9.1. Overview

This is a Phase 3, double-blind, randomized, placebo-controlled, multicenter study to determine the efficacy and safety of luspatercept (ACE-536) versus placebo in subjects with anemia due to very low, low, or intermediate MDS with ring sideroblasts who require RBC transfusions.

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

9.2. Study Population Definitions

Study populations to be analyzed are defined as follow:

Intent-to-treat (ITT): The intent-to-treat (ITT) population will consist of all randomized subjects regardless of whether or not the subject received IP.

Safety: The Safety Population will consist of all subjects who were randomized and received at least one dose of IP. Subjects will be included in the treatment group corresponding to the IP they actually received.

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

A total sample size of 210 (140 in experimental arm [luspatercept (ACE-536)], 70 in control arm [placebo]) will have 90% power to detect the difference between a response rate of 0.30 in the experimental arm (luspatercept [ACE-536]) and a response rate of 0.10 in the control arm (placebo). The sample size calculation is based on one-sided alpha of 0.025, test statistics on difference of proportions using pooled estimate of variance and 10% dropout rate.

9.4. Randomization and Stratification

A 2:1 randomization will be used as this is an orphan disease with a limited number of subjects available. Subjects will be randomized to receive luspatercept or placebo at a 2:1 ratio. A 2:1 randomization scheme would enrich the number of participants exposed to the active treatment group (Dumville, 2006).

Subjects will be randomized to receive luspatercept or placebo at a 2:1 ratio. Randomization will be accomplished by an IRT to ensure timely registration and randomization. A stratified randomization schedule will be implemented. Randomization will be stratified by baseline RBC transfusion burden and baseline IPSS-R risk category (Greenberg, 2012; Appendix D).

Stratification will be based on the following factors:

- RBC transfusion burden at baseline
  - ≥ 6 RBC units/8 weeks (mean of the two consecutive 8 weeks periods immediately prior to randomization)

  - < 6 RBC units/8 weeks (mean of the two consecutive 8 weeks periods immediately prior to randomization)
- IPSS-R at baseline
  - Very low, low
  - Intermediate

9.5. 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. Myelodysplastic syndrome (MDS) diagnoses as well as RBC transfusion dependence will be summarized using frequency tabulations.

9.6. 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.

9.7. Efficacy Analysis

9.7.1. Primary Efficacy Analysis

The primary efficacy analysis will be the comparison of the response rates in the two treatment arms in ITT population. The primary efficacy endpoint of transfusion independent response is defined as the absence of any RBC transfusion during any consecutive 56 day period during the Primary Phase of the Treatment Period (first 24 weeks of double-blind treatment) ie, days 1 to 56, days 2 to 57, days 3 to 58, etc.

Subjects discontinued from the Primary Phase of the Treatment Period without achieving at least 56 days consecutive of RBC transfusion independence will be counted as non-responders.

For the primary efficacy endpoint, 56-day RBC transfusion independence, the response rate will be calculated using the number of responders divided by number of subjects in the ITT population (responders plus non-responders). The response rates of the subjects who were randomized to luspatercept and the placebo will be calculated. In the primary efficacy analysis, the statistical hypothesis is

$$H_0 : P_1 = P_2$$
$$H_a : P_1 > P_2$$

where P_1 denotes the true response rate in the luspatercept group, and P_2 denotes the true response rate in the placebo group. The number and percentage of subjects in the ITT population

who achieve the response will be presented by treatment group. The Cochran–Mantel–Haenszel (CMH) test will be used to test the difference between the 2 response rates at a 1-sided significance level of 0.025 with randomization factors as strata.

Additional details will be outlined in the SAP.

9.7.2. Secondary Efficacy Analyses

9.7.2.1. Key Secondary Efficacy Analyses

The key secondary endpoint, proportion of subjects achieving RBC-TI with duration ≥ 12 weeks, will be tested in the same manner as primary efficacy endpoint using the CMH test.

The analyses for the key secondary endpoint will be based on the ITT population. In order to perform hypothesis testing on multiple endpoints while controlling the overall Type I error rate, a sequential testing approach will be employed where the order of the endpoints to be tested are pre-specified. The primary efficacy endpoint will be tested first at the one-sided 0.025 significance level. If superiority of luspatercept is demonstrated for the primary efficacy endpoint then the key secondary endpoint will be tested, at a one-sided 0.025 significance level.

Proportion of subjects achieving RBC-TI with duration ≥ 12 weeks is the absence of any RBC transfusion during any consecutive 84 day period during the Treatment Period (Weeks 1-24; Weeks 1-48), ie, days 1 to 84, days 2 to 85, days 3 to 86, etc. Subjects discontinued from the Treatment Period without achieving at least 84 consecutive days of RBC transfusion independence will be counted as non-responders.

Full details will be included in the SAP.

9.7.2.2. Additional Secondary Efficacy Analyses

Other secondary variables will be analyzed descriptively, unless otherwise specified, and will be based on the ITT population. Kaplan-Meier methods will be used to estimate curves for time to event secondary variables. Counts and percentages will be used to describe categorical secondary variables.

Hemoglobin (Hgb) increase ≥ 1.0 g/dL is defined as proportion of subjects with ≥ 1.0 g/dL Hgb increase compared to baseline that is sustained over any consecutive 56-day period in the absence of RBC transfusions.

Total RBC units transfused over 16 weeks is defined as the total number of RBC units transfused over a fixed period of 16 weeks (weeks 9-24; weeks 32-48) compared to the total number of RBC units transfused in the 16 weeks immediately prior to randomization.

Proportion of subjects achieving RBC-TI with duration ≥ 8 weeks (Weeks 1-48) is the absence of any RBC transfusion during any consecutive 56-day period during the Treatment Period (Weeks 1-48).

Proportion of subjects achieving modified erythroid response (mHI-E) is defined as proportion of subjects meeting modified HI-E criteria (Cheson, 2006; Appendix E) sustained over any consecutive 56-day period during the Treatment Period. Red blood cell (RBC) transfusions administered for a pre-transfusion Hgb of > 9.0 g/dL will count in the RBC transfusion response evaluation.

Duration of RBC-TI will be determined only for subjects who achieve RBC TI ≥ 8 weeks on treatment. Duration of RBC-TI is defined as the longest RBC-TI period during the Treatment Period. Subjects who maintain RBC-TI through the end of the Treatment Period will be censored at the date of treatment discontinuation or death, whichever occurs first.

Time to RBC-TI will be summarized only for subjects who achieve RBC TI ≥ 8 weeks on treatment. It is defined as the time between randomization and the date onset of TI is first observed (ie, Day 1 of 56 days without any RBC transfusions).

Proportion of subjects achieving hematological response to neutrophils (HI-N) is defined as proportion of subjects meeting HI-N criteria (Cheson, 2006; Appendix E) sustained over any consecutive 56-day period during the Treatment Period.

Proportion of subjects achieving hematological response to platelets (HI-P) is defined as proportion of subjects meeting HI-P criteria (Cheson, 2006; Appendix E) sustained over any consecutive 56-day period during the Treatment Period.

Mean Change in Mean Daily Dose of Iron Chelation Therapy (ICT)

The change in daily dose for each subject is calculated as the difference of post-baseline mean daily dose and baseline mean daily dose. Analysis of covariance (ANCOVA) will be used to compare the treatment difference between groups, with the stratification factors and baseline ICT value as covariates.

Mean Serum Ferritin Decrease

The change is calculated as the difference of post-baseline mean serum ferritin and baseline mean serum ferritin. Analysis of covariance (ANCOVA) will be used to compare the treatment difference between groups, with the stratification factors and baseline serum ferritin value as covariates.

Time to progression to AML is defined as the time between randomization and first diagnosis of AML as per WHO classification of ≥ 20% blasts in peripheral blood or bone marrow. Subjects with diagnosis of AML will be considered to have had an event. Subjects who have not progressed to AML at the time of analysis will be censored at the last assessment date which does not indicate progression to AML.

Overall survival (OS) is defined as the time between randomization and death/censored date. Subjects who die, regardless of the cause of death, will be considered to have had an event. Subjects who are alive at the time of analysis will be censored at the last assessment date at which the subject was known to be alive. All subjects who were lost to follow-up will also be censored at the time of last contact.

Full analysis details will be included in the SAP.

9.8. 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, treatment-emergent adverse events (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 treatment group. Clinically significant hematologic and non-hematologic laboratory abnormalities will be listed and summarized according to the NCI CTCAE (version 4.03) by treatment group.

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 treatment group.

9.9. Other Analysis

Change in health related quality of life questionnaires utilizing EORTC QLQ-C30 CCI [redacted], changes from baseline in overall score and sub-scores will be analyzed and compared between treatment groups using repeated measures of Analysis of Variance (ANOVA)/ANCOVA using the screening scores as covariates where appropriate. Various schemes will be assessed for missing data imputation.

CCI [redacted]

9.10. Timing of Analyses

9.10.1. Interim Analysis

An interim analysis to assess futility will be performed when approximately 105 subjects have completed the Primary Phase of the Treatment Period (first 24 weeks of double-blind treatment) or discontinued before reaching 24 weeks of double-blind treatment (50% information for primary endpoint). There will be no plan to claim luspatercept superiority based on efficacy results so the type one error rate remains at 0.025 one-sided for the final analysis.

Conditional power for primary endpoint will be calculated assuming the observed trend continues for the rest of the data. If it is 10% (corresponding to a futility boundary of p-value ≥0.201 using beta-spending function) or less, with confirmative data for secondary and other efficacy endpoints, the DMC may recommend stopping the study for futility.

This interim analysis will be performed by an independent statistician not affiliated with the study. The sponsor will remain blinded throughout the study.

9.10.2. Final Analysis

Final analysis will be performed when all 210 subjects have completed 48 weeks of treatment or discontinued before 48 weeks.

There is no plan to claim luspatercept superiority based on interim analysis efficacy results, thus the type one error rate remains at 0.025 one-sided for the final analysis.

Additional follow-up analysis for efficacy and safety will be performed when all subjects have been followed for at least 3 years from the last dose of IP.

Full details will be included in the SAP.

9.11. Other Topics

CCI [redacted]

9.11.2. Data Monitoring Committee

An external, independent, unblinded DMC will be comprised of experts in MDS not involved in ACE-536-MDS-001 protocol, an independent Geriatrician/Hypertension Expert, an independent Statistician, and may include additional ad hoc members. Representatives of the Sponsor will be attending the blinded part of the DMC meetings. The Sponsor will not have access to the unblinded data during DMC meetings.

During the course of the study, the DMC will review the unblinded safety data regularly as well as safety and efficacy data in accordance with the guidelines for the preplanned analyses and the procedure pertaining to monitoring of AML progression outlined in the DMC charter. An independent third party will prepare the reports of aggregate data summaries and individual subject data listings, as appropriate, to the DMC members for each scheduled meeting.

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

Operational details for the DMC will be detailed in the DMC charter.

9.11.3. Steering Committee

A Steering Committee will be established by charter for this study. The Steering Committee will be comprised of Study Investigators, Sponsor representatives, and may include additional ad hoc members. The Steering Committee will review blinded data. The SC will serve in an advisory capacity to the Sponsor. The SC may advise and recommend to the Sponsor the following (but not limited to):

- 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 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.

Operational details for the SC will be detailed in a separate SC charter.

Note: The SC is separate from the DMC.

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9.11.5. Subgroup Analysis

Appropriate subgroup analyses by stratification factors and other baseline characteristics for clinical activity may be conducted as exploratory analyses. Full details will be included in the SAP.

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 7.2.1.2 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 will be recorded by the Investigator from the time the subject signs informed consent until 42 days after the last dose of IP as well as those SAEs made known to the Investigator at any time thereafter that are suspected of being related to IP. 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 IP, action taken regarding the IP, 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 4.0);
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

Adverse events 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 the IP 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 IP 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 IP caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP 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 IP 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 IP as a result of an AE or SAE, as applicable (eg, discontinuation, interruption, or dose reduction of IP, 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. 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 IP 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).

10.4. 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.

10.4.1. Females of Childbearing Potential:

Pregnancies and suspected pregnancies (including elevated βhCG or positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring while the subject is on IP, or within 12 weeks of the subject's last dose of IP, are considered immediately reportable events. Investigational product 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 IP 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.

10.4.2. Male Subjects

If a female partner of a male subject taking IP becomes pregnant, the male subject taking IP 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 male latex condom or nonlatex condom NOT made out of natural (animal) membrane (for example, polyurethane), during any sexual contact with FCBP prior to starting investigational product and continue for 12 weeks following the last dose of IP, even if he has undergone a successful vasectomy.

10.5. Other Malignancies/Pre-malignancies

Events of new malignancy, pre-malignant lesions (excluding benign tumors or benign neoplasia) are to 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. All SAE criteria (eg, hospitalization) should be marked if applicable, and all events must be marked as an "Important Medical Event" even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the CRF and subject's source documents. Documentation related to the diagnosis of malignancy must be provided at the time of reporting as a serious adverse event (eg, any confirmatory histology or cytology results, X-rays, 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 the Myelodysplastic Syndrome (MDS) studies, these also include progression to high/very high risk of MDS (per IPSS-R; Greenberg, 2012);-myeloproliferation (eg, clinically significant increases in blasts), progression to AML, 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.

10.6. 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 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 is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent until 42 days after the last dose of IP) or any SAE made known to the Investigator at any time thereafter that are suspected of being related to IP. 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.

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 Investigator Brochure.

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, suspected unexpected serious adverse reactions (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.

In addition, any report of progression to high risk MDS or AML if the case is in the luspatercept arm, upon unblinding regardless of causality, will be reported as an expedited safety report to the regulatory authorities, as requested.

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

- Any AE suspected of being related to the use of IP 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.

11. DISCONTINUATIONS

11.1. Treatment Discontinuation

Subjects will have an End of Treatment (EOT) visit at the time of IP discontinuation. All subjects who received at least one dose of IP will be followed for at least 3 years post last dose of IP.

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

- Lack of Efficacy
- Adverse Event
- Withdrawal by subject
- Death
- Lost to follow-up
- Pregnancy
- Protocol violation
- Study terminated by Sponsor
- Disease Progression as per IWG criteria for altering natural history of MDS (Cheson, 2006; Appendix E)
  - For subjects with 5-10% blasts, a 2nd bone marrow sample should be collected within 4 weeks for clinical assessment (eg, cytomorphology, cytogenetics) to confirm progression before discontinuing subjects from treatment.
- Other (to be specified on the eCRF)
  - Including treatment discontinuation guidance related to dose modification Table 6.

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.

11.2. Study Discontinuation

Subjects who discontinue from treatment for any reason will be followed via telephone contact by the site or subject site visit for collection of data on survival, cause(s) of death, progression to AML, other malignancies/pre-malignancies, post-treatment therapy(ies) for MDS at the 42-Day and 12-Week Follow-up assessments and then every 3 months after the 12-Week Follow-up assessment for at least 3 years after last dose of IP 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 may be considered sufficient reasons for discontinuing a subject from the study:

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

The reason for study discontinuation should be recorded on the End of Study 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).

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

The blind must not be broken during the course of the study unless in the opinion of the Investigator, it is absolutely necessary to safely treat the subject. If it is medically imperative to know what IP the subject is receiving, IP should be temporarily discontinued if, in the opinion of the Investigator, continuing IP can negatively affect the outcome of the subject's treatment.

The decision to break the blind in emergency situations remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, the Investigator may contact the Medical Monitor prior to breaking the blind to discuss unblinding, mainly in the interest of the subject.

The Investigator should ensure that the code is broken only in accordance with the protocol. The Investigator should promptly notify the Medical Monitor of the emergency unblinding and the reason for breaking the blind, which should be clearly documented by the Investigator in the subject's source documentation.

Emergency unblinding should only be performed by the Investigator through the IRT by using an emergency unblinding personal identification number (PIN), and the Investigator should call IRT for unblinded dose information.

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 Good Clinical Practice 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 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.

Investigational product (IP) product 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 the investigational product, and it is the opinion of the Investigator(s) that these subjects continue to receive benefit from treatment, the Sponsor may choose to initiate an open-label, roll-over or extension study under a separate protocol to allow these subjects continued access to luspatercept following their participation in this study ACE-536-MDS-001.

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; 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 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, if 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 CRFs (if paper) and of documentation of corrections for all subjects;
- IP 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, Food and Drug Administration [FDA], European Medicines Agency [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.

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.

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18. APPENDICES

APPENDIX A: Table of Abbreviations

Table 7: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ActRIIB	Activin receptor type IIB
ADA	Antidrug antibodies
AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC	Area under the curve
β-hCG	β-subunit of human chorionic gonadotropin
BM	Bone marrow
BMA	Bone marrow aspirate
BMP	Bone morphogenetic protein
BSC	Best supportive care
CBC	Complete blood count
CXDX	Cycle X Day X
C_{max}	Maximum plasma concentration of drug
CMH	Cochran–Mantel–Haenszel
CMML	Chronic myelomonocytic leukemia
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form

Table 7: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
EEA	European Economic Area
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EOT	End of treatment
EPO	Erythropoietin
ESA	Erythropoiesis- stimulating agents
FAB	French-American-British
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GDF	Growth Differentiation Factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
Hgb	Hemoglobin
HI-E	Hematological improvement-erythroid
HI-N	Hematological improvement-neutrophils
HI-P	Hematological improvement-platelets
HIV	Human Immunodeficiency Virus
HMA	Hypomethylating agents
HR	Hazard ratio
HRQoL	Health-related quality of life
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICT	Iron chelation therapy
IMiDs	Immune-modulatory drugs (a proprietary series of drugs with immunomodulatory and other properties)
IND	Investigational New Drug
Int	Intermediate
IP	Investigational Product
IPSS	International Prognostic Scoring System

Table 7: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
IPSS-R	International Prognostic Scoring System-Revised
IRB	Institutional Review Board
IRT	Integrated Response Technology
ITT	Intent to treat
IWG	International Working Group
IWGMDS	International Working Group on Morphology of Myelodysplastic Syndrome
MDS	Myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
OS	Overall survival
PK	Pharmacokinetics
pRBC	Packed red blood cell
Q3W	Every 3 weeks
QoL	Quality-of-life
RA	Refractory anemia
RAEB	Refractory anemia with excess blasts
RAEB-T	Refractory anemia with excess blasts in transformation
RARS	Refractory anemia with ring sideroblasts
RBC	Red blood cell
RBC-TI	Red blood cell transfusion independence
RCMD-RS	Refractory cytopenia with multilineage dysplasia with ringed sideroblasts
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Steering Committee
SF3B1	splicing factor 3B subunit 1
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction

Table 7: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
TD	Transfusion dependent
TEAE	Treatment-emergent adverse event
TGF	Transforming growth factor
TI	Transfusion independence
ULN	Upper limit of normal
US	United States
USP	United States Pharmacopeia
WFI	Water for injection
WHO	World Health Organization

APPENDIX B: Myelodysplastic Syndromes World Health Organization Classification System (2016)

Peripheral blood and BM findings and cytogenetics of myelodysplastic syndromes (MDS)					
Name	**Dysplastic lineages**	**Cytopenias[a]**	**Ring sideroblasts as % of marrow erythroid elements**	**Bone marrow (BM) and peripheral blood (PB) blasts**	**Cytogenetics by Conventional karyotype analysis**
MDS with single lineage dysplasia (MDS-SLD)	1	1 or 2	<15% / <5%[b]	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with multilineage dysplasia (MDS-MLD)	2 or 3	1-3	<15% / <5% b	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with ring sideroblasts (MDS-RS)					
MDS-RS with single lineage dysplasia (MDS-RS-SLD)	1	1 or 2	≥15% / ≥5% [b]	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS-RS with multilineage dysplasia (MDS-RS-MLD)	2 or 3	1-3	≥15% / ≥5% [b]	BM <5%, PB <1%, No Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with isolated del(5q)	1-3	1-2	None or any	BM <5%, PB <1%, no Auer rods	del(5q) alone or with 1 additional abnormality except -7 or del(7q)
MDS with excess blasts (MDSEB)					
MDS-EB-1	0-3	1-3	None or any	BM 5-9% or PB 2-4%, no Auer rods	Any
MDS-EB-2	0-3	1-3	None or any	BM 10-19% or PB 5-19% or Auer rods	Any
MDS, unclassifiable (MDS-U)					
• with 1% blood blasts	1-3	1-3	None or any	BM <5%, PB=1%[c], no Auer rods	Any
• with single lineage dysplasia and pancytopenia	1	3	None or any	BM <5%, PB <1%, no Auer rods	Any
• based on defining cytogenetic abnormality	0	1-3	<15%[d]	BM <5%, PB <1%, no Auer rods	MDS-defining abnormality
Refractory cytopenia of childhood	1-3	1-3	None	BM <5%, PB <2%	Any

[a] Cytopenias defined as haemoglobin <10 g/dL, platelet count <100 x 10^9/L, and absolute neutrophil count <1.8 x 10^9/L; rarely, MDS may present with mild anaemia or thrombocytopenia above these levels. PB monocytes must be <1 x 10^9/L
[b] If SF3B1 mutation is present.
[c] 1% PB blasts must be recorded on at least two separate occasions.
[d] Cases with ≥15% ring sideroblasts by definition have significant erythroid dysplasia, and are classified as MDS-RS-SLD

Sources: Arber DA, Orazi A, Hasserjian R, Thiele J, Borwitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia. Blood 2016;127(20):2391-405.

APPENDIX C: French-American-British (FAB) Myelodysplastic Syndromes (MDS) Classification System

MDS Subtype	Peripheral Blasts (%)	Bone Marrow Blasts (%)	AML Transformation	Median Survival (months)	MDS Diagnoses (%)
Refractory anemia (RA)	**≤1**	**<5**	**10-20**	**30-65**	**10-40**
Refractory anemia with ringed sideroblasts (RARS)	**≤1**	**<5**	**10-35**	**34-83**	**10-35**
Refractory anemia with excess blasts (RAEB)	**<5**	**5-20**	**>50**	**8-18**	**25-30**
Refractory anemia with excess blasts in transformation (RAEB-T)	**≥5**	**21-29**	**60-100**	**4-11**	**10-30**
Chronic myelomonocytic leukemia (CMML)	**<5**	**≤20**	**>40**	**15-32**	**10-20**

Key: AML = acute myelogenous leukemia; RA = refractory anemia; RARS = refractory anemia with ringed sideroblasts; RAEB = refractory anemia with excess blasts; RAEB-T = refractory anemia with excess blasts in transformation; CMML = chronic myelomonocytic leukemia.

Data from Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR, et al. Proposals for the classification of the myelodysplastic syndromes. Br J Haematol 1982;51(2):189–99.

APPENDIX D: International Prognostic Scoring System Score - Revised

IPSS-R Cytogenetic Risk Groups*,**

Cytogenetic Prognostic Subgroups	Cytogenetic Abnormalities
Very good	-Y, del(11q)
Good	Normal, del(5q), del(12p), del(20q), double including del(5q)
Intermediate	del(7q), +8, +19, i(17q), any other single or double independent clones
Poor	-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), Complex: 3 abnormalities
Very poor	Complex: >3 abnormalities

IPSS-R Prognostic Score Values*

Prognostic Variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good	-	Good	-	Intermediate	Poor	Very Poor
BM Blasts (%)	≤2	-	>2 - <5	-	5 - 10	>10	-
Hemoglobin (g/dL)	≥10	-	8 - <10	<8	-	-	-
Platelets (x 10^9/L)	≥100	50 - <100	<50	-	-	-	-
ANC (x 10^9/L)	≥0.8	<0.8	-	-	-	-	-

IPSS-R Prognostic Risk Categories/Scores*

Risk Category	Risk Score
Very Low	≤1.5
Low	>1.5 - 3
Intermediate	>3 - 4.5
High	>4.5 - 6
Very High	>6

IPSS-R: Prognostic Risk Category Clinical Outcomes*

	No. pts	Very Low	Low	Intermediate	High	Very High
Subjects (%)	7012	19%	38%	20%	13%	10%
Survival***	-	8.8	5.3	3.0	1.6	0.8
AML/25%***,^	-	NR	10.8	3.2	1.4	0.7

*Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Solé F, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood 2012;120(12):2454-65.

***Medians, years.

^ Median time to 25% AML evolution.

Schanz J, Tüchler H, Solé F, Mallo M, Luño E, Cervera J, et al. New comprehensive cytogenetic scoring system for primary myelodysplastic syndromes (MDS) and oligoblastic acute myeloid leukemia after MDS derived from an international database merge. J Clin Oncol 2012;30(8):820-9.

APPENDIX E: International Working Group Response Criteria for Myelodysplastic Syndromes

Altering Natural History of MDS According to IWG Criteria for MDS (Cheson, 2006)	
Category	**Response Criteria (responses must last at least 4 weeks)**
Complete Remission (CR)	Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines[a] Persistent dysplasia will be noted[a,b] Peripheral blood[c] – Hgb ≥ 11 g/dL – Platelets ≥ 100 X 10^9/L – Neutrophils ≥ 1.0 X 10^9/L[b] Blasts 0%
Partial Remission (PR)	All CR criteria if abnormal before treatment except: – Bone marrow blasts decreased by ≥ 50% over pre-treatment but still > 5% – Cellularity and morphology not relevant
Marrow CR[b]	Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pre-treatment[b] Peripheral blood: if HI responses, they will be noted in addition to marrow CR[b].
Stable Disease (SD)	Failure to achieve at least PR, but no evidence of progression for > 8 wks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pre-treatment.
Relapse After CR or PR	At least 1 of the following: – Return to pre-treatment bone marrow blast percentage – Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets[c] – Reduction in Hgb concentration by ≥ 1.5 g/dL or transfusion dependence
Cytogenetic Response	Complete: – Disappearance of the chromosomal abnormality without appearance of new ones Partial: – At least 50% reduction of the chromosomal abnormality
Disease Progression	For subjects with: – Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts – 5%-10% blasts: ≥ 50% increase to > 10% blasts – 10%-20% blasts: ≥ 50% increase to > 20% blasts – 20%-30% blasts[d]: ≥ 50% increase to > 30% blasts Any of the following: – ≥ 50% decrease from maximum remission/response in granulocytes or platelets[c] – Reduction in Hgb by ≥ 2 g/dL – Transfusion dependence
Survival	Endpoints: – Overall: death from any cause – Event free: failure or death from any cause – PFS: disease progression or death from MDS – DFS: time to relapse – Cause-specific death: death related to MDS

KEY: CR = complete remission; FAB = French-American-British; Hgb = hemoglobin; HI = hematologic improvement; IWG = International Working Group; MDS = myelodysplastic syndromes; PR = partial remission; PFS= progression-free survival; DFS= disease-free survival.

[a] Dysplastic changes should consider the normal range of dysplastic changes (modification).

[b] Modification to IWG (2000) response criteria.

[c] Criteria not applicable for ACE-536-MDS-001 patient population.

[d] 20 – 30% blasts is considered AML according to WHO classification (Vardiman, 2009).

Notes: Deletions to IWG criteria are not shown. To convert hemoglobin from grams per deciliter to grams per liter, multiply grams per deciliter by 10.

Source: Cheson, BD, Greenberg PL, Bennett JM, Lowenberg B, Wijermans PW, Nimer SD, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood 2006;108 (2):419-25.

Appendix E: International Working Group Response Criteria for Myelodysplastic Syndromes (Continued)

Hematologic Improvement According to IWG Criteria (Cheson, 2006)	
Hematologic Improvement[a]	**Response criteria (responses must last at least 8 week)[b]**
Erythroid Response (HI-E) (pre-treatment, <11 g/dL)	– Hemoglobin increase by ≥ 1.5 g/dL – Relevant Reduction in units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 wk compared with the pretreatment transfusion number in the previous 8 wk
Platelet Response (HI-P) (pre-treatment, <100 X 109/L)	– Absolute increase of ≥ 30 X 10^9/L for subjects starting with > 20 X 10^9/L platelets – Increase from < 20 X 10^9/L to > 20 X 10^9/L and by at least 100%[b]
Neutrophil Response (HI-N) (pre-treatment, <1.0 X 109/L)	– At least 100% increase and an absolute increase > 0.5 X 10^9/L[b]
Progression or Relapse After HIc	At least 1 of the following: – At least 50% decrease from maximum response levels in granulocytes or platelets – Reduction in Hgb by ≥ 1.5 g/dL – Transfusion dependence

KEY: HI-E = hematologic improvement erythroid response; HI-N = hematologic improvement neutrophil response; HI-P = hematologic improvement platelet response; IWG = International Working Group; RBC = red blood cell.

[a] Pretreatment counts averages of at least 2 measurements (not influenced by transfusions, ie, no RBC transfusions for 2 weeks and no platelet transfusions for 1 week) ≥ 1 week apart (modification).

[b] Modification to IWG (2000) response criteria.

[c] In the absence of another explanation, such as acute infection, repeated courses of chemotherapy (modification), gastrointestinal bleeding, hemolysis, and so forth. It is recommended that the 2 kinds of erythroid and platelet responses be reported overall as well as by the individual response pattern.

Note: Deletions to the IWG criteria are not shown. To convert hemoglobin levels from grams per deciliter to grams per liter, multiply grams per deciliter by 10.

Source: Cheson, BD, Greenberg PL, Bennett JM, Lowenberg B, Wijermans PW, Nimer SD, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood 2006;108 (2):419-25.

APPENDIX F: European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire (Version 3.0)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

APPENDIX F: European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire (Version 3.0) (continued)

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

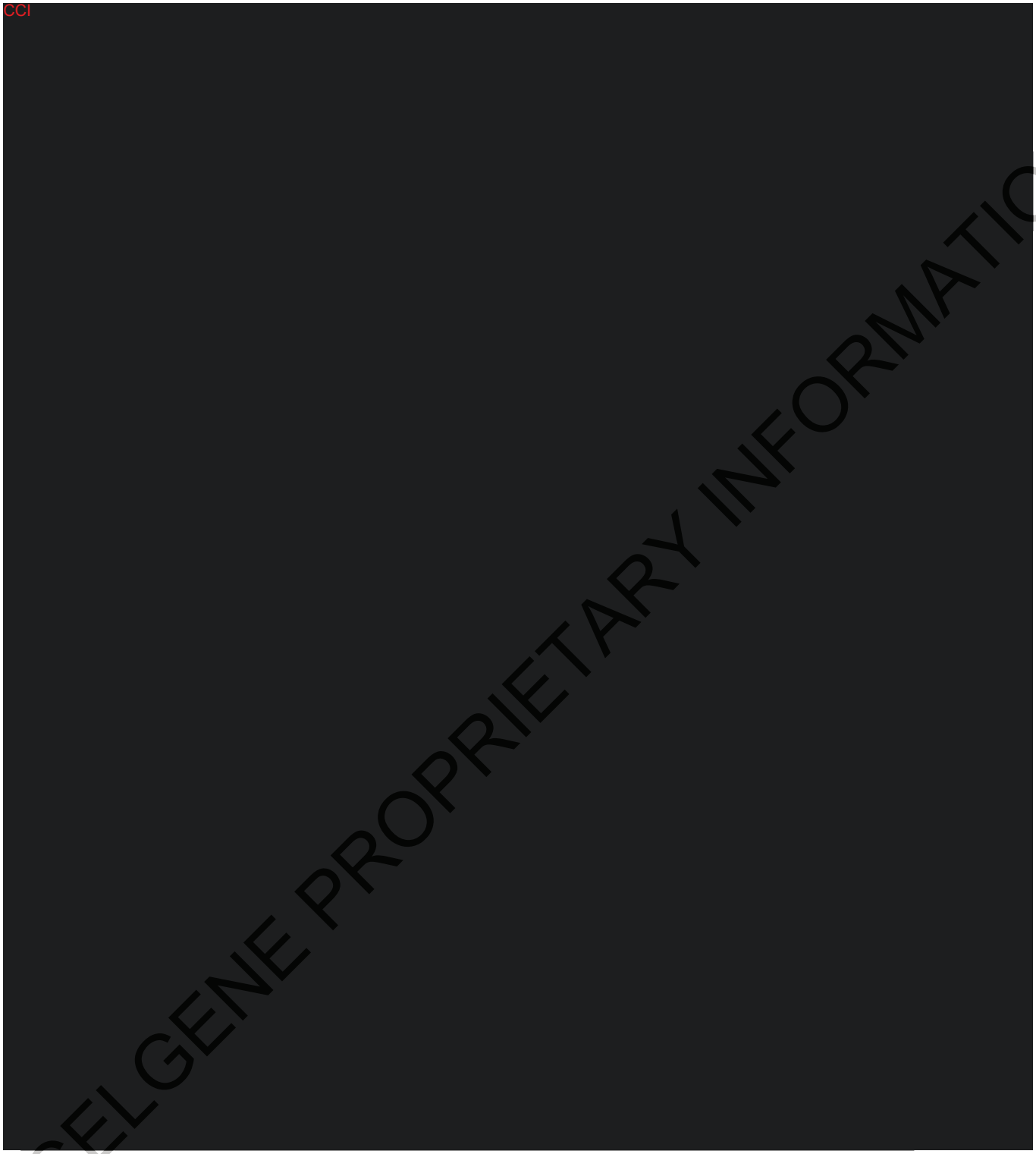
APPENDIX G: Eastern Cooperative Oncology Group (ECOG) Performance Status

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.

CCI

CCI



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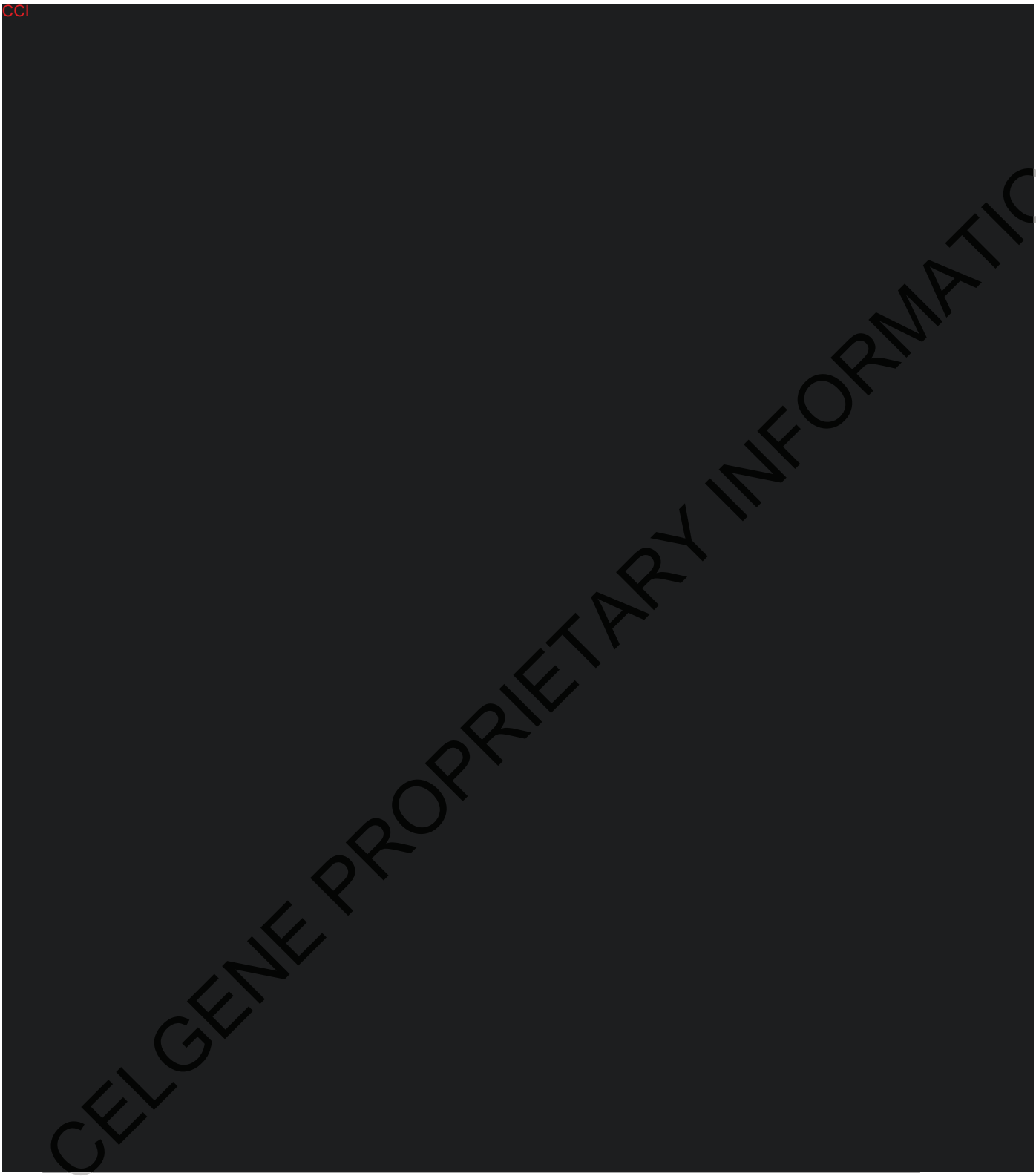

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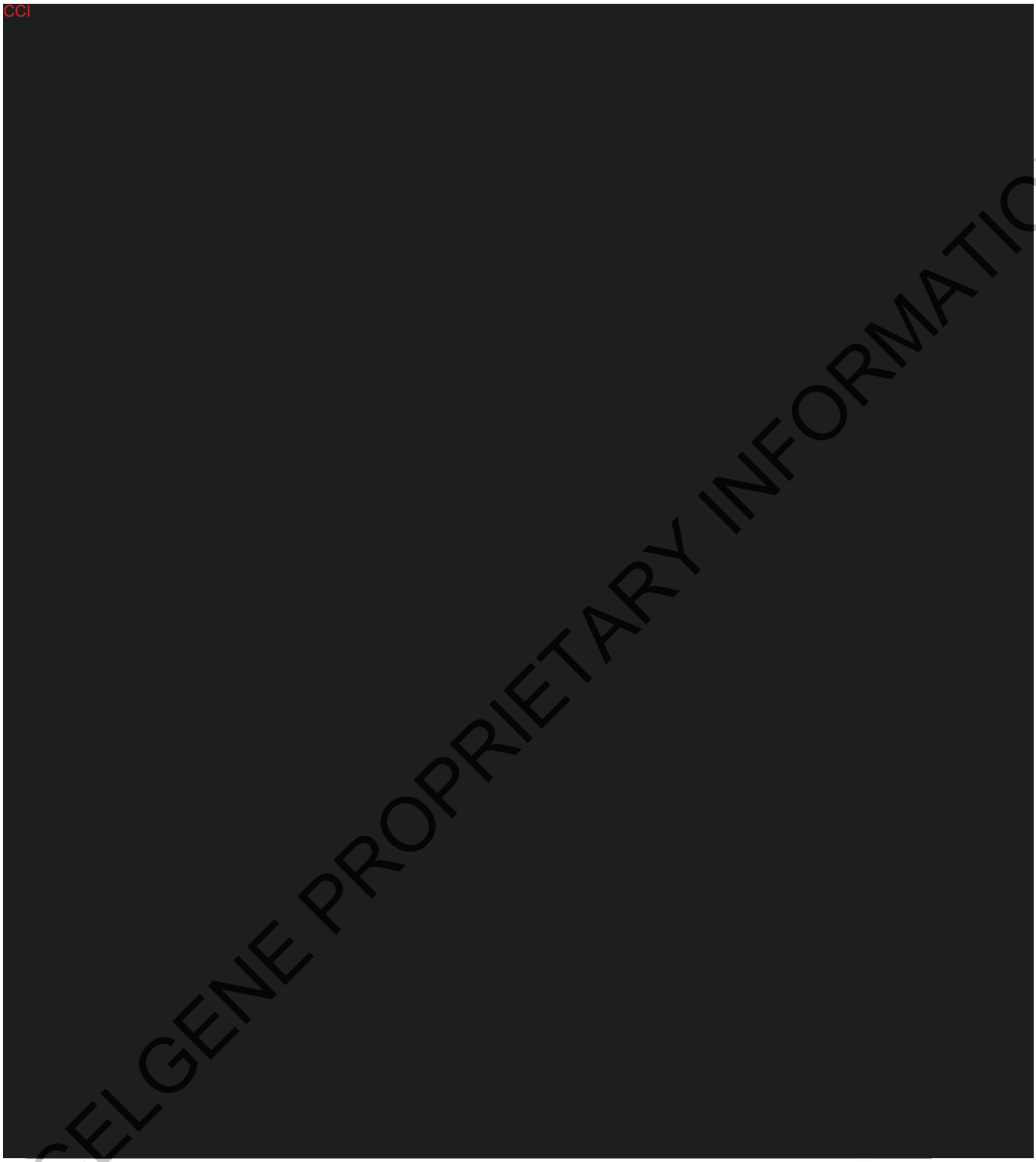

Celgene Signing Page

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: PPD
Title: PPD
Date: Tuesday, 09 May 2017, 09:55 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- **Removal of "progression to acute myeloid leukemia (AML) or high/very high risk category MDS per IPSS-R" from the dose modification and treatment discontinuation criteria as per Steering Committee request**

Update to the protocol to remove "Progression to acute myeloid leukemia (AML) or high/very high risk category MDS per International Prognostic Scoring System – Revised (IPSS-R)" from the dose modification and treatment discontinuation criteria to avoid redundancy as "progression to AML and high/very high risk category MDS per IPSS-R" is covered by the criteria for disease progression per International Working Group (IWG) (Cheson, 2006) used in the protocol.

Revised sections: Protocol Summary; Section 1.3.2, Rationale for the Study; Figure 2: Overall Study Design (footnotes); Section 3, Overall Study Design; Section 6, Section 6.2.2; Section 6.2.3; Procedures; Section 7.2.1.2, Table 6 Dose Modification: Dose Delay, Dose Reduction and Discontinuation Guidelines; Section 11.1, Treatment Discontinuation

- **Clarification on the anti-drug antibodies (ADA) and pharmacokinetic (PK) sample collection in the Follow-up period to maintain the blinding of the study**

Update to the protocol to include ADA sampling for all subjects in the Follow-up period rather than only when tested positive at the End of Treatment (EOT) visit as an available ADA antibody status for a subject potentially unblinds the Sponsor and/or the clinical site to a subject's assigned treatment arm.

Revised sections: Protocol Summary; Table 3 Study Endpoints; Section 3; Table 4: Table of Events; Section 6.4; Section 6.5; Section 6.8.2

- **Clarification on the timing and allowed time window for the Week 25 Visit**

Update to the protocol to clarify the timing of the Week 25 visit procedures and myelodysplastic syndromes (MDS) disease assessments.

Revised sections: Protocol Summary; Table 3: Study Endpoints; Section 3; Section 6; Section 6.2.2; Table 4: Table of Events

- **Modified protocol criteria related to dose modifications (Dose Delay, Dose Reduction and Discontinuation) measures related to potential cases of leukocytosis**

Updates to the protocol language CCI [redacted] to further strengthen dose modification and treatment stopping guidance related to potential cases of leukocytosis as well as to monitor progression to high/very high risk MDS or AML as events of interest throughout the study and to report these events to regulatory agencies, as requested.

Revised section: Protocol Summary; Section 3.1; Section 3.2; Section 6.1; Section 6.2.2; Section 6.8.2; Table 6: Dose Modification: Dose Delay, Dose Reduction, and Discontinuation Guidelines; Section 9.11.2; Section 10.5; Section 10.7.

- **Extended the Posttreatment Follow-up Period from "at least 2 years" to "at least 3 years" from the date of last dose of investigational product (IP)**

Updates to the protocol language based on feedback received from CCI [redacted] to reflect the collection of all cases of cancers occurring in subjects for at least 3 years after the last investigational product is taken.

Revised section: Protocol Summary; Table 3: Study Endpoints; Section 3.1; Section 3.2; Figure 2: Overall Study Design; Table 4: Table of Events; Section 6.1; Section 6.2; Section 6.8.2; Section 9.10.2; Section 11.1; Section 11.2

The amendment also includes several other minor clarifications and corrections:

- Administrative change to the Medical Monitor/ Emergency Contact Information (Cover page).
- Correction in Table 3 (Study Endpoints) to reflect the correct timeframes corresponding with a 16-week period.
- Clarification in Section 4.2 (Inclusion criterion 5) regarding required wash out period for both prior erythropoiesis stimulating agents (ESA) and granulocyte colony stimulating factor (G-CSF) treatment.
- Clarification in Section 4.2 (Inclusion criterion 8) regarding the requirement to use contraception in females of childbearing potential if they are sexually active.
- Clarification in Section 4.3 (Exclusion criterion 5) regarding the sequence of assessments evaluated excluding iron deficiency.
- Clarification in Section 4.3 (Exclusion criterion 20); Table 4 (Table of Events) including footnotes; and Section 6.1 regarding timing of local testing confirming the Human Immunodeficiency Virus (HIV), Hepatitis B, and/or Hepatitis C status.
- Clarification in Section 6 regarding the exceptional use of local laboratories to determine study eligibility after sponsor consultation (eg, hemolyzed sample etc.).
- Clarification in Section 7.2 regarding the IP administration of volumes greater than 1.2 mL and the maximum total dose per administration that should not be exceeded.
- Clarification in Section 8.1.1 that iron-chelating therapy at time of randomization should be on a stable or decreasing dose for at least 8 weeks.
- CCI [redacted]
- Clarification in Appendix E regarding criteria related to the definition of disease progression not applicable for the ACE-536-MDS-001 patient population.
- Administrative changes (eg, consistency of acronym use throughout the document per Celgene Style Guide, spelling, grammatical error corrections, etc.) were also made throughout the document.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- **Modified protocol criteria related to contraception measures to align with definition of "highly effective contraception measures" as per Clinical Trial Facilitation Group (CTFG) guidelines**

Updates to the protocol language regarding contraception and pregnancy testing for females of child bearing potential (FCBP) to align with definition of "highly effective contraception measures" as per Clinical Trial Facilitation Group (CTFG) guidelines were requested CCI [redacted]

Revised sections: Section 1.2.2.1, Potential Risks of Human Use; Section 4.2, Inclusion Criteria 8 and 9

- **Added monitoring of other malignancies/pre-malignancies as "important medical events"**

CCI [redacted] the Scientific Steering Committee (SSC) recommended monitoring of other malignancies/pre-malignancies during the Treatment Period and for the duration of the Long-term Follow-up Period as "important medical events." Designation as an "important medical event" will require sites to report events of other malignancies/pre-malignancies under the same guidelines as a serious adverse event. These additional measures will further strengthen safety monitoring throughout the course of the study. CCI [redacted]

New section: Section 10.5, Other Malignancies/Pre-malignancies

Revised sections: Protocol Summary; Section 3.2, Study Duration for Patients; Section 5, Table 4 Table of Events; Section 6, Procedures; Section 6.1, Screening Period; Section 6.2.1, Primary Phase of Treatment Period: Weeks 1-24; Section 6.2.2, MDS Disease Assessment: Week 25 Visit; Section 6.8.2, Long-term Follow-up; Section 11.2, Study Discontinuation

- **Added site guidance regarding collection of transfusion data**

As additional assurance that all transfusion data is collected throughout the course of the study (including transfusions that may have occurred in between study visits at local institutions), specific guidance for sites has been included in the protocol amendment. CCI [redacted]

Revised sections: Section 5, Table 4 Table of Events; Section 6.1, Screening Period; Section 6.2, Treatment Period; Section 6.2.1, Primary Phase of Treatment Period: Weeks 1-24; Section 6.2.3, Extension Phase of the Treatment Period: After Week 25 Visit; Section 7.2, Treatment Administration and Schedule

- CCI [redacted]

- **Included dose modification and treatment discontinuation criteria regarding leukocyte increase and disease progression as per International Working Group (IWG) criteria (Cheson, 2006)**

Additional dose modification and treatment discontinuation rules to account for potential cases of leukocytosis and inclusion of disease progression per IWG criteria as treatment discontinuation criteria have been incorporated in the protocol amendment based upon CCI [redacted].

Revised sections: Protocol Summary; Section 1.3.2, Rationale for the Study; Figure 2 (footnotes); Section 3, Overall Study Design; Section 6, Procedures; Section 4.2, Inclusion Criterion 3; Section 7.2.1.2, Table 6 Dose Modification: Dose Delay, Dose Reduction and Discontinuation Guidelines; Section 11.1, Treatment Discontinuation

- **Accounted for update of World Health Organization (WHO) classification system (Arber 2016) and included French-American-British (FAB) classification system for baseline MDS diagnosis**

As ring sideroblast positive disease is a key attribute of the study's patient population additional language was added to the protocol taking into consideration the recent update to the WHO classification criteria (Arber, 2016), which further expanded the definition of ring sideroblast positive disease to also include patients with ≥ 5% ring sideroblasts and confirmation of SF3B1 mutation along with patients who solely meet the previously established ≥ 15% threshold. In addition, the Scientific Steering Committee (SSC) agreed to this modification and also recommended use of the French-American-British (FAB) classification system in addition to the WHO classification system to determine eligibility related to baseline MDS diagnosis.

Revised sections: Section 1.1.1.2, Ring Sideroblasts; Section 3.1, Study Design, Section 4.2, Inclusion Criterion 3; Section 6.1 Screening Period

- **Extended collection of transfusion data after treatment discontinuation**

The duration of transfusion data collection has been extended to 16 weeks after last dose of IP or End of Treatment visit (whichever is later) CCI [redacted]

CCI based on their assessment of another Celgene clinical study. This additional transfusion data should aid in the characterization of the luspatercept risk-benefit profile.

Revised sections: Protocol Summary; Section 3.1, Study Design and Figure 2: Overall Study Design; Section 5, Table 4 Table of Events; Section 6.2.1, Primary Phase of Treatment Period: Weeks 1-24; Section 6.8.2, Long-term Follow-up

- **Included upper pre-transfusion Hgb threshold of 10 g/dL to protocol eligibility criterion related to requirement of transfusions**

With the older demographic in myelodysplastic syndromes (MDS), patients often develop overlapping comorbidities. When erythrocyte production is affected in MDS, patients frequently present with signs and symptoms of anemia including pallor, tachycardia, hypotension, fatigue, headache and exercise intolerance, or with signs and symptoms of worsening of an underlying condition such as angina pectoris, heart failure, or a pulmonary disorder. Patients with such co-morbidities may have more symptoms at a higher baseline Hgb level than patient who do not have such co-morbidities. Due to this fact, some practitioners choose to transfuse their older MDS patients with multiple co-morbidities at a higher Hgb level of 10 g/dL than they would younger and/or more fit patients. This was discussed and agreed to with the Scientific Steering Committee (SSC).

It is important to note that subjects may still receive transfusions at a lower Hgb threshold during the Treatment Period if clinically indicated at the investigators discretion as outlined in Protocol Section 8.1.2. Additional language has been added to Section 8.1.2 as per SSC recommendation to provide further clarification on ensuring consistency in transfusion practices in regard to pre-transfusion Hgb threshold after study entry.

Revised sections: Section 4.2, Inclusion Criterion 6; Section 6.1, Screening Period; Section 8.1.2, RBC Transfusions

- **Added language to allow for the participation of patients with > 2.0 upper limit of normal (ULN) serum bilirubin if in the presence of diagnosed or known Gilbert syndrome.**

Gilbert syndrome, also known as Gilbert-Meulengracht syndrome, is a benign hereditary condition characterized by intermittent unconjugated hyperbilirubinemia in the absence of hepatocellular disease or hemolysis (Fretzayaz, 2012). Patients with Gilbert syndrome are asymptomatic and typically have otherwise normal liver serum chemistries (VanWagner, 2015). This is a benign condition that does not otherwise affect normal liver function and should not exclude patients from the trial.

Revised section: Section 4.3, Exclusion Criterion 14

- **Revised eligibility criteria to exclude patients with significant cardiac dysfunction based on known local ECHO/MUGA results**

To further ensure patients with significant cardiac dysfunction are not enrolled into study, the Scientific Steering Committee (SSC) recommended that patients with known ejection fraction < 35% be excluded (based upon local ECHO or MUGA performed within 6 months of randomization date).

Revised sections: Section 4.3, Exclusion Criterion 19

- **Revised eligibility criteria to allow use of experimental agents prior to randomization**

As the MDS population is an older demographic, many patients have overlapping comorbidities that may require treatment, which may include investigational agents. Contingent that the last dose of the investigational agent is at least 5 weeks from date of randomization (or 5 times the half-life, if half-life is known), these patients should not be excluded.

Revised sections: Section 4.3, Exclusion Criteria 1 and 8

- **Revised eligibility criteria to allow enrollment of patients who received a prior sub-therapeutic course of hypomethylating agent or lenalidomide**

As the investigational use of active therapy (eg, hypomethylating agents, lenalidomide) is common in the clinical setting in certain countries (eg, US) for lower risk, non del5q, MDS patients who are erythropoiesis-stimulating agent (ESA) refractory; patients who may have received sub-therapeutic courses of these agents and discontinued due to intolerance should not be excluded from the protocol. The Scientific Steering Committee recommended the following maximum durations of prior treatment with these agents to ensure only patients receiving sub-therapeutic courses are enrolled.

Lenalidomide = no more than 1 calendar week of treatment

Hypomethylating agents = no more than 2 doses

Revised section: Section 4.3, Exclusion Criterion 1

- **Decreased the ESA/G-CSF/GM-CSF washout window to 4 weeks from date of randomization**

In order to ensure that the required ESA/growth factor washout period can be completed within protocol 5-week screening window, the Scientific Steering Committee (SSC) recommended decreasing the washout period to 4 weeks to avoid unnecessary screen failures.
Revised section: Section 4.2, Inclusion Criterion 5

- **Updated applicable protocol sections to align with Investigator's Brochure (IB) Edition 8 (IB update occurring in parallel)**

Revised sections: Section 1.2, Compound Background; Section 1.2.1.1, Toxicology Studies; 1.2.2.1, Potential Risks of Human Use; Section 1.3.1, Study Rationale and Purpose

- **Added information related to benefit/risk and added section titled Overall Benefit Risk Assessment to the protocol**

CCI [redacted] information related to benefit/risk and an overall benefit risk assessment has been included in the protocol to allow the investigator to review the information and form his/her opinion of the benefit/risks to the patient in the current clinical trial.

New section: Section 1.2.2.2, Overall Benefit Risk Assessment

Revised sections: Section 1.2.2.1, Potential Risks of Human Use;

The amendment also includes several other minor clarifications and corrections:

- Update to sponsor medical monitor contact information on protocol page 2.
- Update to sponsor therapeutic area head title on protocol page 3.Additional supportive information added to Section 1.3.1 Study Rationale Clarification in Protocol Summary that bone marrow aspirate (or biopsy) for assessment of MDS disease is both efficacy and safety assessmentClarification in Section 4.3 regarding history of other malignancies (Exclusion criterion 15)Clarification in Section 4.3 (Exclusion criterion 20); Section 5, Table 4 Table of Events; and Section 6.1, Screening Period regarding assessment of known history of Human Immunodeficiency Virus (HIV), Hepatitis B, and/or Hepatitis C active infection. CCI [redacted] Clarification in Section 4.3 (Exclusion criterion 22) regarding exclusion of vulnerable patients. CCI [redacted] .Clarification in Section 6.1 regarding bone marrow sample collection requirements to determine study eligibility CCI [redacted] Update to Section 7.1 with current information regarding investigational product (IP) stability data Clarification in Section 7.1 regarding supply of placebo Clarification in Section 7.3 regarding randomization processUpdate to Section 7.4 to account for differences in local regulations between countries regarding packing and labeling of investigational product (IP)Clarification in Section 8.1 on allowance of attenuated vaccines (eg, influenza vaccine) as concomitant medication if clinically indicatedClarification in Section 8.1.2 regarding pre-transfusion hemoglobin (Hgb) threshold recommendation during the Treatment PeriodSection 17 was updated to include additional citations added during this protocol amendment.Administrative changes (eg, consistency of acronym use throughout document per Celgene Style Guide, spelling, grammatical error corrections, etc.) were also made throughout document

Supportive Literature Used in the Summary of Changes

Arber DA, Orazi A, Hasserjian R, Thiele J, Borwitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia. Blood 2016;127(20):2391-405.

Cheson BD, Greenberg PL, Bennett JM, Lowenberg B, Wijermans PW, Nimer SD, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood 2006;108(2):419-25.

Fretzayaz A, Moustaki M, Liapi O, Karpathios T. Gilbert syndrome. Eur J Pediatric 2012;171(1):11-5.

VanWagner LB, Green RM. Evaluating elevated bilirubin levels in asymptomatic adults. JAMA 2015;3; 313(5):516-7.