Official Title of Study:

A Phase 2, Multicenter, Single-arm Study to Evaluate the Efficacy, Pharmacokinetics, and Safety of Luspatercept (ACE-536) for the Treatment of Anemia due to IPSS-R Very Low, Low or Intermediate Risk Myelodysplastic Syndromes (MDS) in Japanese Subjects who are Not Requiring Red Blood Cell Transfusion

PROTOCOL(S) ACE-536-MDS-003

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A PHASE 2, MULTICENTER, SINGLE-ARM STUDY TO EVALUATE THE EFFICACY, PHARMACOKINETICS, AND SAFETY OF LUSPATERCEPT (ACE-536) FOR THE TREATMENT OF ANEMIA DUE TO IPSS-R VERY LOW, LOW OR INTERMEDIATE RISK MYELODYSPLASTIC SYNDROMES (MDS) IN JAPANESE SUBJECTS WHO ARE NOT REQUIRING RED BLOOD CELL TRANSFUSION

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

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PROTOCOL SUMMARY

Study Title

A Phase 2, Multicenter, Single-arm Study to Evaluate the Efficacy, Pharmacokinetics, and Safety of Luspatercept (ACE-536) for the Treatment of Anemia due to IPSS-R Very Low, Low or Intermediate Risk Myelodysplastic Syndromes (MDS) in Japanese Subjects who are Not Requiring Red Blood Cell Transfusion

Indication

Treatment of anemia due to very low, low, or intermediate risk myelodysplastic syndromes (MDS) according to the International Prognostic Scoring System – Revised (IPSS-R) in subjects who are not requiring red blood cell (RBC) transfusion (ie, no RBC transfusion in the 16 weeks prior to enrollment).

Myelodysplastic syndromes, primarily affecting older adults, 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) (Ades, 2014; Brunning, 2008; Catenacci, 2005; Fenaux, 2009; Steensma, 2013; Visconte, 2014; Zeidan, 2013).

Lower hemoglobin (Hgb) levels and RBC-TD 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 patients (Zeidan, 2013). In addition, long-term RBC-TD has 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).

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; Hellstrom-Lindberg, 2013; Kao, 2008; Malcovati, 2005; Platzbecker, 2012). Subjects in the lower risk groups also often become dependent on frequent RBC transfusions, which leads to decreased HRQoL and increased morbidity and mortality (Hellstrom-Lindberg, 2003; Malcovati, 2005). Thus, the therapeutic goal in RBC - transfusion independent (TI) patients is to increase Hgb levels and prevent from becoming RBC-TD.

Luspatercept (ACE-536), an erythroid maturation agent, 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 Fc portion of human immunoglobulin G1 (IgG1-Fc). Luspatercept acts on endogenous inhibitors of late-stage erythropoiesis (eg, growth and differentiation factor 11, GDF11) to increase release of mature erythrocytes into circulation. Nonclinical data have demonstrated that luspatercept binds to negative regulators governing late-stage erythroid development to inhibit their action, thereby promoting the maturation of erythrocytes in the bone marrow. These findings suggest that luspatercept may represent a novel therapeutic approach to anemia, particularly in diseases in which ineffective erythropoiesis is a contributing factor, as in β-thalassemia and MDS.

Objectives

Primary objective:

- To evaluate the hematologic improvement – erythroid response (HI-E) per the International Working Group (IWG) (Cheson, 2006) from W1D1 through Week 24 for the treatment of anemia due to IPSS-R very low, low, or intermediate risk MDS in Japanese subjects who are not requiring RBC transfusion

Secondary objectives:

- To evaluate modified HI-E (mHI-E) per IWG (Cheson, 2006)
- To evaluate HI-E per IWG (Cheson, 2006) from W1D1 through Week 48
- To evaluate the time to HI-E and duration of HI-E
- To evaluate the time to mHI-E and duration of mHI-E
- To evaluate the proportion of subjects who maintain TI at Week 24, Week 48 and Week 72
- To assess the safety of luspatercept
- To assess the pharmacokinetics (PK) of luspatercept
- To assess the frequency of antidrug antibodies (ADA) and effects on efficacy, safety, or PK
- To assess the number and percentage of subjects progressing to AML; time to AML progression
- To assess the overall survival

Study Design

ACE-536-MDS-003 is a Phase 2, multicenter, single-arm study. The primary objective of the study is to evaluate HI-E per IWG (Cheson, 2006) from W1D1 through Week 24 for the treatment of anemia due to IPSS-R very low, low, or intermediate risk MDS in Japanese subjects who are not requiring RBC transfusion.

The study is divided into a Screening Period, a Treatment Period and a Post-Treatment Follow-up Period.

Screening Period:

Subject screening procedures are to take place within 35 days prior to Week 1 Day 1 (W1D1) (after the subject has given written informed consent). During the Screening Period, the subject will undergo safety and other assessments to determine eligibility for the study.

Central review of bone marrow aspirate smear and peripheral blood smear will be used to confirm MDS diagnosis according to the World Health Organization (WHO) 2016 classification (Appendix B) and to determine the baseline IPSS-R risk classification (Greenberg, 2012). A bone marrow biopsy will be collected only when adequate aspirate is not attainable.

Treatment Period:

The first dose of investigational product (IP) should be administered within 3 days of enrollment at the latest.

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 erythropoiesis stimulating agents (ESA)s.

Subjects should receive IP through to a minimum of the 24-week MDS Disease Assessment Visit scheduled for Day 169 unless the subject experiences unacceptable toxicities, withdraws consent, or meets any other treatment discontinuation criteria.

The MDS Disease Assessment (Section 6.4.2) on Day 169 (and every 24 weeks thereafter [ie, Day 337, Day 505, etc.] consists of the investigator's assessment of clinical benefit from IP and status of underlying disease. For subjects to remain on treatment beyond this timepoint, both of the following criteria must be confirmed in each subject:

- Evidence of clinical benefit defined by either one of the following two criteria:
  - HI-E based on IWG (Cheson, 2006) (Appendix D) (Hgb increase of ≥ 1.5 g/dL for the 8 weeks within the 12 weeks immediately preceding Day 169 and every 24 weeks thereafter [ie, Day 337, Day 505, etc.])
  - Maintain RBC transfusion independence
- Absence of disease progression per IWG criteria for altering natural history of MDS (Cheson, 2006) (Appendix E) based on central morphological assessment of bone marrow, peripheral blood and cytogenetics results

Based on the outcome of these assessments, subjects will either be discontinued from treatment with IP, undergo End of Treatment (EOT) evaluations and enter the Post-Treatment Follow-up Period or continue the treatment as long as the above criteria continue to be met or until the subject experiences unacceptable toxicities, withdraws consent, or meets any other discontinuation criteria.

Post-Treatment Follow-up Period:

All subjects who have received at least one dose of IP should undergo EOT and 42-Day Follow-up evaluations.

This includes (but is not limited to) the collection of adverse events (AEs), concomitant drugs and RBC-transfusion data (until 8 weeks after last dose of IP or the EOT Visit, whichever occurs later).

In addition, subjects will continue to be followed for 5 years from the date of the first dose of IP, or 3 years from the last dose (whichever occurs later), for monitoring for other malignancies/pre-malignances and progression to AML in the Long-term Post-Treatment Follow-up Period along with data collection of subsequent MDS therapies, and overall survival unless the subject withdraws consent from the study, dies or is lost to follow-up. For that purpose, subjects will be followed after treatment every 12 weeks for 3 years from the date of last dose of IP and every 6 months thereafter, if applicable.

An antidrug antibodies (ADA) sample(s) may be required in the Post-Treatment Follow-up Period for subjects, who terminate the Treatment Period with less than 1 year of ADA monitoring if a subject is ADA positive at the time of treatment discontinuation.

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

Study Population

Adult subjects (≥ 20 years) with anemia due to a IPSS-R very low, low, or intermediate risk MDS according to the WHO 2016 classification and a bone marrow blast count of < 5% (Arber, 2016; Greenberg, 2012), who are not requiring RBC transfusion (ie, no RBC transfusion administered within 16 weeks prior to W1D1 - except transfusions due to blood loss or infection that occurred between 16 and 8 weeks prior to W1D1), and ESAs naïve or previously used ESAs but not administered ESAs within 8 weeks prior to W1D1.

Length of Study

The expected duration of the study is approximately 8 years, which consists of approximately 2 years of enrollment, approximately 1 additional year of luspatercept treatment after the last subject is enrolled, and 5 years of follow up from first dose of IP, or 3 years from last dose (whichever occurs later), to complete the Post-Treatment 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 and/or exploratory analysis, as prespecified in the protocol, whichever is the later date.

The sponsor may end the trial when all key endpoints and objectives of the study have been analyzed and the availability of a roll-over protocol exists into which 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.

Study Treatments

Eligible subjects will be administered luspatercept (ACE-536): starting dose of 1.0 mg/kg subcutaneous injection every 3 weeks (21 days; Q3W). Dose levels can be increased in a stepwise manner beyond the starting dose to 1.33 mg/kg, and up to a maximum of 1.75 mg/kg.

For a detailed description of study treatments please refer to Section 7.

Overview of Key Efficacy Assessments

Efficacy assessments include the assessment of hematological parameters (eg, hemoglobin, platelet count, neutrophils), collection of transfusion data (eg, RBC transfusions) and central cytomorphology and cytogenetics review of bone marrow aspirate and peripheral blood for MDS disease assessment.

Response assessment according to IWG criteria (Cheson, 2006) is to be performed at the 24-Week MDS Disease Assessment Visit (ie, Day 169) and every 24 weeks (ie, 168 days) thereafter.

For a detailed description of efficacy assessments please refer to Section 6.4.

Overview of Key Safety Assessments

Safety assessments include hematology (complete blood count [CBC] with differential) and serum chemistry analyses, recording of adverse events, physical exam, vital signs and electrocardiograms (ECGs). In addition, subjects will be monitored for progression to AML and other malignancies/pre-malignancies.

Overview of Pharmacokinetic Assessments

Serial serum samples will be collected in all subjects to be received the study drug to analyze luspatercept concentrations in serum from W1D1 through 24-Week MDS Disease Assessment. The sampling time points for the dense PK in the initial 10 subjects will be W1D1, W1D3, W2D1, W2D3, W3D1, W4D1, W10D1, W13D1, W16D1, W17D1, W18D1, W19D1, W22D1, 24-Week MDS Disease Assessment, and for the sparse PK in other 10 subjects will be W1D1, W2D1, W3D1, W4D1, W10D1, W16D1, W22D1, 24-Week MDS Disease Assessment. Also, serum samples will be collected every 12 weeks for up to 1 year from the first dose in all subjects.

PK parameters including, but not limited to area under the concentration time curve (AUC), maximum plasma concentration of drug (C_{max}), time to maximum plasma concentration of drug (T_{max}), terminal elimination half-life ($t_{1/2}$), apparent clearance of drug from plasma after extravascular administration (CL/F), and apparent volume of distribution during the terminal phase after extravascular administration (V/F) will be estimated for each subject.

Statistical Methods

The sample size calculation is based on one sample binomial exact test. The null hypothesis to be tested is that the proportion of subjects achieving HI-E is ≤ 10%; the alternative hypothesis is that the proportion of subjects achieving HI-E is > 10%. With these hypotheses, a sample size of 20 subjects are required with a power of 95% at a one-sided 0.025 alpha level if the expected proportion is 45%.

The primary efficacy endpoint of HI-E per IWG (Cheson, 2006) is defined as proportion of subjects meeting HI-E criteria of ≥ 1.5 g/dL increase in Hgb sustained over any consecutive 56-day period in the absence of RBC transfusions from W1D1 through Week 24. Subjects discontinued from the treatment period without achieving HI-E will be counted as non-responders. Dose modification guidance for luspatercept in Section 7.2.2 defines that, if predose Hgb is ≥ 12.0 g/dL at the day of dosing, the dose should be delayed until Hgb is < 11.0 g/dL. For subjects who meet this criterion and then have their dose delayed, if their Hgb levels temporarily decrease to < 1.5 g/dL but achieve ≥ 1.5 g/dL again after treatment resumption, this period (ie, the time from dose delay to achieving a Hgb increase of ≥ 1.5 g/dL again) will be included as the period of sustained Hgb increase of ≥ 1.5 g/dL.

As the primary efficacy analysis, one sample binomial one sided exact test will be performed based on intent-to-treat (ITT) population, to provide p-value (significance level: 0.025). The number and percentage of subjects who achieve the response and 95% confidence interval (CI) will be presented based on the ITT population.

There is no planned interim analysis for this study.

The primary analysis will be performed when all enrolled subjects have completed 24 weeks of treatment or discontinued before 24 weeks.

Additional follow-up analysis for efficacy and safety will be performed when all subjects have been followed for 5 years from the date of the first dose of IP, or 3 years from the last dose (whichever occurs later) during the Post-Treatment Follow-Up Period of the study.

For more details on statistical considerations please refer to Section 9 of the protocol.

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1. INTRODUCTION

1.1. Myelodysplastic Syndromes

Myelodysplastic syndromes (MDS), primarily affecting older adults, 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 red blood cell (RBC) transfusion dependent anemia, increased risk of infection, and/or hemorrhage, as well as a potential to progress to acute myeloid leukemia (AML) (Ades, 2014; Brunning, 2008; Catenacci, 2005; Fenaux, 2009; Steensma, 2013; Visconte, 2014; Zeidan, 2013).

Lower hemoglobin (Hgb) levels and 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 patients (Zeidan, 2013). In addition, long-term RBC transfusion dependence has 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).

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; Hellstrom-Lindberg, 2013; Kao, 2008; Malcovati, 2005; Platzbecker, 2012). Patients in the lower risk groups also often become dependent on frequent RBC transfusions, which leads to decreased HRQoL and increased morbidity and mortality (Hellstrom-Lindberg, 2003; Malcovati, 2005). Thus, the therapeutic goal in RBC- transfusion independent (TI) patients is to increase Hgb levels and prevent from becoming RBC- transfusion dependent (TD).

Diagnosis of MDS is made according to the World Health Organization (WHO) classification system. Also, the International Prognostic Scoring System (IPSS) and the International Prognostic Scoring System – Revised (IPSS-R) are internationally used for prognostic prediction, and the International Working Group IWG) including Japan released treatment response criteria for MDS (Cheson, 2006). These systems and criteria are internationally standardized and therefore no differences exist in the clinical practices among countries including Japan.

Patients with MDS can be categorized into 1 of 5 risk groups according to the IPSS-R (very low, low, intermediate, high, and very high) based on cytogenetics, Hgb, platelets and absolute neutrophil count (ANC) levels and bone marrow (BM) blast percentages obtained at diagnosis. The 5 risk groups showed significantly different risk of progression to AML and overall survival (OS). The median survival rate is 8.8 years for patients with low risk MDS and is as short as 0.8 years for very high-risk MDS (Germing, 2012).

In lower risk MDS, the risk of progression to AML 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 (Germing, 2012). In these patients, the main priorities are the treatment of cytopenias, primarily anemia, and the improvement in QoL (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.

A research revealed the prevalence rate of MDS in Japan was 3.8 (95% CI 3.6–4.1) cases per 100000 for men and 2.4 (95% CI 2.2–2.6) cases per 100 000 for women in 2008. Median age at diagnosis was 76 years (interquartile range 68–82 years). Incidence sharply increased with age, particularly in those aged over 70 years, with 3.1 cases per 100 000 men and 1.1 cases per 100 000 women in those aged 65–69 years versus 17.7 and 8.9 cases per 100 000, respectively, in those aged over 85 years (Chihara 2014).

1.1.1. Current Treatment Options for Lower Risk MDS

The standard of care for lower risk MDS remains supportive treatment with erythropoiesis stimulating agents (ESA)s such as epoetin alfa or darbepoetin (DAR), 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 (National Comprehensive Cancer Network [NCCN], 2018; European Society for Medical Oncology [ESMO], 2014 [Fenaux, 2014]; European LeukemiaNet [ELN], 2014 [Malcovati, 2013]; Japanese Society of Hematology [JSH], 2013).

1.1.1.1. Erythropoiesis Stimulating Agents

The use of ESAs (ie, recombinant erythropoietin [EPO] or darbepoetin [DAR]) is the standard of care for low and intermediate IPSS risk patients with symptomatic anemia and an endogenous serum erythropoietin (sEPO) level < 500 U/L, and is recommended by European, United States (US), and Japanese treatment guidelines. The use of granulocyte-colony stimulating factor (G-CSF) may be employed as needed but is not required, although in some cases it may further improve the efficacy of the ESA (NCCN, 2017; ESMO, 2014 [Fenaux, 2014]; ELN, 2014 [Malcovati, 2013]; JSH, 2013).

The European and Japanese guidance also recommends the use of ESAs for patients who have a low RBC transfusion burden (< 2 units/month) and/or an endogenous sEPO levels ≤ 500 U/L (ESMO, 2014 [Fenaux, 2014]; ELN, 2014 [Malcovati, 2013]; JSH, 2013). However, major favorable prognostic factors for response to ESAs are a low or no RBC transfusion requirement (< 2 units/month) and an endogenous sEPO level < 500 U/L (Fenaux, 2013). Responses to ESAs are best in patients with low endogenous levels (eg, < 500 U/L) of EPO, normal blast counts and lower IPSS/WHO Prognostic Scoring System (WPSS) scores (Hellstrom-Lindberg, 2003; Santini, 2011).

Efficacy of ESAs in lower risk MDS patients have recently been demonstrated in 2 Phase 3 studies:

In the EPOANE3021 Phase 3 study, a total of 130 subjects with IPSS low or int-1 risk MDS and anemia ≤ 10 g/dL with a requirement of RBC transfusion ≤ 4 units/8 weeks and an endogenous sEPO level < 500 U/L, were randomized 2:1 to receive either epoetin alfa or matching placebo. Subjects were stratified by endogenous sEPO level (sEPO < 200 U/L versus sEPO ≥ 200 U/L) and prior transfusion status at screening (yes versus no).

In the modified intent-to-treat (ITT) analysis 2/45 (4.4%) subjects in the placebo group achieved the primary endpoint of IWG 2006 erythroid response versus 27/85 (31.8%) in the epoetin alfa group ($p < 0.001$). All of the responding subjects were in the stratum with endogenous sEPO < 200 U/L during screening. In that stratum, 20/40 (50%) subjects without prior transfusions demonstrated erythroid response during the first 24 weeks, compared with 7/31

(22.6%) subjects with prior transfusions (2 subjects with prior transfusion reached the primary endpoint based on reduction of RBC units transfused by an absolute number of at least 4 units every 8 weeks compared to the 8 weeks prior to baseline). The median duration of erythroid response in the epoetin alfa group was 197 days. The percentage of subjects who were transfused in the epoetin alfa group decreased from 51.8% in the 8 weeks prior to baseline to 24.7% between weeks 16 and 24, compared to the placebo group which had an increase in transfusion rate from 48.9% to 54.1% over the same time periods (Fenaux, 2016; Fenaux, 2018a). In an additional post-hoc analysis conducted by the response review committee with modified IWG 2006 criteria an erythroid response rate of 39/85 (45.9%) in the epoetin alfa group was estimated (Fenaux, 2017); Fenaux, 2018a).

In the ARCADE Phase 3 study, a total of 146 subject with IPSS low or int-1 risk MDS and anemia ≤ 10 g/dL, requirement of RBC transfusion < 4 units/8 weeks, and an endogenous sEPO level ≤ 500 U/L were randomized 2:1 to receive either darbepoetin alfa (DAR) or matching placebo (PBO). In the ITT analysis, 29 (59.2%) subjects in the PBO group achieved the primary endpoint (percentage of participants with at least 1 RBC transfusion during the double-blind treatment period: weeks 5 to 24) versus 35 (36.1%) subjects in the DAR group (p = 0.008). Transfusion rates were less with lower baseline sEPO for darbepoetin alfa (≤ 100 U/L: 23%, > 100 U/L: 57%, 95% confidence interval non-overlapping) but not placebo. The proportion achieving the hematologic improvement – erythroid response (HI-E), which was defined as a ≥ 1.5 g/dL increase from baseline in hemoglobin with a mean rise of ≥ 1.5 g/dL for 8 weeks without transfusions as per IWG 2006 criteria, was significantly increased with DAR versus PBO; DAR:14.7% (11 of 75 evaluable) versus PBO:0% (0 of 35 evaluable), p = 0.016. All subjects with HI-E (n=11) in the double-blind period had baseline sEPO ≤ 100 U/L and 10/11 had no transfusions in the 16 weeks before randomization (none had transfusions in the 8 weeks before). The mean duration of response was 235 (21 days standard error) days. It should be noted, however, that the primary endpoint was switched during the course of the study. Before unblinding and while enrollment was ongoing, transfusion incidence from weeks 5 to 24 became the primary endpoint and HI-E a secondary endpoint (Platzbecker, 2017c).

In Japan, DAR was approved in 2014 regardless of patients' sEPO levels based on the results of a Phase 2 study conducted in 50 patients in Japan and Korea. However, the study only included the subjects with EPO < 500 U/L (Jang, 2015) and JSH Guideline recommends DAR to patients who have low serum EPO (< 500 mU/mL) (JSH, 2013).

1.1.1.2. Red Blood Cell Transfusions

Lower-risk MDS are characterized mainly by anemia and supportive care, primarily RBC cell transfusions, remain an important component of their treatment, but exposes patients to insufficient correction of anemia, alloimmunization, and organ iron overload. Treatment aimed at preventing anemia recurrence should therefore be used whenever possible (Fenaux, 2013).

In many patients with lower-risk MDS, anemia (ie, average hemoglobin levels < 10 g/dL) 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. For those patients, it is recommended to administer transfusions at sufficiently high hemoglobin thresholds (ie, at least 8 g/dL and 9 or 10 g/dL in cases of comorbidities worsened by anemia [eg, coronary artery disease, heart failure] or in cases of poor functional tolerance). In addition, a sufficient number

of RBC concentrates should be transfused each time, over 2 or 3 days if needed, to increase the hemoglobin level to > 10 g/dL and thereby limit the effects of chronic anemia such as cardiac failure, falls, fatigue and lower quality-of-life (Nordic MDS Group Guideline, 2017; Fenaux, 2013; ESMO, 2014 [Fenaux, 2014]).

However, the development of transfusion dependency significantly worsens the survival of patients with MDS (Malcovati, 2005). In addition, long-term RBC transfusion dependency has several detrimental clinical effects including iron overload, economic consequences, and a negative impact on patients' QoL (Hellstrom-Lindberg, 2003; Jansen, 2003; Thomas, 2007).

1.1.1.3. Lenalidomide

Lenalidomide (Revlimid®) is approved in Japan for MDS associated with a del(5q) abnormality. In the US, it is approved 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. Lenalidomide is the standard of care (in countries where lenalidomide 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 for a median duration of transfusion independence of 44 weeks. However, it is not approved for the remaining majority of MDS.

1.1.1.4. Hypomethylating Agents

Azacitidine for injection (Vidaza®) is a hypomethylating agent (HMA) currently approved in 30 other countries including Japan, Canada, Switzerland, and Australia for the treatment of MDS (approvals for specific subtypes vary by country).

Azacitidine is indicated for treatment of patients with the following French-American-British (FAB) classification subtypes of MDS in the US: refractory anemia (RA) or refractory anemia with ringed sideroblasts (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 multilineage dysplasia, according to WHO classification.

In Japan, azacitidine is approved for treatment of various subtypes of MDS and no limitation to use only for higher-risk MDS. However, data supporting the use in the lower-risk MDS patient population is currently limited, and it is not recommended for first-line therapy in this population (JSH, 2013).

1.2. Luspatercept Background

1.2.1. Mechanism of Action

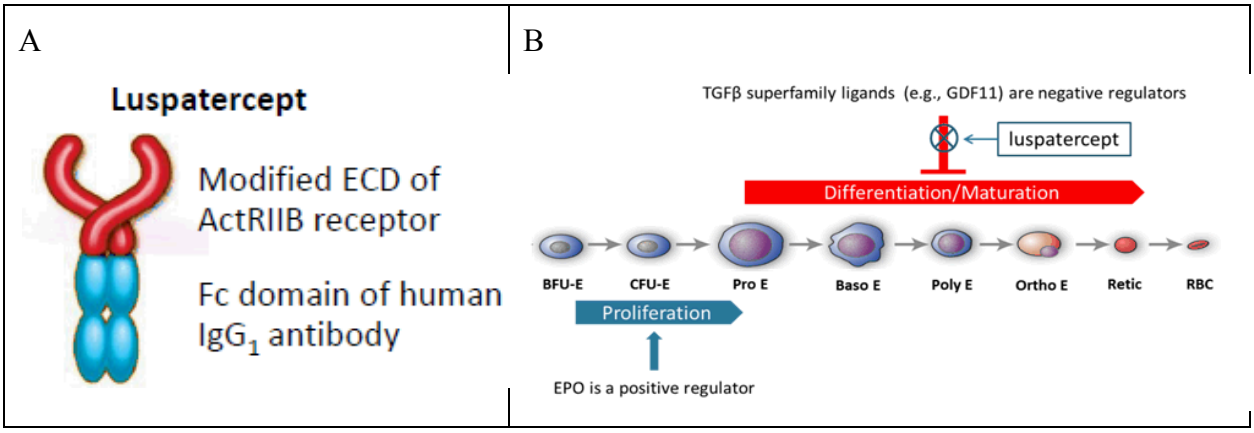
Luspatercept (ACE-536), an erythroid maturation agent, is a recombinant fusion protein consisting of a modified form of the extracellular domain (ECD) of the human activin receptor

type IIB (ActRIIB) linked to the immunoglobulin G1 - fragment crystallizable (IgG1-Fc) domain (Figure 1A). The ActRIIB receptor and its ligands are members of the transforming growth factor-beta (TGF-β) superfamily, a group of proteins involved in the development, differentiation, and/or maturation of various tissues. No species differences have been described in the ligand-receptor interactions among members of the TGF-β superfamily as the ligands and receptors are highly conserved across species (Massague, 1998). Thus, observations from pharmacology studies of luspatercept or its murine ortholog RAP-536 in animal models provide significant insight into the potential of luspatercept to treat human disease.

Members of the TGF-β superfamily ligands, through their binding to activin receptors, are involved in modulating the differentiation of late-stage erythrocyte precursors (normoblasts) in the bone marrow. Luspatercept acts as a ligand trap for growth differentiation factor 11 (GDF11) and other TGF-β superfamily ligands to suppress Smad2/3 signaling. In nonclinical experiments, luspatercept has been shown to bind with high affinity to some TGF-β superfamily ligands (eg, GDF11, bone morphogenetic protein 6 [BMP6] and activin B) but substantially less to others (eg, bone morphogenetic protein 9 [BMP9] and activin A). The mechanism of action (MOA) of luspatercept is independent from that of erythropoietin (EPO) (Suragani, 2014). While EPO stimulates proliferation and differentiation of early erythroid progenitors, luspatercept as an erythroid maturation agent promotes stimulation of the later, maturation phase of erythroblast differentiation and maturation in the bone marrow (refer to Figure 1B).

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

Figure 1: Luspatercept Schematic Representation and Mechanism of Action



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

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

1.2.2. Nonclinical Studies with Luspatercept

Please refer to the IB for information concerning the available nonclinical studies including pharmacology, toxicology, drug metabolism of the investigational product (IP). The most recent version of the luspatercept IB should be reviewed prior to initiating the study.

1.2.3. Summary of Clinical Experience

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

Across the ex-Japan Phase 2, multicenter, open-label, dose-finding program in MDS, responses to luspatercept treatment were observed in the majority of subjects at 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 HI-E in a substantial proportion of MDS subjects within the initial 3 months of treatment.

Luspatercept is currently being assessed in the ex-Japan Phase 2 study for subjects with lower risk MDS and anemia. Data is available for 58 subjects treated with doses of ≥ 0.75 mg/kg every 3 weeks for up to 5 cycles. Subjects had HI-E rates of 76% (19/25) (baseline endogenous sEPO < 200 U/L), 58% (7/12) (200-500 U/L), and 43% (6/14) (> 500 U/L) and rates of RBC-TI of 53% (10/19) (< 200 U/L), 44% (4/9) (200-500 U/L), and 14% (2/14) (> 500 U/L). Although the efficacy rates are higher in the lower sEPO level subjects than in the higher sEPO level subjects, luspatercept showed the efficacy in subjects with any sEPO level. For the subjects who are low (RBCs < 4 units within 8 weeks prior to dosing) and high (RBCs ≥ 4 units within 8 weeks prior to dosing) transfusion burden, HI-E rates were 65% (11/17) and 62% (21/34), and rates of RBC-TI were 75% (6/8) and 29% (10/34), respectively (Platzbecker, 2017a).

Based on these preliminary Phase 2 study results, a Phase 3, randomized, open-label, active controlled study will be conducted in subjects with very low- to intermediate-risk MDS (IPSS-R) who require RBC transfusions (ACE-536-MDS-002).

Luspatercept was also assessed in the MEDALIST trial outside Japan (Fenaux, 2018b; Fenaux, 2020); a Phase 3, randomized, double-blind study in subjects with very low- to intermediate-risk MDS (IPSS-R) with ring sideroblasts (RS) who require RBC transfusions and who were refractory, intolerant, or ineligible to receive an ESA. Subjects (N = 229) were randomized in a 2:1 ratio against placebo. Of 153 subjects receiving luspatercept, 58 (37.9%) achieved the primary endpoint of RBC-TI for ≥ 8 weeks compared with 10 of 76 subjects (13.2%) receiving placebo (odds ratio [OR] 5.1, p < 0.0001). Of those receiving luspatercept, 43 of 153 (28.1%) achieved the key secondary endpoint of RBC-TI for ≥ 12 weeks (Weeks 1 to 24) compared with 6 of 76 (7.9%) receiving placebo (OR 5.1, p = 0.0002). Subjects receiving luspatercept were more likely to achieve a modified hematologic improvement – erythroid response, defined as a reduction in transfusion of ≥ 4 RBC units/8 weeks or a mean hemoglobin increase of ≥ 1.5 g/dL/8 weeks in the absence of transfusions, compared with subjects receiving placebo (52.9% versus 11.8% during Weeks 1 to 24; p < 0.0001). Luspatercept was well tolerated and resulted in a significantly reduced transfusion burden.

Additionally, luspatercept is currently being assessed in two ex-Japan Phase 2 studies in β-thalassemia subjects (A536-04 and A536-06) in which luspatercept has demonstrated clinically significant efficacy in both RBC transfusion dependent and non-transfusion dependent subjects. Further, an ex-Japan Phase 3, randomized, double-blind study to determine the efficacy and

safety of luspatercept versus placebo in subjects with β-thalassemia who require regular red blood cell transfusions (ACE-536-B-THAL-001) is ongoing. A536-04 study title is A Phase 2, Open-Label, Ascending Dose Study to Evaluate the Effects of ACE-536 in Patients With Beta-Thalassemia Intermedia (NCT01749540), A536-06 study title is An Open-Label Extension Study to Evaluate the Long-Term Effects of ACE-536 in Patients With β-Thalassemia Previously Enrolled in Study A536-04 (NCT02268409), and the ex-Japan Phase 3 study title is A Phase 3, Double-Blind, Placebo Controlled Multicenter Study to Determine the Efficacy and Safety of Luspatercept (ACE-536) in Adults With Transfusion Dependent Beta (β)-Thalassemia (NCT02604433)

Additional information regarding clinical experience with luspatercept is summarized in the current version of the luspatercept IB. Please note that there have been no luspatercept exposure to date in Japanese subjects.

1.2.3.1. Potential Risks of Human Use

Increases in hematologic parameters (ie, RBC, Hgb, hematocrit, reticulocytes) are expected as 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 luspatercept 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 subjects regardless of causality in the open-label Phase 2 studies in MDS include (in order of decreasing frequency in the extension study) nasopharyngitis, fatigue, cough, diarrhea, dyspnea, hypertension, arthralgia, edema peripheral, pneumonia, and headache. Adverse events reported in at least 15% of subjects regardless of causality (in order of decreasing frequency) in the open-label Phase 2 studies in β-thalassemia included pyrexia, headache, diarrhea, asthenia, bone pain, myalgia, oropharyngeal pain, arthralgia, musculoskeletal pain, back pain, influenza, dizziness, rhinitis, abdominal pain, nausea, pharyngitis, and vomiting**.**

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

Luspatercept has exhibited toxicity both in terms of maternal health and fetal development in reproductive toxicity studies in preclinical species. If luspatercept is taken during pregnancy, a teratogenic effect in humans cannot be ruled out. If a woman becomes pregnant while taking luspatercept, the medication must be stopped immediately. In addition, since it is unknown if luspatercept is excreted in human breast milk, breastfeeding is prohibited. Male and female subjects of childbearing potential participating in studies of luspatercept must be willing to abstain from sexual intercourse or use adequate contraception during the treatment period of the study and for at least 12 weeks after discontinuation of study therapy.

Hematologic malignancies were observed in rats in a nonclinical juvenile toxicity study at high doses not being used in humans. No related tumors developed in adult rats and monkeys in similar studies.

Please refer to the current version of IB for additional information regarding findings from toxicology studies. It is unknown if humans will experience any of the effects of luspatercept that were noted in the rat and monkey toxicology studies. Safety effects will be monitored closely through adverse event (AE) reporting, clinical laboratory tests, vital signs, and physical examinations.

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

1.2.3.2. 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

Anemia is the predominant cytopenia observed in adult MDS and is present in 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 transfusion support. Of the approximately 80% to 90% of patients with MDS that develop anemia, 40% of those patients become transfusion dependent (TD). Lower hemoglobin (Hgb) levels and RBC transfusion-dependence have been associated with inferior cardiovascular outcomes and increased mortality in patients with MDS, representing a strong rationale for the 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 quality-of-life (QoL), iron overload and its associated complications, immune-related disorders, and increased risk of infections (Hellstrom-Lindberg, 2003; Jansen, 2003; Thomas, 2007).

The use of ESAs is standard of care in lower risk MDS patients with endogenous sEPO $\leq$ 500 U/L according to treatment guidelines (NCCN, 2017; ESMO, 2014 [Fenaux, 2014]; ELN, 2014 [Malcovati, 2013]; JSH, 2013). Recent Phase 3 studies with epoetin alfa and darbepoetin have demonstrated efficacy, but limited in both magnitude and size of patient population in whom a clinically significant effect is seen (see Section 1.1.1.1). In Japan, DAR has been approved in patients with low- or intermediate-1-risk primary MDS (according to IPSS). However, Efficacy in patients with EPO > 500 U/L has not been assessed (Jang, 2015).

Therefore, a new therapeutic option that would prevent the RBC-TI subjects to become RBC-TD for a sustained period of time with high therapeutic effect would provide an important clinical benefit in this patient population.

Luspatercept has a novel mechanism of action distinct from ESAs which may be more beneficial in the treatment of anemia in IPSS-R lower-risk MDS patients. Preliminary ex-Japan Phase 2

results for luspatercept demonstrate promising results for erythroid response (HI-E), transfusion independence and duration of response in subjects who are requiring RBC transfusion as well as in subjects who are not requiring RBC transfusion.

Based on the ex-Japan Phase 2 study results, a Phase 3, randomized, open-label, direct comparison study with epoetin alfa and luspatercept will be conducted in subjects with very low- to intermediate-risk MDS (IPSS-R) who require RBC transfusions (ACE-536-MDS-002).

In parallel with the Phase 3 study, this study (ACE-536-MDS-003) was planned to evaluate the pharmacodynamics (PD) and efficacy in subjects with very low- to intermediate-risk MDS (IPSS-R) who are RBC-TI, and to evaluate PK in Japanese subjects.

1.3.2. Rationale for the Study Design

ACE-536-MDS-003 is a Japanese Phase 2, multicenter, single-arm study. The primary objective of the study is to evaluate HI-E of luspatercept from W1D1 through Week 24 for the treatment of anemia due to IPSS-R very low, low, or intermediate risk MDS in Japanese subjects who are not requiring RBC transfusion at least in the 16 weeks prior to Week 1 Day 1 (W1D1) - except transfusions due to blood loss or infection that occurred between 16 and 8 weeks prior to W1D1.

The multicenter nature of the study will provide assurance that the results are likely to have general applicability.

1.3.2.1. Rationale for the Study Population

This study targets subjects who have symptomatic anemia accompanied by Hgb concentration < 10.0 g/dL and are not requiring RBC transfusion to evaluate the PD and efficacy in IPSS-R very low- to intermediate-risk MDS subjects who are not influenced by RBC transfusions. The subjects will be ESAs naïve or previously used ESAs but not administered ESAs within 8 weeks prior to W1D1 to washout the effects of ESAs.

The IPSS-R classification has been chosen to define this Phase 2 study population because this classification provides better discrimination of MDS progression risk factors compared with the original IPSS (Greenberg, 1997) for evaluating clinical outcomes (survival duration and time to progression of AML) for MDS subjects (Greenberg, 2012). For the purpose of this study, subjects with IPSS-R very-low, low and intermediate risk will be referred to as lower risk MDS.

Subjects in the lower risk groups often become dependent on frequent RBC transfusions, which leads to decreased HRQoL and increased morbidity and mortality (Hellstrom-Lindberg, 2003; Malcovati, 2005). Thus, the therapeutic goal in this subject population is to increase Hgb level and prevent from becoming RBC-TD, which is evaluated in this study.

Subjects can be enrolled to this study regardless of their baseline endogenous EPO level. According to the recent published data (Suzuki, 2015), the endogenous EPO level has a strong correlation with transfusion dependency, and a significantly larger proportion of patients showed serum EPO levels higher than 500 U/L in TD patients (68 % of TD versus 14 % of TI patients). Since the target population of the study is lower risk MDS subjects who are not requiring RBC transfusion, it is anticipated that most of the patients have EPO levels < 500 U/L. However, there is an unmet need for patients with EPO level ≥ 500 U/L in Japan because the use of ESAs are not recommended for these patients, and therefore, it is allowed to enroll subjects with EPO level ≥ 500 U/L. As described before, in the preliminary ex-Japan Phase 2 study results for

luspatercept, HI-E rates are 76% (19/25) (baseline endogenous sEPO < 200 U/L), 58% (7/12) (200-500 U/L), and 43% (6/14) (> 500 U/L) and rates of RBC-TI of 53% (10/19) (< 200 U/L), 44% (4/9) (200-500 U/L), and 14% (2/14) (> 500 U/L) (Platzbecker, 2017a).

This study is being conducted to gain additional experience in Japanese subjects and in particular to evaluate luspatercept in subjects with earlier stage non transfusion dependent disease.

1.3.2.2. Rationale for Study Endpoints

The primary endpoint of HI-E is defined per IWG (Cheson, 2006) as the proportion of subjects achieving ≥ 1.5 g/dL increase in Hgb over any consecutive 56-day period in the absence of RBC transfusions and reflects the direct clinical benefit of the treatment in lower risk MDS subjects who are not requiring RBC transfusion because the therapeutic goal in this population is to increase Hgb level and prevent subjects from becoming RBC-TD.

While HI-E based on the IWG 2006 criteria is standard hematologic response criteria in lower-risk MDS, difficulties in interpretation of the criteria were reported in the EPOANE3021 Phase 3 study for epoetin alfa, in particular in the subjects who had to transiently discontinue the study treatment due to a rapid/excessive rise in Hgb level, and therefore often had responses of less than 8 week durations (due to drug interruption). To address these difficulties, an ad hoc analysis of erythroid response was conducted by adding some conditions including the condition of "patients with an increase in Hgb level by at least 1.5 g/dL lasting less than 8 weeks due to epoetin alfa discontinuation were considered responders if, when restarting epoetin alfa at lower dose, Hgb still increased by at least 1.5 g/dL" (Fenaux, 2016; Fenaux, 2018a). Recently, this undesired effect of dosing interruption on HI-E evaluation was also discussed in the IWG and modification of the criteria was suggested, which further supports the importance of addressing the effect of dosing interruption to avoid misinterpretation of HI-E outcome (Platzbecker, 2019; Platzbecker, 2020). Similar to epoetin alfa, the undesired effects of dosing interruption due to predose Hgb ≥ 12.0 g/dL on HI-E assessment is also expected in luspatercept treatment, especially for lower risk MDS patients who are not requiring RBC transfusion. Therefore, in this ACE-536-MDS-003 study, for subjects who have a dose delay meeting the dose interruption criterion of predose Hgb ≥ 12.0 g/dL, if their Hgb levels temporarily decrease to < 1.5 g/dL but achieve ≥ 1.5 g/dL again after treatment resumption, this period (ie, the time from dose delay to achieving a Hgb increase of ≥ 1.5 g/dL again) will be included as the period of sustained Hgb increase of ≥ 1.5 g/dL for HI-E evaluation.

In the ARCADE Phase 3 study for DAR, HI-E as per IWG 2006 criteria was defined as ≥ 1.5 g/dL increase from baseline in Hgb with a mean rise of ≥ 1.5 g/dL for 8 weeks without transfusions. To ensure better comparison of efficacy data between luspatercept and DAR, modified HI-E (mHI-E) per IWG 2006 criteria defined as ≥ 1.5 g/dL mean increase in Hgb compared to baseline over any consecutive 56-day period in the absence of RBC transfusions is added in the secondary endpoints.

Other secondary objectives include evaluation of efficacy (eg, time to and duration of HI-E and mHI-E, duration of transfusion independence; HRQoL) as well as safety and PK. Safety is assessed by evaluating adverse events and laboratory data. Adverse events and abnormal laboratory value severity will be graded using version 4.03 of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE). Biomarkers will also be measured as exploratory endpoints.

1.3.3. Rationale for Dose, Schedule and Regimen Selection

The starting dose level of 1.0 mg/kg up to a maximum dose level of 1.75 mg/kg are based on clinical data from the ongoing ex-Japan Phase 2 A536-03 and A536-05 studies in MDS. Preliminary results indicate that the dose levels of up to 1.75 mg/kg have been generally safe and well-tolerated. 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 to 0.5 mg/kg subcutaneous Q3W). Selection of the dosing schedule (every 3 weeks, Q3W) was mainly based on the duration of the luspatercept responses in MDS patients. In the ex-Japan Phase 2 studies, the clinically significant increase in hemoglobin was maintained with the Q3W dosing schedule.

The same dosage and the administration regimen are considered appropriate for Japanese patients for the following reasons:

- Luspatercept is an immunoglobulin G1 (IgG1) fusion protein and catabolism is expected to take place through the normal proteolytic pathways. No ethnic difference in drug elimination is expected.
- Serum exposure to luspatercept is approximately proportional to dose (0.125 to 1.75 mg/kg), with no evidence of target-mediated disposition.
- Luspatercept clearance tended to be higher with increasing body weight. Thus, luspatercept dose is based on body weight. This is expected to limit higher exposure due to lower average body weight in Asian populations.
- Sufficient clinical experiences have been gained in ex-Japan clinical trials for luspatercept in doses up to 1.75 mg/kg and no major safety issues are identified. MTD has not been reached at 1.75 mg/kg.
- The 1 mg/kg starting dose is only 57% of the highest therapeutic dose (1.75 mg) in ex-Japan clinical trials and considered to be safe for Japanese patients.
- The pharmacological effect on Hgb increase is exposure dependent and thus dose titration may be needed to achieve an adequate efficacy while avoiding Hgb overshoots. Close monitoring via dose modifications to manage Hgb increase within desired level is implemented in this Phase 2 study.
- 117 Asian patients (including 12 subjects from Taiwan) have been enrolled into Phase 3 β-thalassemia study (with luspatercept doses of up to 1.25 mg/kg for 48 weeks). No safety concerns in Asian population have been identified.

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

1.3.4. Rationale for Exploratory Biomarkers

ActRIIB ligands (eg, GDF11 and Activin B)

Luspatercept binds with high affinity to both GDF11 and Activin B and inhibits subsequent signaling downstream of Activin Receptor IIB. Growth differentiation factor 11 and Activin B are present in the serum and bone marrow and nonclinical studies have demonstrated increased circulating GDF11 levels in a murine model of MDS. It is possible that baseline levels of these proteins in patients may correlate with response.

MDS-associated Molecular Mutations (eg, SF3B1)

Emerging literature describes the prognostic impact of gene mutations in MDS patients. For example, Haferlach, et al surveyed genetic aberrations in 944 patients and demonstrated that 90% of the population had at least one mutation. Forty-seven genes were significantly mutated and many of the mutations were linked to higher risk groups and/or blast elevation. Of the 47 genes, almost half affected survival, suggesting that molecular profiling of multiple target genes could be valuable for classification and prognosis in MDS patients (Haferlach, 2014). In particular, SF3B1 and other genes involved in ribonucleic acid (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 ring sideroblast (RS)+ patients (Malcovati, 2011; Papaemmanuil, 2011) and thought to be causally related to chromosome stability, deoxyribonucleic acid (DNA) repair and gene regulation that may result in anemia and thrombocytopenia (Pellagatti, 2015; Visconte, 2014). Preliminary results from ongoing Phase 2 studies of luspatercept in MDS indicate that subjects harboring a SF3B1 mutation had increased HI-E response rates to luspatercept (A536-03, A536-05) but similar rates of RBC-TI (8 weeks) (Platzbecker, 2017a).

In this study, we will make a preliminary assessment by evaluating the prognostic value of a discrete subset of MDS-related gene mutations in the study population, as well as evaluating the impact of these mutations on clinical benefit with luspatercept. Bone marrow aspirates will be collected from subjects at screening as the baseline for molecular biomarker analyses. While the IPSS-R prognostic classification system remains the gold standard for risk stratification of subjects with MDS at diagnosis, prognostic risk factors in addition to cytogenetics, blast count and cytopenias are being identified that will be important in understanding the study population. Finally, we also propose to collect and store an aliquot of bone marrow mononuclear cells for future analyses such as assessment of RNA expression to allow us to develop a gene signature that predicts response.

Terminal erythropoiesis

As previously mentioned, luspatercept acts on late stages of erythroid differentiation, through a mechanism unique from that of EPO. We hypothesize that patients may respond differently to luspatercept depending on the stage at which erythropoiesis is affected in their bone marrow. For example, responders may have bone marrow that is “primed” and rich in late-stage erythroid precursors compared to non-responders. As such, we propose to isolate bone marrow mononuclear cells from patients and using flow cytometry, measure the extent of terminal erythroid differentiation in each patient (Hu, 2013) at baseline and after treatment. Subsequently, we will make a preliminary assessment by comparing this phenotypic profile to response to determine whether there is a correlation between erythroid differentiation state and response to luspatercept. We will make a preliminary evaluation of the profile after treatment to determine which erythroid populations are modified following administration of luspatercept.

SARS-CoV-2

Subjects who have evidence of a prior infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may be at risk for potential long-term sequelae. The sequelae could potentially affect the safety profile of luspatercept. In addition, some health authorities

may want to know coronavirus disease 2019 (COVID-19) status as prior infection with SARS-CoV-2 may increase toxicity and/or impact interpretation of study events or results.

2. STUDY OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives

Primary Objective
The primary objective of the study is to evaluate HI-E per IWG (Cheson, 2006) from W1D1 through Week 24 for the treatment of anemia due to IPSS-R very low, low, or intermediate risk MDS in Japanese subjects who are not requiring RBC transfusion.
Secondary Objective(s)
The secondary objectives are: • To evaluate mHI-E per IWG (Cheson, 2006) • To evaluate HI-E per IWG (Cheson, 2006) from W1D1 through Week 48 • To evaluate the time to HI-E and duration of HI-E • To evaluate the time to mHI-E and duration of mHI-E • To evaluate the proportion of subjects who maintain TI at Week 24, Week 48 and Week 72 • To assess the safety of luspatercept • To assess the PK of luspatercept • To assess the frequency of antidrug antibodies (ADA) and effects on efficacy, safety, or PK • To assess the number and percentage of subjects progressing to AML; time to AML progression • To assess the overall survival
Exploratory Objective(s)
The exploratory objectives are: • To make a preliminary assessment of molecular and cellular markers in the bone marrow and/or in peripheral blood at baseline and during therapy that may provide further prognostic classification of MDS subtypes and potentially impact luspatercept efficacy • To make a preliminary assessment of molecular and cellular markers in the bone marrow and/or in peripheral blood at baseline and during therapy that may provide information on luspatercept mechanism of action and on-therapy markers predictive of response or relapse • To make a preliminary assessment of the effect of luspatercept on HRQoL [redacted] • To assess impact of SARS-CoV-2 serologic status on subjects receiving luspatercept and MDS and to support health authority requests.

Table 2: Study Endpoints

Endpoint	Name	Description	Timeframe
Primary	Hematologic improvement in erythroid response (HI-E) per IWG (Cheson, 2006)	Proportion of subjects achieving HI-E over any consecutive 56-day period in the absence of RBC transfusions	W1D1 through Week 24

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
Secondary	Modified hematologic improvement in erythroid response (mHI-E) per IWG (Cheson, 2006)	Proportion of subjects achieving ≥ 1.5 g/dL mean increase in hemoglobin compared to baseline over any consecutive 56-day period in the absence of RBC transfusions	W1D1 through Week 24; W1D1 through Week 48
	Hematologic improvement in erythroid response (HI-E) per IWG (Cheson, 2006)	Proportion of subjects achieving HI-E over any consecutive 56-day period in the absence of RBC transfusions	W1D1 through Week 48
	Time to HI-E	Time from first dose to first onset of achieving ≥ 1.5 g/dL increase in hemoglobin over any consecutive 56-day period in the absence of RBC transfusions	W1D1 through Week 24; W1D1 through Week 48
	Time to mHI-E	Time from first dose to first onset of achieving ≥ 1.5 g/dL mean increase in Hgb compared to baseline over any consecutive 56-day period in the absence of RBC transfusions	W1D1 through Week 24; W1D1 through Week 48
	Duration of HI-E	Maximum duration of achieving ≥ 1.5 g/dL increase in hemoglobin for subjects who achieve Hgb increase ≥ 56 days in the absence of RBC transfusions	W1D1 through EOT
	Duration of mHI-E	Maximum duration of achieving ≥ 1.5 g/dL mean increase in Hgb compared to baseline for subjects who achieve mean Hgb increase ≥ 56 days in the absence of RBC transfusions	W1D1 through EOT
	RBC-TI	Proportion of subjects who maintain RBC-TI from W1D1 through Week 24, 48, and 72.	W1D1 through Week 24; W1D1 through Week 48; W1D1 through Week 72
	Safety	Type, frequency, severity of AEs and relationship of AEs to luspatercept	Screening through 42 days post last dose
	PK	C_{max}, AUC, T_{max}	W1D1 through 1-year post first dose

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
Secondary	Antidrug antibodies (ADA)	Frequency of antidrug antibodies and effects on efficacy, or safety, or PK	W1D1 through 1-year post first dose
	Progression to AML	Number and percentage of subjects progressing to AML; time to AML progression	W1D1 through 5 years from first dose or 3 years from last dose (whichever occurs later)
	Overall survival	Time from date of W1D1 to death due to any cause	W1D1 through 5 years from first dose or 3 years from last dose (whichever occurs later)
Exploratory	Molecular and cellular markers in the bone marrow and/or in peripheral blood	Evaluation of biomarkers that may potentially impact luspatercept efficacy, predict response or relapse, help to better understand MOA and/or provide further prognostic classification of MDS subtypes. Molecular markers (eg, SF3B1) include evaluation of MDS-associated gene mutations and their impact on drug efficacy, clinical response or relapse, disease progression, drug MOA and prognostication of MDS.	Baseline through End of Treatment
	Health-related quality of life (HRQoL)	[redacted]	Screening through End of Treatment
	SARS-CoV-2 Serology	Exploratory measurements of SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG) from serum	Screening through EOT

ADA = antidrug antibodies; AE = adverse event; AML = acute myeloid leukemia; AUC = area under the concentration-time curve; C_{max} = maximum plasma concentration of drug; [redacted] EOT = End of Treatment; [redacted] – Anemia; Hgb = hemoglobin; HI-E = hematologic improvement – erythroid response; IgG = immunoglobulin G; IWG = International Working Group; MDS = myelodysplastic syndromes; MOA = mechanism of action; PK = pharmacokinetics; RBC = red blood cell; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TI = transfusion independent/ independence; T_{max} = time to maximum plasma concentration of drug; W1D1 = Week 1 Day 1.

3. OVERALL STUDY DESIGN

3.1. Study Design

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

This is a Phase 2, multicenter, single-arm study to evaluate the efficacy, safety and PK of luspatercept (ACE-536) for the treatment of anemia due to IPSS-R very low, low or intermediate risk MDS in Japanese subjects who are not requiring RBC transfusion.

The study is divided into the Screening Period, a Treatment Period and a Post-Treatment Follow-up Period. See Figure 2 for more details and refer to Section 6 for a 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 35 days prior to W1D1. During the Screening Period, subjects will undergo safety and other assessments to determine eligibility for the study. Subjects deemed eligible for the study will be enrolled using integrated response technology (IRT).

Central review of bone marrow aspirate smear and peripheral blood smear will be used to confirm MDS diagnosis according to the WHO 2016 classification (Appendix B) and to determine the baseline IPSS-R risk classification (Greenberg, 2012). A bone marrow biopsy will be collected only when adequate aspirate is not attainable.

The sponsor may review key eligibility criteria as well as relevant data (eg, central laboratory reports and cytomorphology/cytogenetic reports) and communicate as necessary with the investigator prior to enrolment of a subject.

Treatment Period

The first dose of IP should be administered on the same day after, but at the latest within 3 days of enrollment.

Subjects will receive IP every 3 weeks (21 days) (ie, at the Week 1 Day 1 (W1D1) Visit, W4D1 Visit; W7D1 Visit, etc.).

Details on IP administration and intra-individual dose titration are outlined in Section 7.

Best supportive care (BSC) may be used in combination with study treatment when clinically indicated per investigator. BSC includes, but is not limited to, treatment with transfusions, antibiotic, antiviral and/or antifungal therapy, and nutritional support as needed. BSC for this study excludes the use of ESAs. Please refer to Section 8 for more details on permitted and prohibited concomitant medications and procedures.

Subjects should receive IP through to a minimum of the 24-week MDS Disease Assessment Visit scheduled for Day 169, unless the subject experiences unacceptable toxicities, withdraws consent, or meets any other treatment discontinuation criteria.

The MDS Disease Assessment (Section 6.4.2) performed on Day 169 (and every 24 weeks thereafter [ie, Day 337, Day 505, etc.] consists of the investigator's assessment of clinical benefit from IP and status of underlying disease. For subjects to remain on treatment beyond this timepoint both of the following criteria must be confirmed in each subject:

- Evidence of clinical benefit defined by either one of the following two criteria:
  - HI-E based on IWG (Cheson, 2006) (Appendix D) (Hgb increase of ≥ 1.5 g/dL for 8 weeks within 12 weeks immediately preceding Day 169 and every 24 weeks thereafter [ie, Day 337, Day 505, etc.])
  - Maintain RBC transfusion independence
- Absence of disease progression per IWG criteria for altering natural history of MDS (Cheson, 2006) (Appendix E) based on central morphological assessment of bone marrow, peripheral blood and cytogenetics results.

Based on the outcome of these assessments, subjects will either be discontinued from treatment with IP and enter the Post-Treatment Follow-up Period or continue the treatment as long as the above criteria continue to be met or until the subject experiences unacceptable toxicities, withdraws consent, or meets any other discontinuation criteria.

For subjects to continue the treatment with IP, scheduled MDS disease assessments will be repeated at the 48-Week MDS Disease Assessment Visit (ie. Day 337) and every 24 weeks thereafter (see Section 6.4.2 for details) to confirm continued clinical benefit and absence of disease progression as per above criteria.

Serial measurements of safety and efficacy will occur at scheduled study visits as outlined in Table 3. Laboratory analyses will be performed centrally. Local laboratories are allowed in cases when timely results are needed (eg, pre-dose Hgb assessments, 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. Where discrepancies are present, results of the central laboratory will be used to determine response assessments.

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 (Section 6.2.2).

Post-Treatment Follow-up Period

The Post-Treatment Follow-up Period consist of the 42-Day Safety Follow-up (Section 6.3.1), which includes (but is not limited to) the collection of adverse events (AEs), concomitant drugs and RBC-transfusion data, and the Long-term Follow-up (Section 6.3.2).

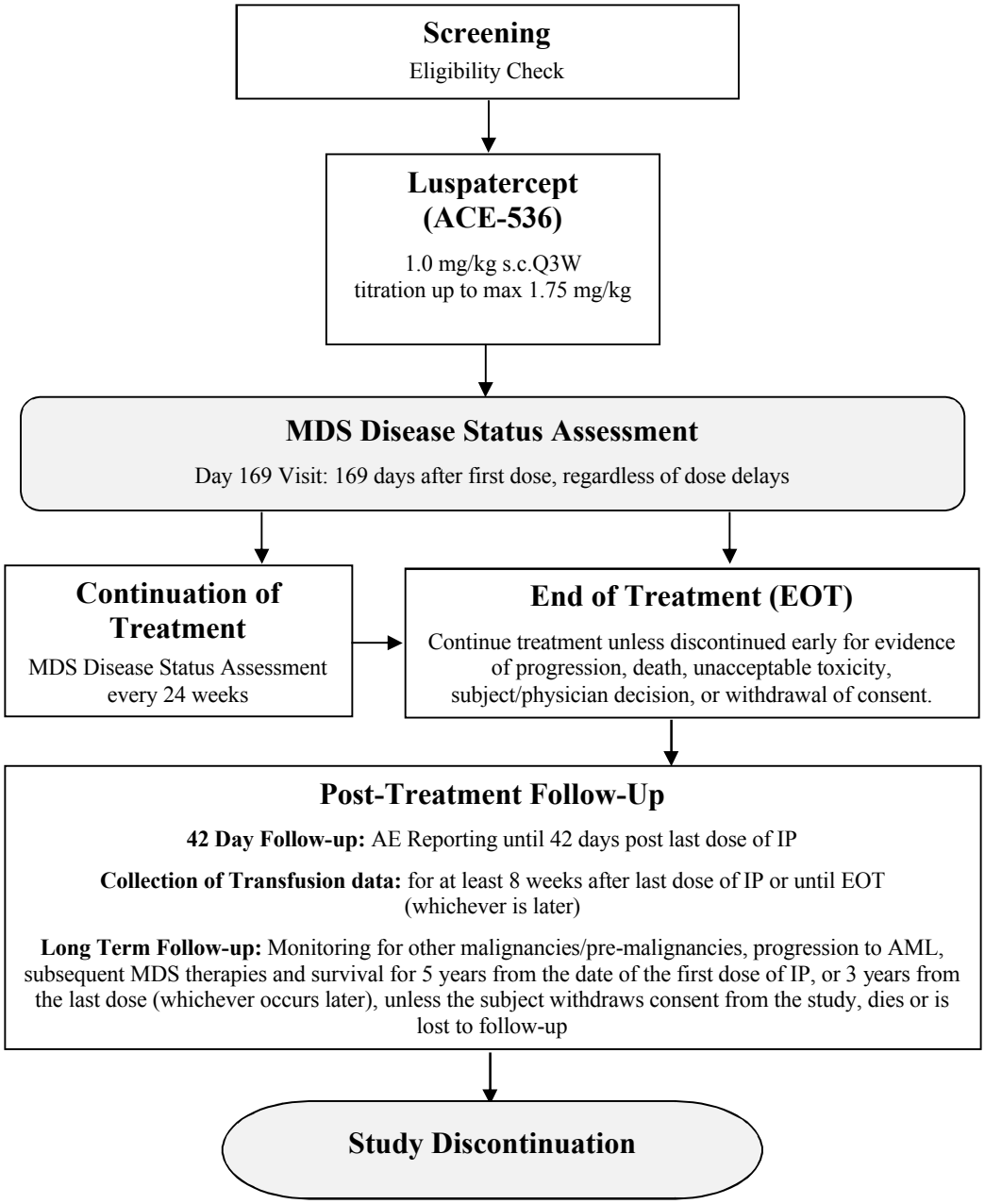
The transfusion data collection will continue until 8 weeks from the date of last dose of IP or from the date of the EOT Visit (whichever is later).

In addition, continuation of monitoring for other malignancies/pre-malignances and progression to AML will occur in the Long-term Post-Treatment Follow-up Period along with data collection of subsequent MDS therapies, and overall survival for 5 years from the date of the first dose of IP, or 3 years from the last dose (whichever occurs later) unless the subject withdraws consent

from the study, dies or is lost to follow-up. For that purpose, visits (which may consist of telephone contacts from the site) will be conducted every 12 weeks for the first 3 years from the date of last dose of IP and every 6 months thereafter, if applicable.

An antidrug antibodies (ADA) sample(s) may be required in the Post-Treatment Follow-up Period for subjects who terminate the Treatment Period with less than 1 year of ADA monitoring if a subject is ADA positive at the time of treatment discontinuation.

Figure 2: Overall Study Design



AE = adverse event; AML = acute myeloid leukemia; EOT = End of Treatment; IP = investigational product; MDS = myelodysplastic syndromes; Q3W = every 3 weeks; SC = subcutaneous.

3.2. Study Duration for Subjects

The duration of participation for subjects who complete the study will be approximately 6 years (and may be shorter or longer for individual subjects) consisting of the following phases:

- Screening Period: up to 35 days prior to W1D1
- Treatment Period: at least up to the 24-week MDS Disease Assessment (ie, Day 169) unless the subject experiences unacceptable toxicities, withdraws consent, or meets any other treatment discontinuation criteria (eg, absence of clinical benefit, or disease progression per IWG criteria for altering natural history of MDS (Cheson, 2006) (Appendix E)
- Post-Treatment Follow-up Period: 5 years from the date of the first dose of IP, or 3 years from the last dose (whichever occurs later), unless the subject withdraws consent from the study, dies or is lost to follow-up. Long-term Follow-up visits may be conducted as telephone contacts from the site.

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 and/or exploratory analysis, as prespecified in the protocol, whichever is the later date.

The sponsor may end the trial when all key endpoints and objectives of the study have been analyzed and the availability of a roll-over protocol exists into which 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.

4. STUDY POPULATION

4.1. Number of Subjects

Approximately 20 subjects with anemia due to IPSS-R very low, low, or intermediate risk MDS who are not requiring RBC transfusion will be enrolled into the study.

4.2. Inclusion Criteria

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

1. Subject is ≥ 20 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. Subject is willing and able to adhere to the study visit schedule and other protocol requirements.
4. Subject has a documented diagnosis of MDS according to WHO 2016 classification (Section 6.1.1, Appendix B) that meets IPSS-R classification (Greenberg, 2012) of very low, low, or intermediate risk disease, and:
   - < 5% blasts in bone marrow
5. Subject has symptomatic anemia with mean Hgb concentration < 10.0 g/dL from 2 measurements (one performed within 1 day prior to W1D1 and the other performed 7 to 35 days prior to W1D1) that does not require RBC transfusion. If more than one measurement exists in the period of 7 to 35 days prior to W1D1, the most recent value will be used.
6. Subject must be TI, as documented by the following criteria:
   - No RBC transfusion administered within 16 weeks prior to W1D1 (except transfusions due to blood loss or infection that occurred between 16 and 8 weeks prior to W1D1)
7. Subject has Eastern Cooperative Oncology Group (ECOG) score of 0, 1, or 2
8. Females of childbearing potential (FCBP), defined as a sexually mature woman who: 1) has achieved menarche at some point, 2) not undergone a hysterectomy or bilateral oophorectomy, or 3) has not been naturallypostmenopausal (amenorrhea following cancer therapy or amenorrhea due to other medical reasons 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 W1D1). Refer to Section 6.1.14 for additional details. She must agree to ongoing pregnancy testing during the course of the study, and after end of study treatment. This applies even if the subject practices true abstinence[1] from heterosexual contact.

- Either commit to true abstinence[1] from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agree to use, and be able to comply with, highly effective contraception[2] 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.
- If breastfeeding, agree to stop breastfeeding prior to the participation in the study and not to resume breastfeeding after treatment discontinuation.

9. Male subjects must:
   - Practice true abstinence[1] (which must be reviewed prior to each IP administration or on a monthly basis [eg, in the event of dose delays]) or agree to use a condom (latex or non-latex, but not made out of natural [animal] membrane) 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.

4.3. Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

1. Subject with the any of the following prior treatments for underlying disease:
   - Disease modifying agents (eg, immune-modulatory drug [IMiDs such as lenalidomide])
     - Except if the subject received ≤ 1 week of treatment with a disease modifying agent ≥ 8 weeks from W1D1, at the investigator's discretion.
   - Hypomethylating agents
     - Subjects may be enrolled at the investigator's discretion contingent that the subject received no more than 2 injections of HMA. The last dose must be ≥ 8 weeks from the date of W1D1.
   - Luspatercept (ACE-536) or sotatercept (ACE-011)
   - Allogeneic and/or autologous hematopoietic cell transplant
2. Subject with myelodysplastic/myeloproliferative neoplasms (MDS/MPN) according to WHO 2016 classification (ie, chronic myelomonocytic leukemia (CMML), atypical chronic myeloid leukemia (aCML), BCR-ABL12, juvenile myelomonocytic leukemia (JMML), MDS/MPN unclassifiable.

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

[2] Highly effective contraception is defined in this protocol as the following (information will also appear in the ICF): Hormonal contraception (ie, birth control pills); intrauterine device (IUD); tubal ligation (tying your tubes); or a partner with a successful vasectomy.

3. Subject with 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.
4. Subject with known clinically significant anemia due to iron, vitamin B12, or folate deficiencies, or autoimmune or hereditary hemolytic anemia, or hypothyroidism, or any type of known clinically significant bleeding or sequestration. Subject with drug induced anemia (eg, mycophenolate).
    - Iron deficiency to be determined by serum ferritin < 100 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).
5. Subject with known history of diagnosis of AML
6. Subject receiving any of the following treatment within 8 weeks prior to W1D1:
    - Anticancer cytotoxic chemotherapeutic agent or treatment
    - ESAs
    - Granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), unless given for treatment of febrile neutropenia
    - Immunosuppressive therapy for MDS
    - Systemic corticosteroid, except for subjects on a stable or decreasing dose for ≥ 1 week prior to W1D1 for medical conditions other than MDS
    - Other RBC hematopoietic growth factors (eg, Interleukin-3)
    - Androgens, unless to treat hypogonadism
    - Hydroxyurea, anagrelide
    - Oral retinoids
    - Arsenic trioxide
    - Interferon and interleukins
    - Investigational drug or device, or approved therapy for investigational use (if 5 times the half-life of the previous investigational drug exceeds 8 weeks, then the time of exclusion should be extended up to 5 times the half-life of the investigational drug)
7. Subject with uncontrolled hypertension, defined as repeated elevations of systolic blood pressure (SBP) of ≥ 150 mmHg and/or diastolic blood pressure (DBP) ≥ 100 mmHg despite adequate treatment, or with a history of hypertensive crisis or hypertensive encephalopathy.
8. Subject with any of the following laboratory abnormalities:
    - Absolute neutrophil count (ANC) < 500/µL (0.5 x 10^9/L)
    - Platelet count < 30,000/µL (30 x 10^9/L) (Exclude subjects that may be at risk of bleeding regardless of platelet counts. This includes [but is not limited to] subjects currently using aspirin or heparin, immediately after surgery, or easily causes

bleeding such as nasal bleeding or subcutaneous bleeding or previous episode of major bleeding where the cause was not effectively treated.)

- Estimated glomerular filtration rate (eGFR) < 40 mL/min/1.73 m^2 (via the 4-variable modification of diet in renal disease [MDRD] formula, Appendix G)
- 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)
- 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.

9. Subject with prior history of malignancies, other than MDS, unless the subject has been free of the disease for ≥ 5 years. However, subjects with the following history/concurrent conditions are allowed if considered as curatively treated:
   - 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)
10. Subject with major surgery within 8 weeks prior to W1D1. Subjects must have completely recovered from any previous surgery prior to W1D1
11. Subject with history of cerebrovascular accident (including ischemic, embolic, and hemorrhagic cerebrovascular accident), transient ischemic attack, deep venous thrombosis (DVT; including proximal and distal), pulmonary or arterial embolism, arterial thrombosis or other venous thrombosis within 6 months prior to W1D1
    Note: prior superficial thrombophlebitis is not an exclusion criterion.
12. Subject with the following cardiac conditions within 6 months prior to W1D1: myocardial infarction, uncontrolled angina, acute decompensated cardiac failure or New York Heart Association (NYHA) Class III-IV heart failure, or uncontrolled cardiac arrhythmia as determined by the investigator. Subjects with a known ejection fraction < 35%, confirmed by a local echocardiogram (ECHO) or multi-gated acquisition (MUGA) scan performed within 6 months prior to W1D1.
13. Subject with uncontrolled systemic fungal, bacterial, or viral infection (defined as ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics, antiviral therapy, and/or other treatment).
14. Subject with known human immunodeficiency virus (HIV), known evidence of active infectious hepatitis B, and/or known evidence of active hepatitis C. Local laboratory testing confirming HIV, hepatitis B, and hepatitis C status should not have been performed beyond 4 weeks prior to the date of ICF signature.

15. Subject with history of severe allergic or anaphylactic reactions or hypersensitivity to recombinant proteins or excipients in luspatercept (see current IB).
16. Pregnant or breastfeeding females.
17. 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.
18. 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.
19. Subject has any condition or receives concomitant medication that confounds the ability to interpret data from the study.
20. Subject has history of active SARS-CoV-2 infection within 4 weeks prior to screening, unless the subject has adequately recovered from COVID-19 symptoms and related complications as per investigator's discretion and following a discussion with the Medical Monitor. Use of a live COVID-19 vaccine is prohibited within 4 weeks prior to W1D1.

5. TABLE OF EVENTS

Table 3: Table of Events

		Screening	Treatment Period								Post-treatment Follow-up		
								Efficacy Assessment *Independent of any dose delays*					
	Section	**Day -35 to -1**	**W1D1 Visit**	**W2D1 Visit**	**W3D1 Visit**	**3-wkly Visits** *W4D1 W7D1 W10D1 etc.*	**Other Visits**	**24-Wk MDS Assess-ment Visit** *D169*	**Every 24 wks** *D337 D505 etc.*	**EOT Visit[a]**	**42-Day Follow-up**	**Long Term Follow-up**	**End of Study**
Section										6.2.2/11.1	6.3.1	6.3.2	11.2
Time window				**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±14days[b]**	**±14days[b]**		**+2 days**	**±7 days**	
Note: Weekly visits as displayed above represent visits as they are scheduled if dosing occurs without any dose delays. In the event of dose delays (eg, due to adverse events) the next dosing visit (every 3 weeks for luspatercept) and associated assessments should be delayed accordingly. Assessments to monitor the condition of the subject should be recorded as unscheduled visits. Please note that efficacy assessments (MDS Disease assessments) always occur at the designated days after W1D1 as indicated above. Dose delays do not affect the timing of these assessments.													
Informed Consent	6.1	X	–	–	–	–	–	–	–	–	–	–	–
Inclusion/Exclusion Evaluation	6.1	X	–	–	–	–	–	–	–	–	–	–	–
Physical Examination	6.1.5	X	–	–	–	–	–	X	X	X	–	–	–
Demographics	6.1.3	X	–	–	–	–	–	–	–	–	–	–	–
Medical History	6.1.4	X	–	–	–	–	–	–	–	–	–	–	–
HIV and Hep B/C Status	6.1.4.1	X	–	–	–	–	–	–	–	–	–	–	–
Prior RBC and Platelet Transfusions	6.1.2	X	–	–	–	–	–	–	–	–	–	–	–

Table 3: Table of Events (Continued)

		Screening	Treatment Period								Post-treatment Follow-up		
								Efficacy Assessment *Independent of any dose delays*					
	Section	**Day -35 to -1**	**W1D1 Visit**	**W2D1 Visit**	**W3D1 Visit**	**3-wkly Visits** *W4D1 W7D1 W10D1 etc.*	**Other Visits**	**24-Wk MDS Assess-ment Visit** *D169*	**Every 24 wks** *D337 D505 etc.*	**EOT Visit[a]**	**42-Day Follow-up**	**Long Term Follow-up**	**End of Study**
Section										6.2.2/11.1	6.3.1	6.3.2	11.2
Time window				**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±14days[b]**	**±14days[b]**		**+2 days**	**±7 days**	
INVESTIGATIONAL PRODUCT (IP)													
IP Administration and Accountability Luspatercept	7	–	X	–	–	X	–	–	–	–	–	–	–
SAFETY ASSESSMENTS													
ECOG Performance Status	6.1.7	X	X	–	–	X	–	X	X	X	–	–	–
Urinalysis	6.1.13	X	X	–	–	Every 12 weeks ie, W13D1, W25D1, etc.	–	–	–	–	–	–	–
ECG (12-lead)	6.1.8	X	–	–	–	–	–	–	–	–	–	–	–
Pregnancy Test and Counseling	6.1.14	X	X	–	–	X	–	–	–	X	–	–	–
Adverse events	6.1.19/10	Continuous, after signing informed consent until 42 days after last IP administration										–	–

Table 3: Table of Events (Continued)

		Screening	Treatment Period								Post-treatment Follow-up		
								Efficacy Assessment *Independent of any dose delays*					
	Section	**Day -35 to -1**	**W1D1 Visit**	**W2D1 Visit**	**W3D1 Visit**	**3-wkly Visits** *W4D1 W7D1 W10D1 etc.*	**Other Visits**	**24-Wk MDS Assess-ment Visit** *D169*	**Every 24 wks** *D337 D505 etc.*	**EOT Visit[a]**	**42-Day Follow-up**	**Long Term Follow-up**	**End of Study**
Section										6.2.2/11.1	6.3.1	6.3.2	11.2
Time window				**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±14days[b]**	**±14days[b]**		**+2 days**	**±7 days**	
SAFETY ASSESSMENTS (Continued)													
Prior and Concomitant medications/ procedures	6.1.18/8	Continuous, 8 weeks prior to W1D1 until 42 days after last IP administration or until the EOT Visit, whichever occurs later										–	–
Vital Signs (Height to be measured only at screening)	6.1.6	X	X	X	X	X	–	X	X	X	–	–	–
Serum Chemistry[c]	6.1.10	X	X	–	–	X	–	X	X	X	–	–	–

Table 3: Table of Events (Continued)

		Screening	Treatment Period								Post-treatment Follow-up		
								Efficacy Assessment *Independent of any dose delays*					
	Section	**Day -35 to -1**	**W1D1 Visit**	**W2D1 Visit**	**W3D1 Visit**	**3-wkly Visits** *W4D1 W7D1 W10D1 etc.*	**Other Visits**	**24-Wk MDS Assess-ment Visit** *D169*	**Every 24 wks** *D337 D505 etc.*	**EOT Visit[a]**	**42-Day Follow-up**	**Long Term Follow-up**	**End of Study**
Section										6.2.2/11.1	6.3.1	6.3.2	11.2
Time window				**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±14days[b]**	**±14days[b]**		**+2 days**	**±7 days**	
EFFICACY ASSESSMENTS													
Hematology[c]	6.1.9	X	X	X	X	X	–	X	X	X	–	–	–
Serum EPO	6.1.11	X	–	–	–	Every 6 weeks: ie, W7D1 W13D1 etc.	–	X	X	X	–	–	–
Serum Ferritin and other iron-related markers	6.1.12	X	X	–	–	X	–	X	X	X	–	–	–
Transfusion Data Collection and Assessment	6.4.1	Assess and record on ongoing basis (prior to each dose of IP) until 8 weeks after last dose of IP or the End of Treatment Visit, whichever occurs later. Clinical site staff must confirm (and document in the subject's source record) if any transfusions were received by the subject (including any at outside local institutions in between study visits) prior to each IP administration. In addition to local procedures in place at the site to capture this information, a patient transfusion diary will be provided to subjects and will be reviewed by the site when/if returned by the subject.									–	–
MDS Disease Assessment	6.4.2	–	–	–	–	–	–	X	X	X	–	–	–
BMA and PB for Cytomorphology and Cytogenetic testing[d, e]	6.1.1	X	–	–	–	–	–	X	X	X	–	–	–

Table 3: Table of Events (Continued)

		Screening	Treatment Period								Post-treatment Follow-up		
								Efficacy Assessment *Independent of any dose delays*					
	Section	**Day -35 to -1**	**W1D1 Visit**	**W2D1 Visit**	**W3D1 Visit**	**3-wkly Visits** *W4D1 W7D1 W10D1 etc.*	**Other Visits**	**24-Wk MDS Assess-ment Visit** *D169*	**Every 24 wks** *D337 D505 etc.*	**EOT Visit**[a]	**42-Day Follow-up**	**Long Term Follow-up**	**End of Study**
Section										6.2.2/11.1	6.3.1	6.3.2	11.2
Time window				**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±14days**[b]	**±14days**[b]		**+2 days**	**±7 days**	
EXPLORATORY/BIOMARKER ASSESSMENTS													
PB for Exploratory Biomarkers (eg, soluble biomarkers, MDS-associated molecular mutations and other markers of drug MOA)	6.1.1 6.7	X	–	–	X	W10D1 W34D1 only	–	X	X	X	–	–	–
BMA for Exploratory Biomarkers (eg, soluble biomarkers, MDS-associated molecular mutations, erythroid differentiation and other markers of drug MOA)[f]	6.1.1 6.7	X	–	–	–	–	–	X	X	X	–	–	–
SARS-COV-2 Serology testing	6.7	X	–	–	–	–	–	–	–	X	–	–	–

Table 3: Table of Events (Continued)

		Screening	Treatment Period								Post-treatment Follow-up		
								Efficacy Assessment *Independent of any dose delays*					
	Section	**Day -35 to -1**	**W1D1 Visit**	**W2D1 Visit**	**W3D1 Visit**	**3-wkly Visits** *W4D1 W7D1 W10D1 etc.*	**Other Visits**	**24-Wk MDS Assess-ment Visit** *D169*	**Every 24 wks** *D337 D505 etc.*	**EOT Visit**[a]	**42-Day Follow-up**	**Long Term Follow-up**	**End of Study**
Section										6.2.2/11.1	6.3.1	6.3.2	11.2
Time window				**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±14days**[b]	**±14days**[b]		**+2 days**	**±7 days**	
PK/ADA ASSESSMENTS (cont.)													
PK Sample Collection[g] *Should be collected prior to IP dosing on a dosing day*	6.5	–	X	X	X	W4D1 W10D1 W16D1 W22D1 for all subjects W13D1 W19D1 for dense PK subjects only	W1D3 W2D3 W17D1 W18D1 for dense PK subjects only	X	And every 12 weeks (± 14 days) from the 24-Week MDS Assessment Visit for up to 1 year from the first dose. Once a subject has been discontinued from treatment, PK samples may no longer be collected as long as ADA are not detectable.		–		
ADA Sample Collection *Should be collected prior to IP dosing on a dosing day*	6.6	–	X	–	–	W4D1 W10D1 W16D1 W22D1 only	–	X	And every 12 weeks (± 14 days) from the 24-Week MDS Assessment Visit for up to 1 year from the first dose. If the subject was discontinued from study treatment earlier than 1 year from the first dose, additional samples will be collected if the last ADA is positive.		–		

Table 3: Table of Events (Continued)

		Screening	Treatment Period								Post-treatment Follow-up		
								Efficacy Assessment *Independent of any dose delays*					
	Section	**Day -35 to -1**	**W1D1 Visit**	**W2D1 Visit**	**W3D1 Visit**	**3-wkly Visits** *W4D1 W7D1 W10D1 etc.*	**Other Visits**	**24-Wk MDS Assess-ment Visit** *D169*	**Every 24 wks** *D337 D505 etc.*	**EOT Visit[a]**	**42-Day Follow-up**	**Long Term Follow-up**	**End of Study**
Section										6.2.2/11.1	6.3.1	6.3.2	11.2
Time window				**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±14days[b]**	**±14days[b]**		**+2 days**	**±7 days**	

[redacted]

Table 3: Table of Events (Continued)

		Screening	Treatment Period								Post-treatment Follow-up		
								Efficacy Assessment *Independent of any dose delays*					
	Section	**Day -35 to -1**	**W1D1 Visit**	**W2D1 Visit**	**W3D1 Visit**	**3-wkly Visits** *W4D1 W7D1 W10D1 etc.*	**Other Visits**	**24-Wk MDS Assess-ment Visit** *D169*	**Every 24 wks** *D337 D505 etc.*	**EOT Visit[a]**	**42-Day Follow-up**	**Long Term Follow-up**	**End of Study**
Section										6.2.2/11.1	6.3.1	6.3.2	11.2
Time window				**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±14days[b]**	**±14days[b]**		**+2 days**	**±7 days**	
FOLLOW UP													
Monitoring for progression to AML and other malignancies/pre-malignancies	6.1.20 6.3.2 10.5	After signing ICF and until 5 years from the first dose of IP, or 3 years from the last dose (whichever occurs later), or until death, lost to follow-up, withdrawal of consent for further data collection											
Posttreatment MDS therapies	6.3.2	–	–	–	–	–	–	–	–	–	X	X	X
Survival Follow-up	6.3.2	–	–	–	–	–	–	–	–	–	X	X	X

ADA = antidrug antibodies; AML = acute myeloid leukemia; BMA = bone marrow aspirate; BMB = bone marrow biopsy; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; [redacted]; EOT = End of Treatment; EPO = erythropoietin; [redacted] – Anemia; Hep = hepatitis; HIV = human immunodeficiency virus; ICF = informed consent form; IP = investigational product; MDS = myelodysplastic syndromes; MOA = mechanism of action; PB = peripheral blood; PK = pharmacokinetics; RBC = red blood cell; RS = ring sideroblast; SARS-COV-2 = severe acute respiratory syndrome coronavirus 2; W = week; wkly = weekly.

[a] 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.

[b] As central laboratory results from bone marrow and peripheral blood samples (ie, cytomorphology, cytogenetic analysis) are required as part of the MDS Disease Assessment, a 14-day window is allowed for the 24-Week MDS Disease Assessment Visit (ie, Day 169 ± 14 days) in order to account for sample collection and turnaround time of results. Please see Section 6.4.2 for details.

[c] If screening assessments are performed within 2 days of W1D1, assessments of serum chemistry and hematology do not need to be repeated on W1D1.

[d] In the event a local BM assessment for MDS diagnosis was made no more than 8 weeks before ICF signature, local BM samples/reports may be allowed for central "over read" after consultation with the sponsor and provided the central lab can confirm the diagnosis using the local samples/reports.

[e] Collection of a BMB is only required when adequate aspirate is not attainable. To allow for cytomorphology assessment and cytogenetic analysis of the BMB please follow guidance for processing the sample provided in the study's Central Laboratory Manual.

[f] Remaining BMA (after quantity sufficient is allocated towards cytomorphology and cytogenetics analysis) will be used for exploratory biomarker studies. An additional bone marrow procedure should not be performed for these samples. Refer to the central laboratory manual for additional information related to sample collection.

[g] If a PK sample is drawn on a dosing day, the PK sample should be drawn prior to luspatercept dosing. All PK samples should be collected along the protocol defined "weekly" visits adapting to dose delays.

[h] Questionnaires should be completed by the subject prior to IP administration.

6. PROCEDURES

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

All of the protocol required assessments are listed in Table 3, with an "X" indicating at which visits the assessments are to be performed. All data obtained from these assessments must be recorded in the subject's source documentation.

Refer to the electronic case report form (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's Central Laboratory Manual.

6.1. Screening Period

Upon giving written informed consent, subjects enter the Screening Period to determine eligibility. Screening evaluations will be performed for all subjects to determine study eligibility. These evaluations must be completed within 35 days of W1D1 unless noted otherwise below. All inclusion/exclusion criteria must be met in order for subjects to be enrolled in the study. Waivers to the protocol will not be granted during the conduct of this trial. Subjects who do not meet the eligibility criteria will be considered screening failures and will not be eligible for enrollment. Subjects who fail screening may undergo rescreening.

Safety laboratory analyses and all laboratory assessments will be performed centrally unless noted otherwise. Screening laboratory values must demonstrate subject eligibility, but may be repeated within the screening window, if necessary.

The following assessments will be performed during screening as specified in the Table of Events (Table 3), after informed consent has been obtained.

The sponsor may review key eligibility criteria as well as relevant data (eg, central laboratory reports and cytomorphology/cytogenetic reports) and communicate as necessary with the investigator prior to enrollment of a subject.

6.1.1. Bone Marrow and Peripheral Blood Samples

Diagnosis of MDS, WHO classification (Appendix B), and IPSS risk classification (Appendix C) will be prospectively determined by independent central pathology and cytogenetics review, and applicable central laboratory results. The screening bone marrow aspirate sample together with peripheral blood should be collected within the protocol screening window or 5 weeks prior to W1D1. Samples should be collected, if possible, no later than 14 days prior to the planned W1D1 in order to allow sufficient time for central review and a repeat bone marrow assessment, if necessary.

The collection of a bone marrow biopsy is only required when an adequate aspirate is not attainable. To allow for cytomorphology assessment and cytogenetic analysis of the bone marrow biopsy please follow the guidance for processing the sample provided in the study's Central Laboratory Manual.

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 and were done within 8 weeks before ICF signature.

- 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 classification (Appendix B) prior to W1D1. 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 W1D1.

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. In the event that cytomorphology/cytogenetic analysis is technical failing at the central laboratory prior to W1D1, local cytomorphology/cytogenetic analysis may suffice for the purposes after consultation with the sponsor. This will require a central "over read" of the local cytomorphology/cytogenetics report, slides and/or photographs by the central laboratory prior to W1D1.

Additionally, in the event a local BM assessment for MDS diagnosis was made no more than 8 weeks before ICF signature, local BM samples/reports may be allowed for central "over read" after consultation with the sponsor and provided the central lab can confirm the diagnosis using the local samples/reports. The sponsor must be consulted prior to enrolling a subject using cytogenetic results from a local laboratory.

Results from central laboratory analysis should be used to determine baseline IPSS-R category (Greenberg, 2012) (Appendix C). In the event historical local BM samples/reports are being used for "over read", local laboratory results obtained from the same date the BM was taken should be used to determine the baseline IPSS-R category, if possible.

The central laboratory will also assess bone marrow and peripheral blood samples during the Treatment Period of the study. During the course of the study, whenever a bone marrow sample is collected, a peripheral blood smear is also to be prepared.

Bone marrow aspirate and/or blood collected at prespecified study time points will also be used for central laboratory exploratory/biomarker analysis (eg, MDS-associated molecular mutations [eg, SF3B1, etc.] and soluble biomarkers).

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

6.1.2. Prior Transfusion History

Transfusion history must be available for at least 16 weeks prior to W1D1. Red blood cell transfusion history will be confirmed to determine the eligibility of an individual study subject. Thus, this information must be collected during the Screening window (prior to W1D1) (including any transfusions at outside local institutions).

For details on the required information to be collected and reported in the eCRF for transfusions please refer to Section 6.4.1.

6.1.3. Demographics

The subject's date of birth, sex, race, and ethnicity will be recorded on the appropriate eCRF - as allowed by local regulations.

6.1.4. Medical History

All relevant medical conditions (including recent surgical history) diagnosed/ occurring prior to screening should be included and recorded in the 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.

6.1.4.1. Assessment of HIV/Hepatitis B/Hepatitis C Status

Local testing confirming HIV, hepatitis B, and hepatitis C status should not have been performed beyond 4 weeks prior to the date of ICF signature. If beyond this window or if information is not available in the medical history, additional local testing is required.

6.1.5. Physical Examination

Information about the physical examination must be present in the subject's source documentation. Significant findings must be reported as AE on the respective eCRF.

Refer to Table 3 for timing of physical examinations during the study.

6.1.6. Vital Signs, Height, and Weight

Vital signs including height (measured at screening only), weight, seated blood pressure (documented as mean of 2 readings obtained approximately 10 minutes apart with the subject seated for approximately 10 minutes prior to initial reading), temperature, and heart rate (HR) are to be reported in the subject's source record and appropriate eCRF.

Subjects must have blood pressure and weight assessed prior to IP administration on days where dosing occurs at the site. For more details, please refer to Section 7.2.1.

Refer to Table 3 for timing of vital signs during the study.

6.1.7. Eastern Cooperative Oncology Group Performance Status

Performance status will be assessed by the investigator during Screening and at other timepoints indicated on Table 3 using ECOG criteria provided in Appendix F.

6.1.8. Electrocardiogram

A 12-lead ECG is performed locally at the study site. The following ECG parameters will be recorded on the respective eCRF(s): eg, HR, PR interval, QRS duration, QT. 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 3 for timing of ECGs during the study.

6.1.9. Hematology

Hematology assessment (eg, RBC count, complete blood count [CBC], white blood cell [WBC] with differential [including myeloblasts], hemoglobin, hematocrit, nucleated red blood cells [nRBC], reticulocytes, platelet count, mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], and red blood cell distribution width [RDW]) will be performed by the central laboratory. Sample collection, processing, storage, and shipment procedures are provided in the study's Central Laboratory Manual.

Local laboratories are allowed in cases when timely results are needed (eg, pre-dose Hgb assessments, 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. Where discrepancies are present, results of the central laboratory will be used to determine response assessments (Section 6.4).

For details regarding assessment of Hgb levels prior to IP dosing to ensure dose modification rules are followed please refer to Section 7.2.1.

Refer to Table 3 for timing of hematology assessments during the study.

6.1.10. Serum Chemistry

Serum chemistry (ie, sodium, potassium, calcium, phosphorus, creatinine, creatinine clearance and/or eGFR, glucose, albumin, alkaline phosphatase, total bilirubin, direct/indirect bilirubin, AST/SGOT or ALT/SGPT, lactate dehydrogenase [LDH]) will be analyzed by the central laboratory. Sample collection, processing, storage, and shipment procedures are provided in the study's Central Laboratory Manual.

Local laboratories are allowed in cases when timely results are needed (eg, adverse events). In these circumstances, a split sample should still be collected and sent to the central laboratory for analysis.

Refer to Table 3 for timing of serum chemistry assessments during the study.

6.1.11. Serum EPO Level

Serum EPO samples will be analyzed by the central laboratory. Sample collection, processing, storage, and shipment procedures are provided in the study's Central Laboratory Manual.

Refer to Table 3 for timing of serum EPO level testing during the study.

6.1.12. Serum Ferritin and Other Iron-Related Markers

Analysis of serum ferritin and other iron-related markers (ie, total serum iron, percent iron saturation, total iron binding capacity, unsaturated iron binding capacity) will be performed/provided by the central laboratory. Sample collection, processing, storage, and shipment procedures are provided in the study's Central Laboratory Manual.

Refer to Table 3 for timing of serum ferritin testing during the study.

6.1.13. Urinalysis

Urinalysis will be conducted by the central laboratory and includes macroscopic, microscopic and quantitative analysis of urine (ie, albumin, protein, creatinine, albumin/creatinine ratio).

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

Refer to Table 3 for timing of urinalysis sample collection during the study.

6.1.14. Pregnancy Testing and Counseling

For the definition of females of childbearing potential (FCBP) please refer to Section 4.2 (Inclusion criterion 8). The investigator will appraise a female subject of their FCBP status according to this definition. Justification for the designation must be recorded in the eCRF and the source document.

A medically supervised serum pregnancy test (ie, a serum beta human chorionic gonadotropin [β-hCG] test with a minimum sensitivity of 25 mIU/mL [conducted at the central laboratory or locally]) is to be obtained and verified negative for a FCBP at screening. Pregnancy testing is not required for non-FCBP subjects.

Additional urine (or serum) pregnancy testing, to confirm negative results and to assess subject eligibility, will be performed within 72 hours prior to the administration of the first dose of IP, unless the screening serum pregnancy test was already performed and verified negative during this time frame.

During the Treatment Period urine or serum pregnancy testing 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 Table 3 for timing of pregnancy testing and counseling during the study.

6.1.15. Sample Collection for Exploratory Biomarker Assessments

Refer to Section 6.7 for more information.

6.1.16. Sample Collection for Pharmacokinetic Analysis and ADA Evaluation

Refer to Section 6.5 and Section 6.6 for more information on PK and ADA sampling, respectively.

[redacted]

6.1.18. Concomitant Medications and Procedures

Information on prior and concomitant medications and procedures are to be reported on the appropriate eCRF starting 8 weeks prior to W1D1. Any prior anticancer treatments should be recorded on the appropriate eCRF(s).

Refer to Section 8 for more information on permitted and prohibited medication.

6.1.19. Adverse Event Evaluation

Ongoing evaluation and reporting of adverse events begins when the subject signs the informed consent form and must be documented on the appropriate eCRF.

Refer to Section 10 for more information.

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

Progression to AML as per WHO classification (Arber, 2016) 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 5 years from the date of the first dose of IP, or 3 years from the last dose (whichever occurs later), or until death, lost to follow-up or withdrawal of consent from the study. For that purpose, subjects will be followed post-treatment every 12 weeks for 3 years from the date of last dose of IP and every 6 months thereafter, if applicable.

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 AEs 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 (SAE), regardless of causal relationship to IP (luspatercept or epoetin alfa), occurring at any time for the duration of the study, from the time of signing the ICF for up to and including long-term follow-up (ie, 5 years from the date of the first dose of IP, or 3 years from the last dose [whichever occurs later]), 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 to the 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.

6.1.21. Information to be Collected on Screening 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 ICF was signed, demographics, the

reason the 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.

6.2. Treatment Period

The subject must receive the first dose of investigational product (IP) within 3 days of enrollment at the latest and can be on the same day as enrollment. For all subsequent visits, an administrative time window of ± 2 days is permitted if not indicated otherwise. If screening assessments are performed within 3 days of W1D1, safety laboratory and physical examinations need not be repeated at W1D1.

Subjects will receive IP every 3 weeks (21 days) (ie, at W1D1 Visit, W4D1 Visit; W7D1 Visit, etc.). For details regarding IP administration including dose adjustments and dose modifications please refer to Section 7.

The following evaluations will be performed at the frequency specified in the Table of Events (Table 3). The evaluations should be performed prior to dosing on the visit day, unless otherwise specified.

- Physical examination (as detailed in Section 6.1.5)
- Administration and accountability of IP (as detailed in Section 7)
- ECOG performance status (as detailed in Section 6.1.7)
- Urinalysis (as detailed in Section 6.1.13)
- Pregnancy testing and counseling (as detailed in Section 6.1.14)
- Adverse event assessment and reporting on an ongoing basis (as detailed in Section 10)
- Concomitant medications and procedures on an ongoing basis (refer to Section 8 for more information on permitted and prohibited medications)
- Vital signs and weight (as detailed in Section 6.1.6)
- Serum chemistry (as detailed in Section 6.1.10)
- Hematology assessments (as detailed in Section 6.1.9)
- Serum EPO level (as detailed in Section 6.1.11)
- Serum ferritin level (as detailed in Section 6.1.12)
- Transfusion data collection and assessment (as detailed in Section 6.4.1)
- Bone marrow aspirate and peripheral blood collection for cytomorphology and cytogenetic testing (as detailed in Section 6.1.1)
- MDS Disease assessment (as detailed in Section 6.4.2)
- Bone marrow aspirate and peripheral blood collection for exploratory Biomarker sample collection (as detailed in Section 6.7)

- PK and ADA sample collection (as detailed in Section 6.5 and Section 6.6, respectively.
- [redacted]
- Monitoring for progression to AML and other malignancies/pre-malignancies (as detailed in Section 6.1.20)

6.2.1. Unscheduled Visits

Should it become necessary to repeat an evaluation (eg, laboratory tests or vital signs), the results of the repeated 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.

6.2.2. End of Treatment

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 of Events (Table 3).

If a subject is discontinued during a regular scheduled visit, all EOT procedures should be completed at that visit.

If a procedure had been performed within 7 days of the EOT Visit, it does not need to be repeated unless clinically indicated as per investigator's discretion (with the exception of blood pressure assessment and sample collection for hematology, chemistry, and urinalysis). A bone marrow assessment procedure should only be performed at EOT if a prior bone marrow assessment has been performed > 90 days apart.

End of Treatment (EOT) Visit procedures/ assessments may occur at the 42-Day Follow-up assessment if a subject is discontinued within ± 7 days of the 42-Day Follow-up assessment.

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

6.3. Post-Treatment Follow-up Period

6.3.1. Safety Follow-up (42-Day Follow-up)

All subjects will be followed for 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, as described in Section 10.1.

Refer to Table 3 for additional assessments to be performed at the 42-Day Follow-up.

Females of childbearing potential must avoid becoming pregnant for 12 weeks after the last dose of IP and male subjects must avoid fathering a child for 12 weeks after the last dose of IP. Refer to Section 10.4 for additional details.

In the case of dose delays that exceed 6 weeks (+2 days) and end in treatment discontinuation, the 42-Day Follow-up Visit will be omitted and replaced by the EOT Visit.

6.3.2. Long-term Follow-up

Transfusion data collection will continue until 8 weeks from the date of last dose of IP or from the date of the EOT Visit (whichever is later) (Section 6.4.1). Subjects should also be followed via telephone contact by the site to verify if transfusions were given outside of the investigative site.

Antidrug antibodies sample(s) may be required in the Post-Treatment Follow-up Period for subjects who terminate the Treatment Period with less than 1 year of ADA monitoring if a subject is ADA positive at the time of treatment discontinuation (Section 6.6).

All subjects discontinued from protocol-prescribed therapy for any reason should be followed for the below events/therapies for 5 years from the date of the first dose of IP, or 3 years from the last dose (whichever occurs later), or until death, lost to follow-up or withdrawal of consent from the study.

- Progression to AML and other malignancies/pre-malignancies (please refer to Section 6.1.20 and Section 10.5 for details)
- Survival (date and cause of death)
- and subsequent MDS therapies

Subjects may be followed via telephone contact by the site for collection of the above data every 12 weeks for the first 3 years from the date of last dose of IP and every 6 months thereafter (if applicable) until 5 years from the date of the first dose of IP, or 3 years from the last dose (whichever occurs later), or until death, lost to follow-up or withdrawal of consent from the study. Refer to Table 3.

Data regarding subsequent MDS therapies, determination of AML progression and other malignancies/pre-malignancies, 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.

6.4. Efficacy Assessment

Treatment response will be assessed locally by the investigator in accordance with IWG 2006 criteria for MDS (Cheson, 2006), through assessment of administered RBC transfusions, hematology parameters, peripheral blood smears, bone marrow aspirates and/or biopsies, and cytogenetics. Central lab, cytomorphology and cytogenetics results will be used for response assessment. Please refer to Section 6.4.1 and Section 6.4.2 below for details.

Other efficacy assessments will include health-related quality of life measurements.

The timing of efficacy assessments (MDS disease assessments and health-related quality-of-life) as well as associated sampling and assessments (ie, bone marrow and peripheral blood samples, RBC transfusion assessment) are specified in the Table of Events (Table 3). Please refer to Section 6.1.1 for details on bone marrow aspirate samples for assessing treatment response.

6.4.1. Transfusion Assessment

During the Treatment Phase transfusions will be assessed and recorded in the eCRF on an ongoing basis (prior to each dose of IP) until 8 weeks after last dose of IP or the End of Treatment Visit, whichever occurs later. Clinical site staff must confirm (and document in the subject's source record) if any transfusions were received by the subject (including any at outside local institutions in between study visits) prior to each IP administration. In addition to local procedures in place at the site to capture this information, a patient transfusion diary will be provided to subjects and will be reviewed by the site when/if returned by the subject.

The following information will be collected for RBC transfusions (and platelet transfusions if applicable) and reported in the eCRF:

- Type, number of units, reason and date of transfusion
- The Hgb value for which any RBC transfusion is given, and the platelet value for which any platelet transfusion is given, (these Hgb and platelet values may be local or central laboratory measurements)

Please find recommendations for adequate source documentation of transfusion history as well as transfusions given during the treatment phase below:

- Signed original or copy of single transfusion record including number of units administered and Hgb/platelet value prior to transfusion.
- Signed record of multiple transfusions done at the same clinic. For each transfusion, the units and dates are specified along with Hgb/platelet value prior to each transfusion.
- If electronic record: signed print-out of administration record(s), specifying unit(s) on specified date(s), plus signed additional documentation of Hgb/platelet values(s) prior to transfusion.
- Signed referral letter(s) specifying date(s) and number(s) of units administered with Hgb/platelet value(s) prior to transfusion(s).

6.4.2. MDS Disease Assessment

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

The 24-Week MDS Disease Assessment Visit should be completed 24 calendar weeks (ie, Day 169) after W1D1, regardless of dose delays.

As central laboratory results from bone marrow and peripheral blood samples (ie, cytomorphology, cytogenetic analysis) are required as part of the MDS Disease Assessment, a 14-day window is allowed for the 24-Week MDS Disease Assessment Visit (ie, Day 169 ± 14 days) in order to account for sample collection and turnaround time of results.

The MDS Disease Assessment by the investigator, associated with this visit to assess clinical benefit, should be completed no sooner than 24 calendar weeks (ie, 169 days) after W1D1 as it requires 24 weeks of transfusion information in addition to central laboratory results from bone marrow and peripheral blood samples (ie, cytomorphology, cytogenetic analysis). 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.

For subjects to remain on treatment beyond this timepoint both of the following criteria must be confirmed in each subject:

- Evidence of clinical benefit defined by either one of the following two criteria:
  - HI-E based on IWG (Cheson, 2006) (Appendix D) (Hgb increase of ≥ 1.5 g/dL for the 8 weeks within the 12 weeks immediately preceding Day 169 and every 24 weeks thereafter [ie, Day 337, Day 505, etc.])
  - Maintain RBC transfusion independence
- Absence of disease progression per IWG criteria for altering natural history of MDS (Cheson, 2006) (Appendix E) based on central morphological assessment of bone marrow, peripheral blood and cytogenetics results.

Based on the outcome of these assessments, subjects will either be discontinued from treatment with IP and enter the Post-Treatment Follow-up Period or continue open-label treatment as long as above criteria continue to be met or until the subject experiences unacceptable toxicities, withdraws consent, or meets any other discontinuation criteria.

In circumstances where the next dose of IP is due to be scheduled prior to cytomorphology/cytogenetics results being available, dosing should not be delayed for this reason contingent that the investigator has confirmed absence of signs of disease progression based on review of peripheral blood parameters. However, the investigator must complete the assessment of cytomorphology/cytogenetics results prior to the following IP administration.

For subjects to continue open-label treatment with IP, MDS disease assessments will be repeated at the 48-Week MDS Disease Assessment Visit and every 24 weeks thereafter (ie, Day 337, Day 505 etc.; a ± 14-day time window to allowed for sample collection) to confirm continued clinical benefit and absence of disease progression as per above criteria.

6.5. Pharmacokinetics

Blood samples will be collected to analyze luspatercept concentrations in serum in all subjects. At each PK time point, approximately 3 mL of peripheral blood will be collected and serum prepared as described in the in the study's Central Laboratory Manual. Blood samples for PK will be taken at the following visits during the study (also see Table 3):

- For the dense PK in the initial 10 subjects, W1D1 (must be collected before the first dose), W1D3, W2D1, W2D3, W3D1, W4D1, W10D1, W13D1, W16D1, W17D1, W18D1, W19D1, W22D1, 24-Week MDS Disease Assessment, and every 12 weeks from the 24-Week MDS Disease Assessment Visit for up to 1 year from the first dose.

- For the sparse PK in other 10 subjects, W1D1 (must be collected before the first dose), W2D1, W3D1, W4D1, W10D1, W16D1, W22D1, 24-Week MDS Disease Assessment Visit, and every 12 weeks (± 14 days) from the 24-Week MDS Disease Assessment Visit for up to 1 year from the first dose.

If a PK sample is drawn on a dosing day, the PK sample should be drawn prior to luspatercept dosing. All PK samples should be collected along the protocol defined "weekly" visits adapting to dose delays (see footnote g under Table 3). Once a subject has been discontinued from treatment, PK samples may no longer be collected as long as ADA are not detectable.

6.6. Antidrug Antibody (ADA)

Blood samples will be collected to assess ADAs against luspatercept in serum. At each ADA sampling time point, approximately 3 mL of peripheral blood will be collected and serum prepared as described in the study's Central Laboratory Manual. 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 3):

- W1D1 (must be collected before the first dose), W4D1, W10D1, W16D1, W22D1, 24-Week MDS Disease Assessment Visit and every 12 weeks (± 14 days) from the 24-Week MDS Disease Assessment Visit.

If an ADA sample is drawn on a dosing day, the ADA sample should be drawn prior to luspatercept dosing. If the last available ADA result at the end of treatment is positive, the subject may be asked to return to the clinical site for additional long-term follow up every 12 weeks (± 14 days) for up to one year after the first dose of luspatercept or until ADA are not detectable, whichever comes first.

The maximum ADA monitoring period will not exceed 1 year from the first luspatercept dose unless justified by safety reasons. ADA sampling per investigator's or sponsor's discretion is allowed and should be recorded as an unscheduled visit.

6.7. Biomarkers, Pharmacodynamics, Pharmacogenomics

Bone marrow aspirate and/or peripheral blood samples for evaluation of exploratory biomarkers such as myeloid-associated molecular mutations and activin receptor IIB ligands and other exploratory biomarkers will be collected at specified timepoints as indicated in the Table of Events (Table 3). These measurements may include, but are not limited to, assessments of SARS-CoV-2 serologic status. If required on study dosing days, samples should be taken prior to IP administration.

Bone marrow aspirate for evaluation of biomarkers will be collected at study time points when a bone marrow procedure is required for MDS disease assessment (eg, cytogenetics and cytomorphology analysis). Please note that the remaining bone marrow aspirate (after sufficient quantity is allocated towards cytomorphology and cytogenetics analysis) will be used for exploratory biomarker studies. An additional bone marrow procedure should not be performed for these samples. Refer to the study's Central Laboratory Manual for additional information related to sample collection.

Activin Receptor IIB ligands and other exploratory biomarkers

Peripheral blood will be collected by the site and sent to central laboratories for analysis of soluble biomarkers. Sample collection, storage and shipping procedures will be provided in the Central Laboratory Manual. Refer to the Table of Events (Table 3) for timing of sample collection.

MDS-associated molecular mutations

Bone marrow aspirate will be collected by the site and sent to a central laboratory for analysis of molecular mutations such as SF3B1 and others. If there is sufficient volume, an aliquot of bone marrow mononuclear cells will be stored frozen for future analysis, such as RNA expression profiling to allow us to develop a gene signature that predicts response. Sample collection, storage and shipping procedures will be provided in the study's Central Laboratory Manual. Refer to the Table of Events (Table 3) for timing of sample collection.

Terminal erythropoiesis

Bone marrow aspirate will be collected by the site and sent to central laboratories for analysis of terminal erythroid differentiation by flow cytometry. Sample collection, storage and shipping procedures will be provided in the Central Laboratory Manual. Refer to the Table of Events (Table 3) for timing of sample collection.

SARS-Cov-2 serology testing

Blood will be collected at screening and EOT for possible measurements of SARS CoV-2 serology (anti-SARS-CoV-2 IgG or total antibody).

The samples will be destroyed five years after the end of trial or earlier if required by law. If subjects decide to withdraw the consent, all previously retained identifiable samples be destroyed to prevent future testing. Since the results of genetic tests are not beneficial to the treatment of an individual subject, they will not be disclosed to the subjects.

6.8. Additional and Optional Research

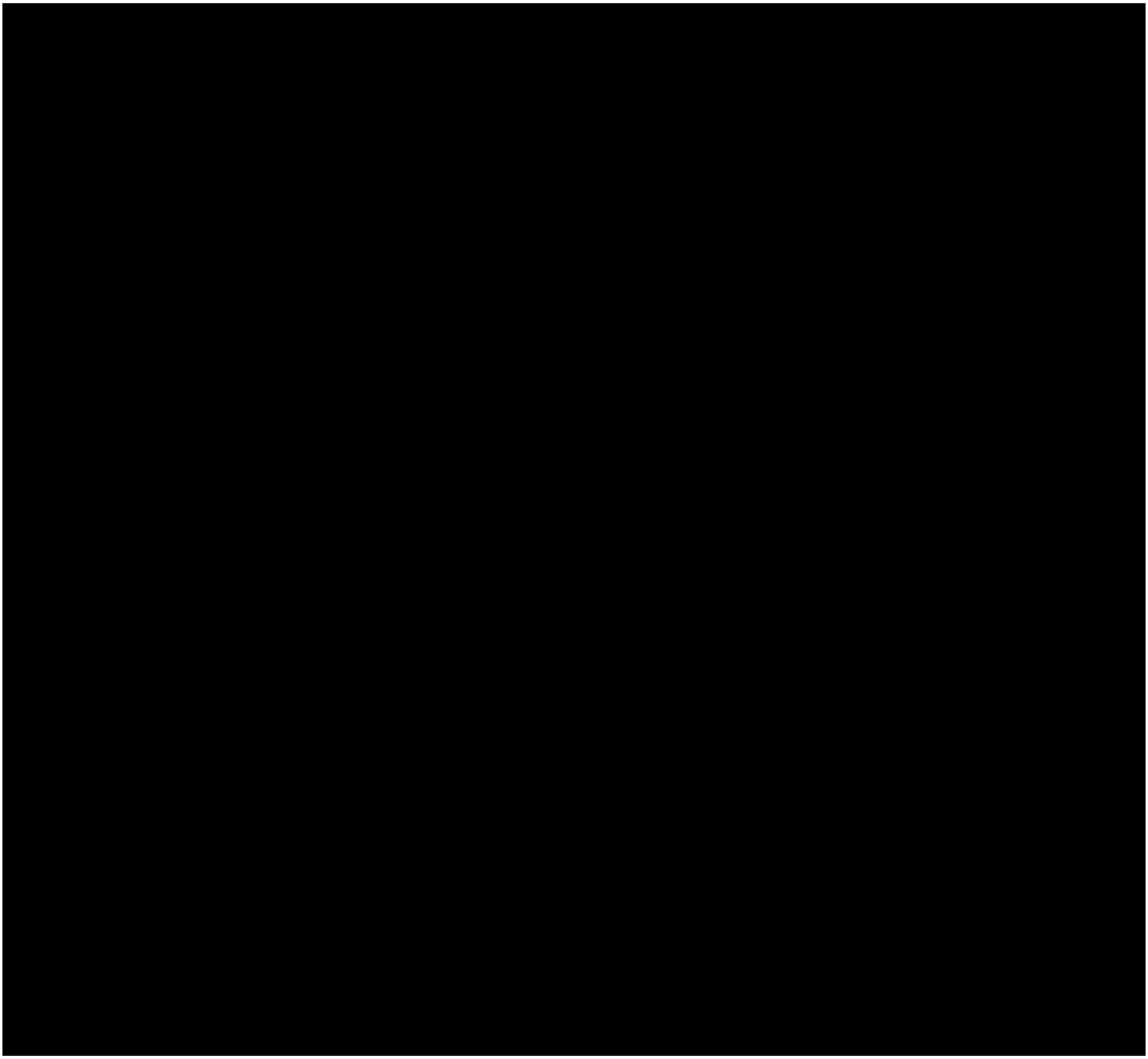
Additional and optional research as described below may be performed using left-over samples originally collected for another test required in this study or using samples collected specifically for biomarker testing. The research may involve genetic tests using DNA or RNA and may lead to the development of new diagnostic tests.

6.8.1. Additional Research

Additional research related to the study drug and/or disease may be performed. The results of this additional research could help to improve the diagnosis and/or the treatment of this disease in the future.

6.8.2. Optional Research

Optional research not related to the study drug or the subject's disease may be performed. The subject's decision to participate in this optional research will not impact their ability to participate in the main study.



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 25 mg and 75 mg vials and when reconstituted, with water for injection, each consists of 50 mg/mL luspatercept in a [redacted] mM citrate buffer-based solution ([redacted] mM citrate, pH [redacted], [redacted]% sucrose, [redacted]% polysorbate 80).

The recommended storage condition for luspatercept for injection (25 mg/vial and 75 mg/vial; lyophilized powder formulation) is 2°C to 8°C. It is recommended that the reconstituted luspatercept for injection, at room temperature, be administered immediately. However, it may be held for up to 24 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 24 hours. Please refer to the pharmacy manual for more details.

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

7.2. Treatment Administration and Schedule

7.2.1. Luspatercept Administration and Schedule

Luspatercept will be administered as a subcutaneous injection every 3 week (21 days; Q3W), at an initial dose level of 1.0 mg/kg. Doses may be titrated up starting at dosing visit W7D1 (ie, Dose 3) as described in Section 7.2.2.

Luspatercept will be administered 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 (changes of body weight of $\leq \pm 5\%$ do not require a dose adjustment) prior to each IP administration.

Subcutaneous injections will be given in the upper arm, thigh, and/or abdomen. Calculated doses requiring reconstituted volume greater than 1.2 mL should be divided into separate similar volume injections across separate sites using the same anatomical location but on opposite sides of the body (example left thigh and right thigh). The maximum volume per subcutaneous injection should not exceed 1.2 mL.

The injection sites can be rotated according to investigator judgment, and the injections can be given in the following order as needed, for example: 1) right upper arm, 2) left upper arm, 3) right upper thigh, 4) left upper thigh.

Clinical site staff must also confirm (and document in the subject's source record) if any transfusions were received by the subject (including any at outside local institutions in between study visits) prior to each IP administration. In addition to local procedures in place at the site to capture this information, a patient transfusion diary will be provided to subjects and will be reviewed by the site when/if returned by the subject.

7.2.2. Luspatercept Dose Adjustment and Dose Modification

Appropriate dose adjustments should be made to maintain hemoglobin concentrations within the target range of 10 g/dL to 12 g/dL (6.2 mmol/L to 7.5 mmol/L) independent of transfusions. Starting as soon as with dosing visit W7D1 (ie, Dose 3) of luspatercept, and assessed by the investigator prior to every subsequent luspatercept dosing, 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 (Table 4), if all of the following criteria are met:

- Subject Hgb levels are below the target range of 10 g/dL to 12 g/dL (6.2 mmol/L to 7.5 mmol/L).
- Subject Hgb level increase compared to the Hgb sample taken prior to the previous luspatercept dose is ≤ 1 g/dL.
- The two most recent prior luspatercept administrations 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 luspatercept administrations (exception of dose delay required due to influence of RBC transfusions). Refer to Table 5.

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 4).

Dose delay and/or reduction or discontinuation may be required due to increased hemoglobin or adverse events. For details on dose modification guidance for luspatercept please refer to Table 5.

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

3rd Dose Reduction	2nd Dose Reduction	1st Dose 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

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

Event at the Day of Dosing (Assessed prior to each IP administration at the respective visit[i])	Action
Any suspected related AE ≥ Grade 3[a,b]	Dose delay[c] until resolved to ≤ Grade 1 or baseline, and then reduce dose by one dose level according to Table 4
> 3 dose reductions due to suspected related AE[a]	Discontinue treatment
ΔHgb > 2.0 g/dL (not influenced by RBC transfusions[d]) compared to pre-dose Hgb of the previous luspatercept administration	Reduce dose by one dose level according to Table 4
Predose Hgb ≥ 12.0 g/dL	Dose delay until Hgb < 11.0 g/dL[d]
≥ 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 complete blood count (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) (Appendix E) AND WBC values return below upper limit of normal Discontinue treatment if: Disease progression per IWG response criteria for altering natural history of MDS (Cheson, 2006) (Appendix E) OR WBC remain above upper limit of normal[e]

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

Event at the Day of Dosing (Assessed prior to each IP administration at the respective visit[i])	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 luspatercept administration. – If presence of ≥ 1% blasts in peripheral blood; discontinue treatment[h]

AE = adverse event; Hgb = hemoglobin; IP = investigational product; IWG = International Working Group; MDS = myelodysplastic syndromes; RBC = red blood cell.

[a] Possibly, probably or definitely related to IP.

[b] Includes systolic blood pressure ≥160 mmHg and diastolic blood pressure ≥100 mmHg.

[c] If dose delay is > 12 consecutive weeks (> 15 weeks from last dose administered), treatment should be discontinued.

[d] 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.

[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.

[i] Every attempt should be taken to assess the blasts count in peripheral blood prior to dosing, however, in circumstances where results are not readily available at the time of planned dosing, the investigator may proceed with dosing provided there are no signs of clinical progression. In this case, results must be evaluated as soon as they become available (but no later than 3 days post dosing). If presence of ≥ 1% blasts in peripheral blood is observed, actions described in table above must be followed immediately.

7.2.3. Overdose

On a per dose basis, an overdose for luspatercept 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 injection 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 subject's enrollment will occur at the end of the Screening Period, once all required screening procedures have been completed and all inclusion and exclusion criteria have been assessed to determine eligibility of the subject. Subjects deemed eligible for the study will be enrolled using IRT.

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 dosing visits and in the event of any dose reduction or dose titration site staff must contact IRT to record the new dose level and obtain the new IP assignment.

7.4. Packaging and Labeling

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

7.5. Investigational Product Accountability and Disposal

7.5.1. Accountability Procedures

Accountability for IP 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 IP received, to whom it was administered (subject-by-subject accounting), and accounts of any IP 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 IP, 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.

7.5.2. Drug Disposal and Destruction

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

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

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

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

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 may be administered at the discretion of the investigator.

All prior/ concomitant medications, used 8 weeks prior to W1D1 until 42 days after the last dose of IP (or until the EOT Visit, whichever occurs later), must be reported on the eCRF. All prior procedures within the 8 weeks prior to W1D1 as well as concomitant procedures (including transfusions) will be recorded on the appropriate eCRF(s).

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

Prior ESAs and G-CSF/GM-CSF should be recorded on the appropriate eCRF(s) regardless of treatment discontinuation 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 EOT visit and enter the Post-Treatment 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 IB and/or package insert.

8.1. Permitted Concomitant Medications and Procedures

8.1.1. 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, shortness of breath, fatigue etc.) or comorbidity.

For any RBC transfusions received during the study, hemoglobin values just prior to transfusion will be collected. Please refer to Section 6.4.1 for details on required data collection.

8.1.2. Corticosteroids

Concurrent systemic corticosteroids used for medical conditions other than MDS is allowed provided the subject is on a stable or decreasing dose for ≥ 1 week prior to W1D1. Use of topical steroids is permitted. Occasional use of corticosteroids before transfusions to prevent allergic reactions is permitted.

8.1.3. Attenuated Vaccines

Administration of attenuated vaccines (eg, influenza vaccine) is allowed if clinically indicated, per investigator discretion with the exception of a live COVID-19 vaccine.

8.1.4. Phlebotomy

Phlebotomy may be performed for emergency/urgency if excessively high Hgb levels occur.

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:

- 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 or as clinically indicated per product label.
- Cytotoxic, chemotherapeutic, targeted or investigational agents/therapies
- Azacitidine, decitabine or other hypomethylating agents
- Lenalidomide, thalidomide and other immunomodulating drugs (IMiDs)
- Hydroxyurea, anagrelide
- Androgens, unless to treat hypogonadism
- Oral retinoids
- Arsenic trioxide
- Interferon and interleukins

Administration of a live COVID-19 vaccine is prohibited within 4 weeks prior to randomization. Live COVID-19 vaccines should not be used during the study, including the treatment period and until 42 days following the last dose of IP.

8.3. Required Concomitant Medications and Procedures

Not applicable.

9. STATISTICAL CONSIDERATIONS

9.1. Overview

This is a Phase 2, multicenter, single-arm study. The primary objective of the study is to evaluate HI-E per IWG (Cheson, 2006) for the treatment of anemia due to IPSS-R very low, low, or intermediate risk MDS in Japanese subjects who are not requiring RBC transfusion.

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 follows:

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

Efficacy Evaluable (EE): The EE population will consist of 1) all subjects who received at least one dose of IP and 2) have at least two hemoglobin assessments ≥ 8 weeks apart post-treatment.

Safety: The safety population will consist of all subjects who were enrolled and received at least one dose of IP. 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

For the primary efficacy endpoint, HI-E, the sample size is based on one sample binomial exact test. The null hypothesis to be tested is that the proportion of subjects achieving HI-E (defined as ≥ 1.5 g/dL increase in Hgb over any consecutive 56-day period in the absence of RBC transfusions) is ≤ 10%; the alternative hypothesis is that the proportion of subjects achieving HI-E is > 10%. With these hypotheses, a sample size of 20 subjects are required with a power of 95% at a one-sided 0.025 alpha level if the expected proportion is 45%. This criterion requires that the lower limit of the 95% confidence intervals for the HI-E rate is greater than 10%.

The selection of a null hypothesis of 10% HI-E rate is based on the results of ARCADE Phase 3 study of darbepoetin, where the proportion of subjects achieving HI-E was reported as 14.7% (95% CI: 8%–25%) (11/75) (Platzbecker, 2017c). Based on the lower limit of 95% CI, the null hypothesis is assumed as 10%. The expected proportion of 45% HI-E rate is based on the preliminary efficacy observed with luspatercept in the ex-Japan Phase 2 study (Platzbecker, 2017a). In the study, HI-E rate was 63% (95% CI: 48%–76%) (32/51 evaluable). Based on the lower limit of 95% CI, the expected proportion is assumed as 45%.

9.4. Background and Demographic Characteristics

Subjects' age, height, weight, and baseline characteristics will be summarized using descriptive statistics, while gender and other categorical variables will be provided using frequency tabulations by dose cohort. Medical history data will be summarized using frequency tabulations

by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. MDS diagnoses will be summarized using frequency tabulations.

9.5. Subject Disposition

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

9.6. Efficacy Analysis

9.6.1. Primary Efficacy Analysis

The primary efficacy endpoint of HI-E per IWG (Cheson, 2006) within 24 weeks is defined as proportion of subjects meeting HI-E criteria of ≥ 1.5 g/dL increase in Hgb sustained over any consecutive 56-day period in the absence of RBC transfusions from W1D1 through Week 24. Subjects discontinued from the Treatment Period without achieving HI-E will be counted as non-responders.

As the primary efficacy analysis, one sample binomial one sided exact test will be performed based on ITT population, to provide p-value (significance level: 0.025). The statistical hypothesis will be as follows,

$$H_0: p \leq 10\%,$$

$$H_a: p > 10\%$$

where p denotes the true response rate. The number and percentage of subjects who achieve the response and 95% CI will be presented based on the ITT population.

Dose modification guidance for luspatercept in Section 7.2.2 defines that, if predose Hgb is ≥ 12.0 g/dL at the day of dosing, the dose should be delayed until Hgb is < 11.0 g/dL. For subjects who meet this criterion and then have their dose delayed, if their Hgb levels temporarily decrease to < 1.5 g/dL but achieve ≥ 1.5 g/dL again after treatment resumption, this period (ie, the time from dose delay to achieving a Hgb increase of ≥ 1.5 g/dL again) will be included as the period of sustained Hgb increase of ≥ 1.5 g/dL. As a sensitivity analysis, the analysis results not applicable to this rule will also be calculated.

Additional details will be outlined in the SAP.

9.6.2. Secondary Efficacy Analyses

The secondary variables will be analyzed descriptively, unless otherwise specified, and will be based on the ITT population and EE 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 variables. Response rate of HI-E per IWG (Cheson, 2006) within 24 weeks, based on the EE population, will be analyzed as a secondary endpoint.

Modified hematologic improvement - erythroid (mHI-E) per IWG (Cheson, 2006) is defined as proportion of subjects meeting mHI-E criteria of ≥ 1.5 g/dL mean increase in Hgb compared to baseline that is sustained over any consecutive 56-day period in the absence of RBC

transfusions from W1D1 through Week 24 (and W1D1 through Week 48) of the Treatment Period. Subjects discontinued from the Treatment Period without achieving a mean Hgb increase ≥1.5 g/dL will be counted as non-responders.

HI-E per IWG (Cheson, 2006) within 48 weeks is defined as proportion of subjects meeting HI-E criteria of ≥ 1.5 g/dL increase in Hgb sustained over any consecutive 56-day period in the absence of RBC transfusions from W1D1 through Week 48 of the Treatment Period. Subjects discontinued from the Treatment Period without achieving HI-E will be counted as non-responders.

For subjects who have a dose delay meeting the dose modification criterion described in Section 9.6.1, if their Hgb levels temporarily decrease to < 1.5 g/dL but achieve ≥ 1.5 g/dL again after treatment resumption, this period (ie, the time from dose delay to achieving a Hgb increase of ≥ 1.5 g/dL again) will be included as the period of sustained Hgb increase of ≥ 1.5 g/dL.

Time to HI-E will be summarized only for subjects who achieve HI-E. It is defined as time from W1D1 to first onset of achieving ≥ 1.5 g/dL increase in Hgb over any consecutive 56-day period in the absence of RBC transfusions. It will be summarized separately for subjects who achieve HI-E within the first 24 weeks and 48 weeks from W1D1, respectively.

Time to mHI-E will be summarized only for subjects who achieve mHI-E. It is defined as the time from W1D1 to first onset of achieving ≥ 1.5 g/dL mean increase in Hgb over any consecutive 56-day period in the absence of RBC transfusions. It will be summarized separately for subjects who achieve mHI-E within the first 24 weeks and 48 weeks from W1D1, respectively.

Duration of HI-E will be determined only for subjects who achieve HI-E during the Treatment Period. Duration of HI-E is defined as the maximum duration of achieving ≥ 1.5 g/dL increase in Hgb for subjects who achieve Hgb increase ≥ 56 days in the absence of RBC transfusions. Subjects who maintain HI-E through the end of the Treatment Period or time of analysis will be censored at the date of treatment discontinuation/time of analysis or death, whichever occurs first.

Duration of mHI-E will be determined only for subjects who achieve mHI-E during the Treatment Period. Duration of mHI-E is defined as the maximum duration of achieving ≥ 1.5 g/dL mean increase in Hgb for subjects who achieve a mean Hgb increase of ≥ 56 days in the absence of RBC transfusions. Subjects who maintain mHI-E through the end of the Treatment Period or time of analysis will be censored at the date of treatment discontinuation/time of analysis or death, whichever occurs first.

Proportion of subjects who maintain RBC-TI is defined as proportion of subjects not being given any RBC transfusion during the Treatment Period and will be calculated at Week 24, Week 48, and Week 72.

Time to progression to AML is defined as the time between W1D1 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 W1D1 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.

9.7. Safety Analysis

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

Adverse events will be coded using MedDRA. Adverse event listings will include the verbatim term and the MedDRA preferred term. Treatment-emergent adverse events will be summarized by system organ class and preferred term. Treatment-emergent adverse events leading to death or to discontinuation from treatment, 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. Clinically significant hematologic and non-hematologic laboratory abnormalities will be listed and summarized according to the NCI CTCAE (version 4.03). Additionally, frequency of ADAs will also be reported.

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.

9.8. Interim Analysis

There is no planned interim analysis for this study.

9.9. Other Topics

[redacted]

9.9.2. Pharmacokinetic Analysis

PK parameters including, but not limited to area under the concentration time curve (AUC), maximum plasma concentration of drug (C_{max}), time to maximum plasma concentration of drug (T_{max}) will be estimated for each subject. Descriptive statistics will be provided for all concentration data and PK parameters.

Full details will be included in the SAP.

9.9.3. Exploratory Analysis

Descriptive statistics will also be provided for exploratory parameters (eg, GDF11, SF3B1, C-reactive protein, SARS-CoV-2 antibody, and other molecular markers). Statistical tests will be applied for these parameters if applicable. Full details will be included in the SAP.

9.9.4. Subgroup Analysis

Appropriate subgroup analyses by baseline endogenous EPO level of < 500 U/L versus ≥ 500 U/L 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 7.2.3 for the definition of overdose). Any sequela of an accidental or intentional overdose of an investigational product which meets the definition of an adverse event, should be reported as an AE on the eCRF. If the sequela of an overdose meets serious criteria, then it must be marked as serious on the eCRF. The overdose itself should not be reported as an AE.

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. Phlebotomy may be performed if excessively high Hgb levels occur.

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. All adverse events (serious/non-serious) will be recorded on the eCRF and in the subject's source documents. Refer to Section 10.5 for instructions on how to report SAEs to Drug Safety.

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.

For each AE, 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 each AE, the investigator must assess the severity/ intensity of the event.

The severity/intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of the Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03).

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

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

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject's life or functioning.

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

10.2.3. Causality

The investigator must determine the relationship between the administration of the IP and the occurrence of an AE 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 each AE 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 each AE, 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 each AE, 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 each AE.

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered (returned to baseline, unless the subject experiences progression of MDS or any other malignancy), 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 as the AE. 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 female partner of a male subject are immediately reportable events. For adequate measures of contraception please refer to Section 4.2.

10.4.1. Females of Childbearing Potential

Pregnancies and suspected pregnancies (including elevated β-hCG or positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring while the subject is on 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 and if applicable the subject

instructed to return any unused portion of the IP to the investigator. 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 (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 within 24 hours of the investigator's knowledge of the event.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as an SAE. 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 as an SAE to Celgene Drug Safety within 24 hours of the investigator's knowledge of the event.

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.

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; the exception being SAEs occurring prior to treatment (after signing the ICF). 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, computed tomography [CT] scans, etc.).

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

Malignancy or cancer is characterized by anaplasia, invasiveness, and metastasis. For 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 serious criterion requires reporting as an SAE within 24 hours of the investigator's knowledge of the event. This instruction pertains to initial SAE reports as well as any follow-up reports.

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 SAEs 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) are to be recorded within the eCRF, but do not require reporting 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.

The SAE is recorded within the eCRF, and the data are transmitted electronically to Celgene Drug Safety. In the event electronic transmission is not available, a paper SAE Report Form will be completed and sent directly to Celgene Drug Safety, ensuring the event is recorded on the eCRF as well.

10.7. Expedited Reporting of Adverse Events

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

Celgene or its authorized representative shall notify the investigators and the heads of the institutes 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, suspected unexpected serious adverse reaction [SUSAR]);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Other important safety information and periodic reports according to the local regulations.

Where required by 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 the IRB/EC (See Section 14.3 for record retention information).

10.8. COVID-19 Reporting

The occurrence of a COVID-19 event will be monitored as part of the assessment of AEs throughout the course of the study. Investigators are to report the occurrence of COVID-19 events, regardless of casual relationship to IP, occurring at any time for the duration of treatment up to 42 days after the last dose.

11. DISCONTINUATIONS

11.1. Treatment Discontinuation

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

- Lack of Efficacy
- Adverse Event
- Withdrawal by subject
- Death
- Lost to follow-up
- Pregnancy
- Protocol violation
- Study terminated by the sponsor
- Other (to be specified on the eCRF)
  - Including treatment discontinuation guidance related to dose modification Section 7.2.2.
- Disease Progression as per IWG criteria for altering natural history of MDS (Cheson, 2006) (Appendix E)
  - For subjects with 5 to 10% blasts, a second bone marrow sample should be collected within 4 weeks for clinical assessment (eg, cytomorphology, cytogenetics) to confirm progression before discontinuing subjects from treatment.

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.

An EOT evaluation will be performed for all subjects who are withdrawn from treatment with IP for any reason as soon as possible after the decision to permanently discontinue treatment has been made (Section 6.2.2). Subjects who received at least one dose of IP will enter the Post-Treatment Follow-up Period (Section 6.3).

11.2. Study Discontinuation

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

- Screen failure

- Adverse event
- Withdrawal by subject
- Death
- Lost to follow-up
- Protocol violation
- Study terminated by sponsor
- Other (to be specified on the eCRF)

The reason for study discontinuation should be recorded in 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

This is a single arm study.

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, prefectural, 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.

IP 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 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 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.

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 details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the 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.

15.3. Investigational Medicinal Product Quality Issues

Issues that call into question IP safety, purity, potency, quality and identity (eg, evidence of suspected tampering of product) must be reported as soon as possible to the study Clinical Trial Monitor and/or Clinical Trial Manager or designee. Report an issue or concern with all sponsor supplied IP suspected to have occurred before the product was transferred to the responsibility of the investigational site (eg, during manufacturing, packaging and labeling, storage, and/or distribution).

This includes suspected quality issues of components co-packaged with the drug, labelling, and IP device/drug combination products, and medical devices.

In the event of a suspected product quality issue, the immediate action to be taken by site is to quarantine the affected product. Do not dispose of the product unless retention presents a risk to personnel (eg, cytotoxic, risk of injury from broken glass or sharps).

When reporting, provide as much product information as possible. Suspected IP quality issues will be investigated and a response will be provided back to the investigational site.

16. PUBLICATIONS

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

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

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

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

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18. APPENDICES

APPENDIX A. TABLE OF ABBREVIATIONS

Table 6: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
aCML	Atypical chronic myeloid leukemia
ActRIIB	Activin receptor type IIB
ADA	Antidrug antibodies
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the concentration-time curve
β-hCG	β-subunit of human chorionic gonadotropin
BM	Bone marrow
BMP6	Bone morphogenetic protein 6
BMP9	Bone morphogenetic protein 9
BSC	Best supportive care
BUN	Blood urea nitrogen
CBC	Complete blood count
CI	Confidence interval
CL/F	Apparent clearance of drug from plasma after extravascular administration
C_{max}	Maximum plasma concentration of drug
CMML	Chronic myelomonocytic leukemia
COVID-19	Coronavirus disease 2019
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DAR	Darbopoetin
DBP	Diastolic blood pressure
DNA	Deoxyribonucleic acid
DVT	Deep venous thrombosis

Abbreviation or Specialist Term	Explanation
EC	Ethics Committee
ECD	Extracellular domain
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EE	Efficacy evaluable
EEA	European Economic Area
eGFR	Estimated glomerular filtration rate
ELN	European Leukemia Net
[redacted]	[redacted]
EOT	End of treatment
EPO	Erythropoietin
ESA	Erythropoiesis stimulating agent
ESMO	European Society for Medical Oncology
EU	European Union
FAB	French-American-British (FAB) classification
[redacted]	[redacted]
FCBP	Females of childbearing potential
GCP	Good clinical practice
G-CSF	Granulocyte-colony stimulating factor
GDF11	Growth differentiation factor 11
GM-CSF	Granulocyte-macrophage colony-stimulating factor
Hgb	Hemoglobin
HI-E	Hematologic improvement – erythroid response
HIV	Human immunodeficiency virus
HMA	Hypomethylating agent
HR	Heart rate
HRQoL	Health-related quality-of-life
IB	Investigator's Brochure
ICF	Informed consent form

Abbreviation or Specialist Term	Explanation
ICH	International Council for Harmonisation
IgG1-Fc	Immunoglobulin G1 - Fragment crystallizable
IMiD	Immune-modulatory drug
IP	Investigational product
IPSS	International prognostic scoring system
IPSS-R	International prognostic scoring system-Revised
IRB	Institutional review board
IRT	Integrated response technology
ITT	Intent-to-treat
IUD	Intrauterine device
IWG	International Working Group
JMML	Juvenile myelomonocytic leukemia
JSH	Japanese Society of Hematology
LDH	Lactate dehydrogenase
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
MDRD	Modification of diet in renal disease
MDS	Myelodysplastic syndromes
MDS/MPN	Myelodysplastic/myeloproliferative neoplasms
mHI-E	modified HI-E
MOA	Mechanism of action
MUGA	Multi-gated acquisition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
nRBC	Nucleated red blood cells
NYHA	New York Heart Association
OS	Overall survival
PBO	Placebo
PD	Pharmacodynamic

Abbreviation or Specialist Term	Explanation
PK	Pharmacokinetics
PQC	Product Quality Complaint
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 ringed sideroblasts
RBC	Red blood cell
RBC-TD	Red blood cell transfusion dependence
RBC-TI	Red blood cell transfusion independence
RDW	Red blood cell distribution width
RNA	Ribonucleic acid
RS	Ring sideroblast
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SBP	Systolic blood pressure
sEPO	Serum erythropoietin
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse events
TD	Transfusion dependent/dependence
TGF-β	Transforming growth factor-beta
TI	Transfusion independent/ independence
T_{max}	Time to maximum plasma concentration of drug
TNM	Tumor nodes metastasis
$t_{1/2}$	Terminal elimination half-life
ULN	Upper limit of normal

Abbreviation or Specialist Term	Explanation
US	United States
V/F	Apparent volume of distribution during the terminal phase after extravascular administration
W1D1	Week 1 Day 1
WBC	White blood cell
WHO	World Health Organization
WPSS	WHO prognostic scoring system

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, Borowitz 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. 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

APPENDIX C. INTERNATIONAL PROGNOSTIC SCORING SYSTEM SCORE – REVISED (CONT.)

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 D. INTERNATIONAL WORKING GROUP RESPONSE CRITERIA FOR HEMATOLOGIC IMPROVEMENT

Hematologic improvement* (Cheson, 2006)	**Response criteria (responses must last at least 8 wk)**
Erythroid response (pretreatment, < 11 g/dL)	Hgb increase by ≥ 1.5 g/dL Relevant reduction of 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. Only RBC transfusions given for a Hgb of ≤ 9.0 g/dL pretreatment will count in the RBC transfusion response evaluation
Platelet response (pretreatment, < 100×10^9/L)	Absolute increase of ≥ 30×10^9/L for patients starting with > 20×10^9/L platelets Increase from < 20×10^9/L to > 20×10^9/L and by at least 100%
Neutrophil response (pretreatment, < 1.0×10^9/L)	At least 100% increase and an absolute increase > 0.5×10^9/L
Progression or relapse after HI‡	At least 1 of the following: At least 50% decrement from maximum response levels in granulocytes or platelets Reduction in Hgb by ≥ 1.5 g/dL Transfusion dependence

Hgb indicates hemoglobin; RBC: red blood cell; HI: hematologic improvement.
*Pretreatment counts averages of at least 2 measurements (not influenced by transfusions) ≥ 1 week apart (modification).
‡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.
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

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) [c]	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) [c]	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,c]	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[c]	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[c]	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[c]	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[c]	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-003 subject 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 F. 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.

APPENDIX G. FOUR-VARIABLE MDRD GFR EQUATION

For Serum Creatinine in mg/dL:

GFR (mL/min/1.73 m²) = 175 × (Scr)-1.154 × (Age)-0.203 × (0.742 if female) × (1.212 if African American) (conventional units)

Creatinine levels in μmol/L can be converted to mg/dL by dividing them by 88.4

Source:

Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.

Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F; Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006 Aug 15;145(4):247-54.

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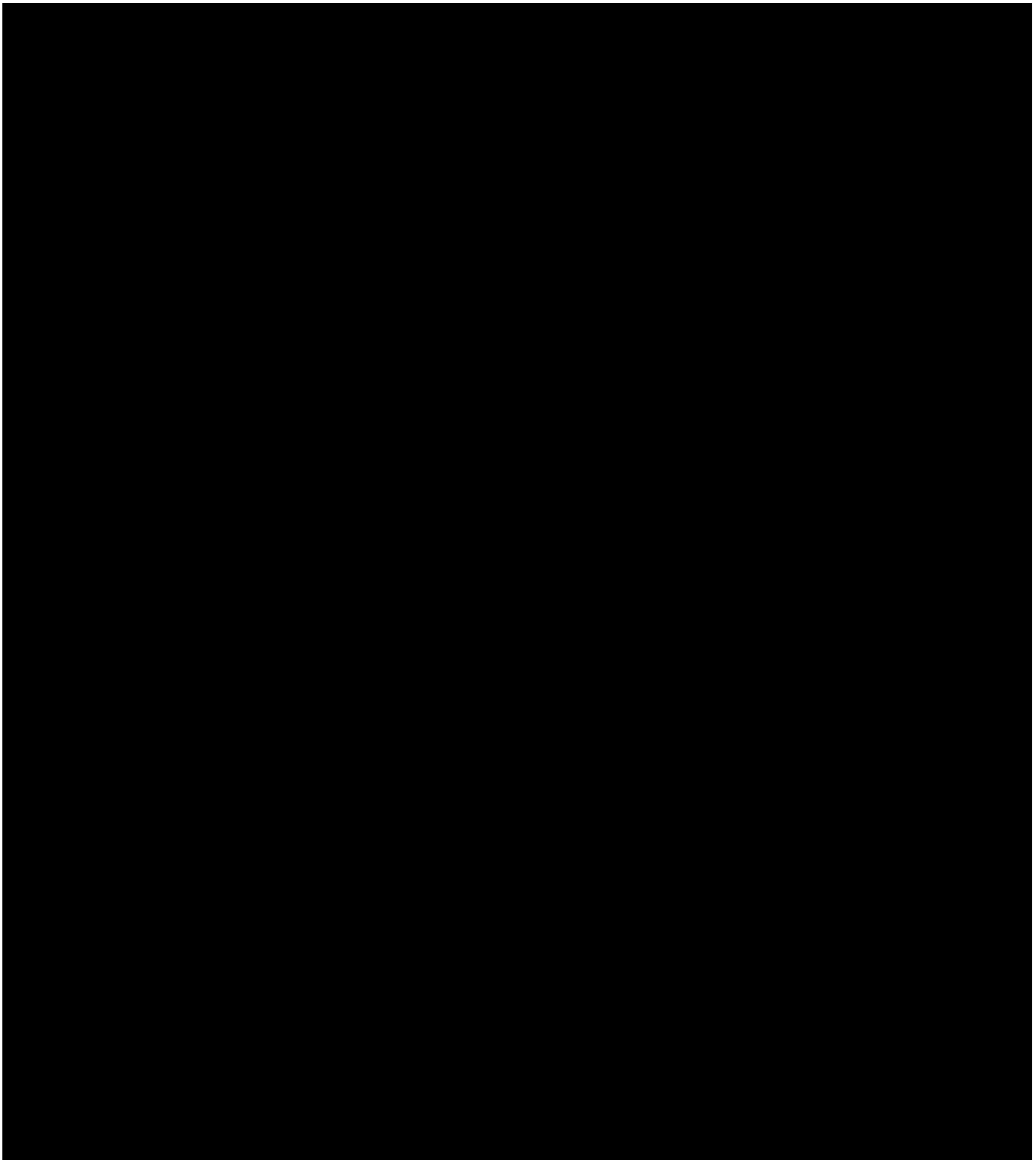

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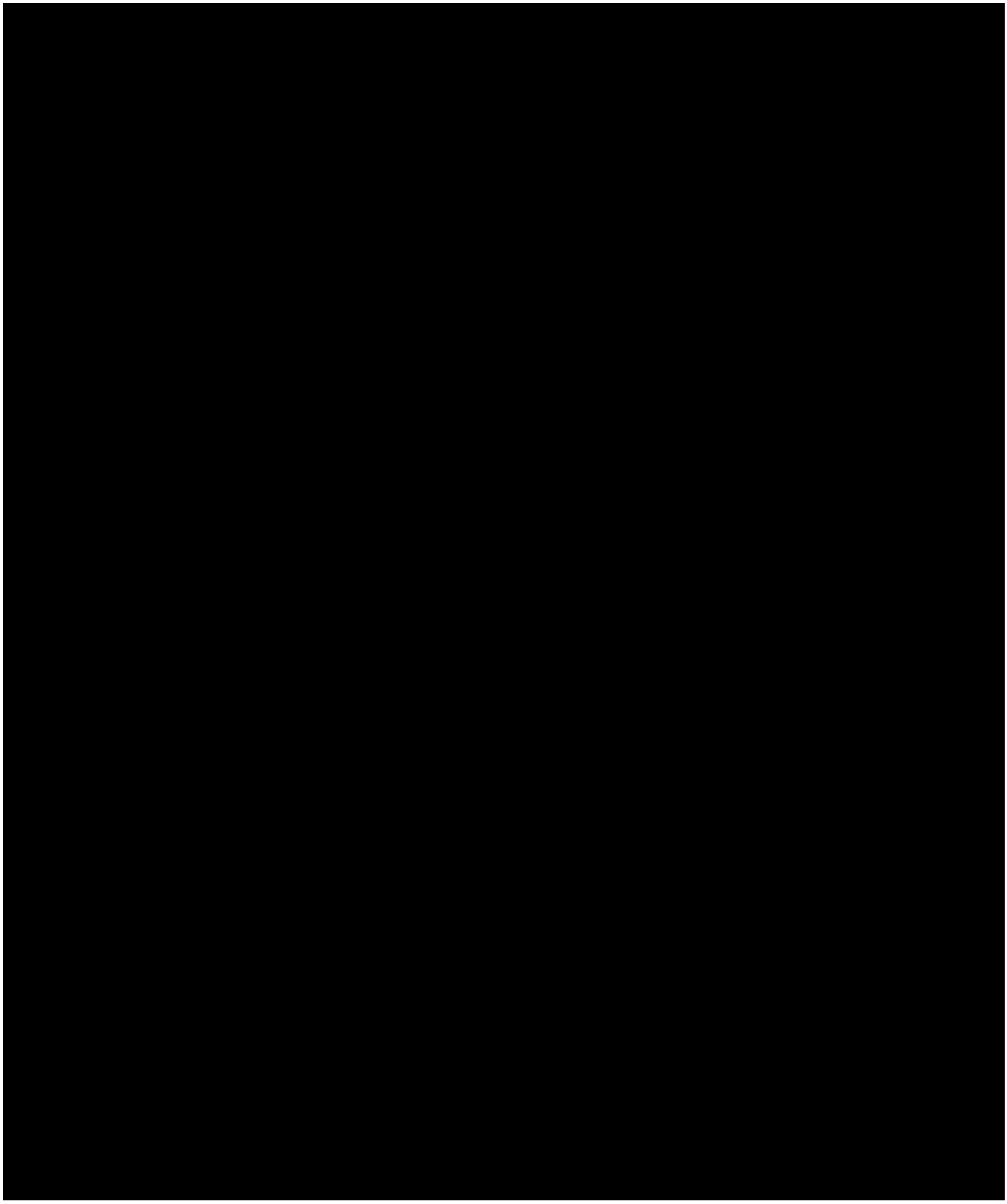

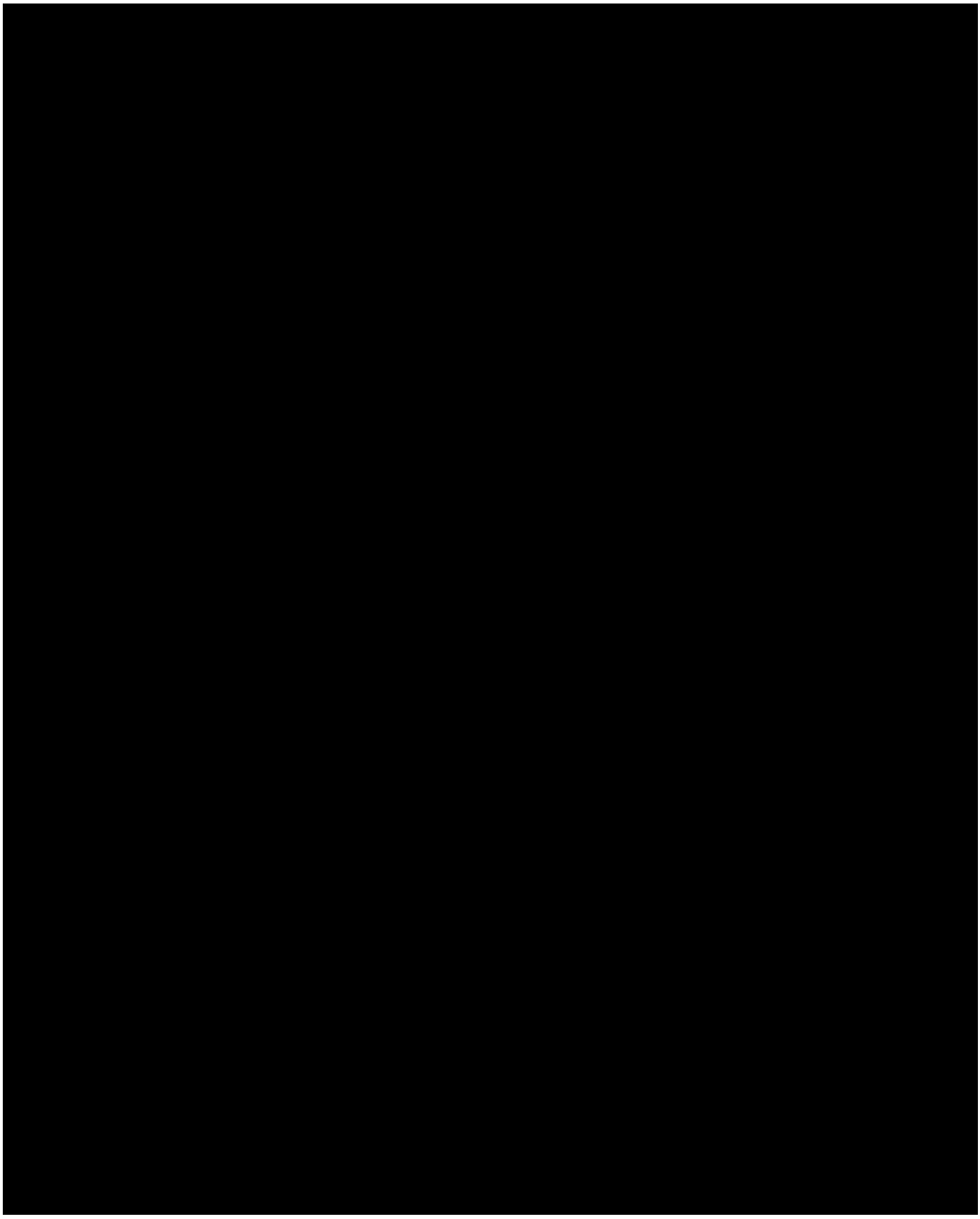

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1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- Clarification of the definition for the primary efficacy endpoint of hematologic improvement – erythroid response (HI-E) per International Working Group (IWG) 2006 criteria and related secondary endpoints

[redacted] herefore, in the ACE-536-MDS-003 study, for subjects who have a dose delay meeting the dose interruption criterion of predose hemoglobin (Hgb) ≥ 12.0 g/dL, if their Hgb levels temporarily decrease to < 1.5 g/dL but achieve ≥ 1.5 g/dL again after treatment resumption, this period (ie, the time from dose delay to achieving a Hgb increase of ≥ 1.5 g/dL again) will be included as the period of sustained Hgb increase of ≥ 1.5 g/dL for HI-E 2006 evaluation. The secondary endpoints of HI-E per IWG 2006 criteria within 48 weeks, time to HI-E and duration of HI-E will use this definition.

Revised sections: Protocol Summary; Section 1.1.1.1 (Erythropoiesis Stimulating Agents); Section 1.3.2.2 (Rationale for Study Endpoints); Section 9.6.1 (Primary Efficacy Analysis); Section 9.6.2 (Secondary Efficacy Analyses)

- Addition of the secondary endpoints of modified HI-E (mHI-E) per IWG 2006 criteria

The ARCADE Phase 3 study for darbepoetin (DAR) defined HI-E per IWG 2006 criteria as ≥ 1.5 g/dL increase from baseline in Hgb with a mean rise of ≥ 1.5 g/dL for 8 weeks without transfusions. To ensure better comparison of efficacy data between luspatercept and DAR, mHI-E per IWG 2006 criteria defined as "≥ 1.5 g/dL mean increase in Hgb compared to baseline over any consecutive 56-day period in the absence of red blood cell (RBC) transfusions" was added in the secondary endpoints. The secondary endpoints of the time to mHI-E and duration of mHI-E were also added. With this modification, the endpoint of "Mean Hgb increase ≥ 1.5 g/dL (defined as proportion of subjects with ≥ 1.5 g/dL mean increase in Hgb compared to baseline that is sustained over a 24-week period from Week 1 Day 1 (W1D1) through Week 24 (and W1D1 through Week 48) of the Treatment Period in the absence of RBC transfusions)" was removed.

Revised sections: Protocol Summary; Section 1.1.1.1 (Erythropoiesis Stimulating Agents); Section 1.3.2.2 (Rationale for Study Endpoints); Section 2 (Table 1 Study Objectives and Table 2 Study Endpoints); Section 9.6.2 (Secondary Efficacy Analyses)

- Addition of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) testing

SARS-CoV-2 testing was added for subjects at baseline, Day (D)169, D337 and End of Treatment (EOT) to determine exposure to this virus and to evaluate the safety of luspatercept in SARS-CoV-2 antibody positive subjects. Language to address use of coronavirus disease 2019 (COVID-19) vaccines was also added to the protocol.

Revised sections: Section 1.3.4 (Rationale for Exploratory Biomarkers); Section 2 (Table 1 Study Objectives and Table 2 Study Endpoints); Section 4.3 (Exclusion Criteria); Section 5 (Table of Events); Section 6.7 (Biomarkers, Pharmacodynamics, Pharmacogenomics); Section 8.1.3 (Attenuated Vaccines); Section 8.2 (Prohibited Concomitant Medications and Procedures); Section 9.9.3 (Exploratory Analysis); Section 10.8 (COVID-19 Reporting).

- Modification of the Long-term Follow-up Period

Update to amend the reference point for the Long-term Follow-up Period from "3 years from the last dose" to "5 years from the date of the first dose of investigational product (IP), or 3 years from the last dose (whichever occurs later)". This modification is to ensure the same reference point for the Long-term Follow-up Period is used across the luspatercept program. In the Long-term Follow-up Period, visits or telephone contacts will be conducted every 12 weeks for the first 3 years from the date of last dose of IP and every 6 months thereafter, if applicable. The expected duration of the study and duration of participation for subjects are updated to approximately 8 years and 6 years, respectively.

Revised sections: Protocol Summary; Section 2 (Table 2 Study Endpoints); Section 3.1 (Study Design, and Figure 2 Overall Study Design); Section 3.2 (Study Duration for Subjects); Section 5 (Table 3 Table of Events); Section 6.1.20 (Monitoring for Progression to AML and Other Malignancies/Pre-malignancies); Section 6.3.2 (Long-term Follow-up)

- Clarification on the assessment of the status of human immunodeficiency virus (HIV), hepatitis B, and/or hepatitis C active infection

Update to the protocol to implement a time frame for local laboratory assessments (within 4 weeks prior to the date of informed consent form [ICF] signature) to be acceptable to determine the status of HIV, hepatitis B, and/or hepatitis C active infection at Screening to align with other luspatercept studies (eg, ACE-536-MDS-002 study [COMMANDS trial]).

Revised sections: Section 4.3 (Exclusion Criteria); Section 5 (Table 3 Table of Events); Section 6.1.4.1 (Assessment of HIV/Hepatitis B/Hepatitis C Status)

[redacted]

Revised sections: Protocol Summary; Section 7.2.1 (Luspatercept Administration and Schedule); Section 7.2.2 (Luspatercept Dose Adjustment and Dose Modification).

- Inclusion of subjects with myelodysplastic/myeloproliferative neoplasms (MDS/MPN) with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) in the study

Exclusion criterion 2 was modified to remove subjects with MDS/MPN-RS-T in alignment with other luspatercept studies (ie, COMMANDS). Subjects with MDS/MPN-RS-T are eligible for the study with this modification. A subgroup analysis showed benefit in this population and this led to incorporation of this population in the United States label for luspatercept in lower risk MDS.

Revised sections: Section 4.3 (Exclusion Criteria)

The amendment also includes several other minor clarifications and corrections:

- [redacted]
- [redacted]
- Update/correction to Section 1.2.3.1 (Potential Risks of Human Use) to clarify that male and female subjects of childbearing potential must be willing to abstain from sexual intercourse or use adequate contraception during the treatment period of the study and for at least 12 weeks after discontinuation of study therapy.
- Updates to the protocol to include minor clarifications/corrections regarding pharmacodynamic and predictive biomarkers in alignment with other luspatercept studies (eg, COMMANDS).

  Revised sections: Section 1.3.4 (Rationale for Exploratory Biomarkers); Section 2 (Table 2 Study Endpoints); Section 5 (Table 3 Table of Events); Section 6.1.1 (Bone Marrow and Peripheral Blood Samples); Section 6.7 (Biomarkers, Pharmacodynamics, Pharmacogenomics).
- Update to Section 4.3 (Exclusion Criteria) and Section 8.2 (Prohibited Concomitant Medications and Procedures) not to use anagrelide within 8 weeks prior to W1D1 and during the course of the study.
- Update/correction to Section 5 (Table of Events) to replace “Day -35 to Randomization” with “Day -35 to -1”.
- [redacted]
- Update to Section 5 (Table of Events) and Section 8 (Concomitant Medications And Procedures) to clarify that concomitant medications must be reported on the

electronic case report form (eCRF) until 42 days after the last dose of IP or the EOT Visit, whichever occurs later.

- Update to the protocol to reflect mandatory confirmation with the subject (and documentation in the subject's source record) whether or not transfusions were received at outside local institutions prior to each IP administration at the site as well as the use of the study patient transfusion diary in alignment with other luspatercept studies (eg, COMMANDS).

  Revised sections: Section 5 (Table of Events); Section 6.4.1 (Transfusion Assessment); Section 7.2.1 (Luspatercept Administration and Schedule)

- Update/correction to Section 6.1.9 (Hematology) to add "reticulocytes" to the list of hematology assessments to ensure consistency with the study's Central Laboratory Manual.

- Update to the protocol to clarify a window for Pharmacokinetics (PK) and antidrug antibodies (ADA) sampling after the 24-Week MDS Disease Assessment Visit. This window allows the sites the ability to schedule this assessment during a dosing or other visit. Language was also added in these sections to clarify PK and ADA sampling timing.

  Revised sections: Section 5 (Table 3 Table of Events); Section 6.5 (Pharmacokinetics); Section 6.6 (Antidrug Antibody [ADA]).

- Update to Section 6.1.1 (Bone Marrow and Peripheral Blood Samples) to include guidance on laboratory values to be used to determine the baseline International Prognostic Scoring System - Revised (IPSS-R) category in case historical local bone marrow (BM) samples/reports are being used for "over read".

- Update to Section 6.3.1 (Safety Follow-up [42-Day Follow-up]) to add language clarifying the replacement of the 42-Day Follow-up Visit with the EOT Visit in cases of dose delays exceeding 6 weeks (+2 days).

- Update/correction to Section 6.6 (Antidrug Antibody [ADA]) to include the 24-Week MDS Disease Assessment Visit as time point for ADA sampling (consistent with Section 5 [Table 3 Table of Events]).

- Update to Section 7.1 (Description of Investigational Products) to include change of both the held for and total in-use time of reconstituted luspatercept from 10 hours at 2°C to 8°C to 24 hours at 2°C to 8°C. A reference to the pharmacy manual is included for more details.

- Update to Section 7.2.1 (Luspatercept Administration and Schedule) to change the allowance for no dose adjustment in cases of changes in body weight from $< \pm 5\%$ to $\leq \pm 5\%$ in alignment with other luspatercept studies (eg, COMMANDS).

- Update to Section 7.2 (Luspatercept Dose Adjustment and Dose Modification) to clarify that the subject Hgb levels should be assessed for dose modifications independently from any transfusions.

- Update to Section 7.2.2 (Table 5 Luspatercept Dose Modification: Dose Delay, Dose Reduction, and Discontinuation Guidelines) to clarify that treatment should be discontinued, if dose delay is > 15 weeks from last dose administered in case of dose delay caused by any suspected related adverse events ≥ Grade 3 and that footnote "d" is applicable if predose Hgb is ≥ 12.0 g/dL.
- Update to Section 7.2.2 (Table 5 Luspatercept Dose Modification: Dose Delay, Dose Reduction, and Discontinuation Guidelines) to allow to proceed with dosing of IP in circumstances where results from the blast count assessment in peripheral blood are not readily available at the time of planned dosing, provided results are evaluated as soon as they become available (but within 3 days post dosing) and actions described in Table 5 are followed immediately in case a presence of ≥ 1% blasts in peripheral blood is observed.
- Update to Section 8.1.4 (Phlebotomy) to clarify that the treatment of excessively high Hgb levels using phlebotomy should only be performed in emergency/urgency situations in alignment with other luspatercept studies (eg, COMMANDS).
- Updated to Section 9.7 (Safety Analysis) to state that frequency of ADA will also be reported.
- [redacted]
- Update to Section 10.2.6 (Outcome) to clarify that progression of MDS or any other malignancy does not need to be followed until recovery, as recovery is not expected for these events in alignment with other luspatercept studies (eg, COMMANDS).
- Update to Section 17 (References) to include new literature references.
- Update to Section 18 (Appendix A Table of Abbreviations) to include new abbreviations in Table 6 Abbreviations and Specialist Terms.
- Update to Section 18 (Appendix E International Working Group Response Criteria for Myelodysplastic Syndromes) to clarify the only categories that are applicable to this study are Stable Disease and Disease Progression in alignment with other luspatercept studies (eg, COMMANDS).
- Update of language throughout the protocol to align with the current protocol template.

  Revised sections: Section 4.2 (Inclusion Criteria); Section 6.8 (Additional and Optional Research); Section 6.8.1 (Additional Research); Section 6.8.2 (Optional Research); Section 10.1 (Monitoring, Recording and Reporting of Adverse Events); Section 10.2.1 (Seriousness) to Section 10.2.6 (Outcome); Section 10.3 (Abnormal Laboratory Values); Section 10.4.1 (Females of Childbearing Potential); Section 10.5 (Other Malignancies/Pre-malignancies) to Section 10.7 (Expedited Reporting of Adverse Events); Section 15.1 (Study Monitoring and Source Data Verification) to Section 15.3 (Investigational Medicinal Product Quality Issues).

- Minor editorial and formatting changes (spelling, grammatical error corrections, etc.) were also made throughout the document.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

[redacted]

- **Modification of Inclusion Criterion 8 on Females of Childbearing Potential**

Update to the protocol to amend the Inclusion Criterion 8 on females of childbearing potential in line with the Supplement to Protocol ACE-536-MDS-002 (ACE-536-MDS-002 Protocol Supplement JP, Version 1: 21 August 2018). The definition of natural menopause is revised to also exclude amenorrhea due to other medical reasons in addition to amenorrhea after cancer therapy. Also, the condition of breastfeeding women for the study enrollment is additionally included in the Inclusion Criterion 8, that is breastfeeding women must agree to stop breastfeeding prior to the participation in the study and not to resume breastfeeding after treatment discontinuation.

Regarding the Footnote 1 on highly effective contraception, update to the protocol to delete unapproved hormonal contraception in Japan, which are injection, implant, transdermal patch, and vaginal ring.

Revised section: Section 4.2 Inclusion Criteria

- **Modification of Exclusion Criterion 7 on Hypertension**

Update to the protocol to amend the Exclusion Criterion 7 on hypertension in line with the Supplement to Protocol ACE-536-MDS-002 (ACE-536-MDS-002 Protocol Supplement JP, Version 1: 21 August 2018). It is revised to also exclude subjects with a history of hypertensive crisis or hypertensive encephalopathy in addition to subjects with uncontrolled hypertension.

Revised section: Section 4.3 Exclusion Criteria

- **Modification of Section 6.7. Biomarkers, Pharmacodynamics, Pharmacogenomics**

Update to the protocol to include the additional information on biomarkers, pharmacodynamics, pharmacogenomics in line with the Supplement to Protocol ACE-536-MDS-002 (ACE-536-MDS-002 Protocol Supplement JP, Version 1: 21 August 2018). The section is revised to include the information on the rules of the storage period of and the disposal of bio-samples, the actions to be taken upon consent withdrawal, and the disclosure of genetic testing results to the subject, that is “The samples will be destroyed five years after the end of trial or earlier if required by law in each country. If subjects decide to withdraw the consent, all previously retained identifiable samples be destroyed to prevent future testing. Since the results of genetic

tests are not beneficial to the treatment of an individual subject, they will not be disclosed to the subjects."

Revised section: Section 6.7. Biomarkers, Pharmacodynamics, Pharmacogenomics