Official Title of Study:

A Phase 3, Open-label, Randomized Study to Compare the Efficacy and Safety of Luspatercept (ACE-536) versus Epoetin Alfa for the Treatment of Anemia Due to IPSS-R Very Low, Low or Intermediate Risk Myelodysplastic Syndromes (MDS) in ESA Naïve Subjects Who Require Red Blood Cell Transfusions

PROTOCOL(S) ACE-536-MDS-002

NCT Number: NCT03682536

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A PHASE 3, OPEN-LABEL, RANDOMIZED STUDY TO COMPARE THE EFFICACY AND SAFETY OF LUSPATERCEPT (ACE-536) VERSUS EPOETIN ALFA FOR THE TREATMENT OF ANEMIA DUE TO IPSS-R VERY LOW, LOW OR INTERMEDIATE RISK MYELODYSPLASTIC SYNDROMES (MDS) IN ESA NAÏVE SUBJECTS WHO REQUIRE RED BLOOD CELL TRANSFUSIONS

The "COMMANDS" Trial

PROTOCOL NUMBER:	**ACE-536-MDS-002**
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SPONSOR NAME/ ADDRESS:	Celgene Corporation 86 Morris Avenue Summit, NJ 07901

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CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

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

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

[redacted]	31 mar 2022
Signature of Celgene Therapeutic Area Head	**dd mmm yyyy**
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By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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

COORDINATING PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Coordinating Principal Investigator	**dd mmm yyyy**
Printed Name of Coordinating Principal Investigator **Institution Name:**_____ By my signature, I agree the protocol has been written to comply with ICH Good Clinical Practices guidelines and agree to offer guidance throughout the study as needed.	

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 4.0:

The primary purpose of this amendment is to add a second interim analysis to test the superiority of the luspatercept arm as well as to remove the requirement to enroll at least 25% of subjects with an endogenous sEPO level of >200 U/L.

The rationale for the inclusion of the second interim analysis for efficacy is to mitigate the negative impact of the coronavirus disease 2019 (COVID-19) pandemic on enrollment and to mitigate the impact of the political crisis in Eastern Europe on future study enrollment. In the event the primary efficacy endpoint at the time of the efficacy IA shows statistical significance (see Section 9.9) this could potentially allow for earlier access to the drug for patients in need.

The rationale for the removal of the requirement to enroll at least 25% of subjects with an endogenous sEPO level of > 200 U/L stems from the observation of subject recruitment in this study and current review of published clinical trials in subjects with lower risk Myelodysplastic Syndromes (MDS). The percentage of the subjects with sEPO level of >200 U/L is lower than 25% in a number of published trials (Fenaux, 2018; Park, 2008; Santini, 2013; Suzuki, 2015). The number of subjects with an EPO level of >200 U/L recruited so far in this study shows a similar pattern, in line with previous publications. The change in proportion of subjects with sEPO level of >200 U/L should not affect the conclusions made between different sEPO populations and therefore the cap originally included for subjects with sEPO level of >200 U/L is now removed.

The protocol summary has been updated to align with the changes in the protocol body.

This protocol amendment applies to all participants.

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SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 4.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Protocol Summary	Match the PK secondary objective stated in Section 2 of the main protocol.	For consistency and alignment between the protocol summary and Section 2 of the protocol.
Medical Monitor / Emergency Contact Information	Update the Medical Monitor and contact information.	To provide the current Medical Monitor and Emergency Contact information.
Protocol Summary; Section 1.3.2.2: Rationale for Stratification Factors; Section 3.1: Study Design; Section 9.4: Randomization and Stratification	Remove the requirement to enroll at least 25% of subjects with an endogenous sEPO level of >200 U/L.	The observation of subject recruitment in this study and current review of published clinical trials in subjects with lower risk Myelodysplastic Syndromes (MDS) supports the removal of the requirement.
Protocol Summary; Section 9.3: Sample Size and Power Considerations; Section 9.7.1: Primary Efficacy Analysis; Section 9.9: Interim Analysis	Add the second interim analysis to test the superiority of the luspatercept arm.	To mitigate the negative impact of the COVID-19 pandemic on enrollment and to mitigate the impact of the political crisis in Eastern Europe on future study enrollment. In the event the primary efficacy endpoint at the time of the efficacy IA shows statistical significance this could potentially allow for earlier access to the drug for patients in need.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 4.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 1.2.3: Overall Benefit Risk Assessment; Section 1.4: Risk/ Benefit Assessment	Extend the Risk Benefit Section. Section 1.2.3: Overall Benefit Risk Assessment was replaced with the new Section 1.4: Risk/ Benefit Assessment.	To incorporate risk benefit information into the protocol that was originally in a separate document, and to be in compliance with the BMS protocol template.
Section 3.1: Overall Study Design	Figure 2: correct a typographical error. The duration of the Long-Term Follow-Up phase from 5 years from the date of last dose of IP to first dose of IP to align with the rest of the protocol.	Correction
Section 6.1.1: Bone Marrow and Peripheral Blood Samples	Clarify that in the event an adjudication by a third reviewer at the central lab is made in case of disagreement between the local pathologist and the central reviewer, the result of the adjudication will be considered the final result and only slides of the most recent BM sample should be used for adjudication. Clarify that central over-read of local bone marrow samples is also allowed during the treatment period of the study in the event the central analysis is technical failing.	Clarification
Section 6.1.6: Vital Signs, Height, and Weight	Clarify that the weight of subjects on the epoetin alfa arm will be assessed at every third dosing visit only, to align with Section 5 Table 3 (Table of Events) and Section 7.2.2.	Clarification and alignment to other protocol sections.
Section 9.2: Study Population Definitions	Include the PK population definition.	To include all study populations into the section of the protocol.
All	Minor formatting and typographical corrections.	Minor, therefore have not been summarized.

PROTOCOL SUMMARY

Study Title

A Phase 3, Open-label, Randomized Study to Compare the Efficacy and Safety of Luspatercept (ACE-536) versus Epoetin Alfa for the Treatment of Anemia Due to IPSS-R Very Low, Low or Intermediate Risk Myelodysplastic Syndromes (MDS) in ESA Naïve Subjects Who Require Red Blood Cell Transfusions

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 erythropoiesis stimulating agent (ESA) naïve subjects who require red blood cell (RBC) transfusions (ie, 2 to 6 packed red blood cell (pRBC) units in the 8 weeks before randomization).

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 transfusion dependence (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).

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 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 efficacy of luspatercept on RBC transfusion independence (RBC-TI; for 12 weeks [84 days] with an associated concurrent mean hemoglobin increase ≥ 1.5 g/dL)

compared with epoetin alfa for the treatment of anemia due to IPSS-R very low, low, or intermediate risk MDS in ESA naïve subjects who require RBC transfusions

Secondary objectives:

- To assess the safety and efficacy of luspatercept compared to epoetin alfa
- To assess health-related quality-of-life (HRQoL) and anemia outcome measures (ie, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire [EORTC QLQ-C30] and the Functional Assessment of Cancer Therapy - Anemia [FACT-An] questionnaire) for subjects treated with luspatercept compared to epoetin alfa
- To evaluate pharmacokinetics for luspatercept in MDS subjects

Study Design

ACE-536-MDS-002 is a Phase 3, multicenter, randomized, open-label, active controlled study. The primary objective of the study is to evaluate RBC-TI in the two treatment arms, luspatercept compared with epoetin alfa, for the treatment of anemia due to IPSS-R very low, low, or intermediate risk MDS in ESA naïve subjects who require RBC transfusions.

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 randomization (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 randomized study.

Central review of bone marrow aspirate smear, peripheral blood smear and cytogenetics will be used to confirm MDS diagnosis according to the World Health Organization (WHO) 2016 classification (Arber, 2016) 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.

Transfusion history must be available for at least 16 weeks immediately preceding and including the date of randomization.

Randomization:

Eligible subjects will be randomized by a central randomization procedure using integrated response technology (IRT) at a 1:1 ratio to either the luspatercept or the epoetin alfa arm. Randomization will be stratified based on RBC transfusion burden at baseline, ring sideroblast status (RS) at baseline and endogenous serum erythropoietin (sEPO) level at baseline.

Treatment Period:

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

In both treatment arms, best supportive care (BSC) may be used in combination with study treatment when clinically indicated per investigator. Best supportive care includes, but is not

limited to, treatment with transfusions, antibiotic, antiviral and/or antifungal therapy, and nutritional support as needed. Best supportive care forthis study excludes the use of ESAs outside of the study treatment.

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, withdrawsconsent, 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 as a transfusion reduction of ≥ 2 pRBC units/8 weeks compared to the baseline (for any consecutive 8-week period within the 12 weeks immediately preceding Day 169 and every 24 weeks thereafter [ie, Day 337, Day 505, etc.]).
- Absence of disease progression per International Working Group (IWG) criteria for altering natural history of MDS (Cheson, 2006) 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) Visit evaluations and enter the Post-treatment Follow-up Period or continue open-label treatment with their assigned IP 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 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 assigned to the luspatercept arm, 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 (GCPs).

Study Population

Adult subjects (≥ 18 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 ESA naïve with endogenous sEPO levels of < 500 U/L and who require RBC transfusions (ie, 2 to 6 units/8 weeks of pRBCs confirmed for a minimum of 8 weeks immediately preceding randomization).

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 or epoetin alfa treatment after the last subject is randomized, 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 randomized by a central randomization procedure using integrated response technology (IRT) at a 1:1 ratio to one of the below treatment arms:

- Experimental Arm: 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 .
- Control Arm: epoetin alfa (EPREX®/ERYPO® or PROCRIT®): starting dose of 450 IU/kg (maximum total starting dose is 40,000 IU) subcutaneous injection once every week (7 days; QW). Dose levels can be increased in a stepwise manner beyond the starting dose to 787.5 IU/kg, and up to a maximum of 1,050 IU/kg (with a maximum total dose of 80,000 IU). Individual epoetin alfa doses according to body weight will be rounded: up to the next 2,000 IU dose level for Starting Dose Level and Dose Level -1; and up to the next 4,000 IU for Dose Level +1 and Dose Level +2 for doses exceeding a calculated dosing of 56,000 IU according to body weight.

Crossover between the treatment arms is not permitted during the Study Treatment Period. For a detailed description of study treatments please refer to Section 7.

Overview of Key Efficacy Assessments

Efficacy assessments include the collection of transfusion data (eg, RBC transfusions), assessment of hematological parameters (eg, hemoglobin, platelet count, neutrophils) and central

cytomorphology and cytogenetics review of bone marrow aspirate and peripheral blood for MDS disease assessment.

Response assessment according to the IWG criteria (Cheson, 2006) is to be performed at the 24-Week MDS Disease Assessment Visit (ie, Day 169) and every 24 weeks thereafter (ie, Day 337, Day 505, etc.).

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) (if clinically indicated). In addition, subjects will be monitored for progression to AML and other malignancies/pre-malignancies.

Statistical Methods

A total sample size of approximately 350 subjects (175 subjects in the experimental arm [luspatercept (ACE-536)], 175 subjects in the control arm [epoetin alfa]) will have 90% power to detect the difference between a red blood cell transfusion independence (RBC-TI) for any 12-week period associated with a concurrent mean hemoglobin increase of 1.5 g/dL response rate of 36% in the experimental arm (luspatercept [ACE-536]) and a response rate of 20 % in the control arm (epoetin alfa), with one interim analysis on futility only when about 105 subjects have completed 24 weeks of treatment, or discontinued before reaching 24 weeks of treatment (30% information for the primary endpoint). The sample size calculation is based on one-sided alpha of 0.025, test statistics on odds ratio of proportions.

The primary efficacy analysis will be the comparison of the response rates in the two treatment arms in the intent-to-treat (ITT) population. The primary efficacy endpoint is defined as the absence of any RBC transfusion of ≥ 12 weeks with a mean hemoglobin increase ≥ 1.5 g/dL during the same time period over the first 24 weeks from baseline (Week 1 through Week 24) during the Treatment Period.

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

The first interim analysis to assess futility will be performed when approximately 105 subjects have completed 24 weeks of treatment or discontinued before reaching 24 weeks of treatment (30% information for primary endpoint).

A second interim analysis for superiority will be performed when approximately 300 subjects have completed 24 weeks of treatment or discontinued before reaching 24 weeks of treatment (85% information for primary endpoint).

The addition of the second interim analysis does not alter the original sample size calculation. The study power remains at 90% for the final analysis with 350 subjects. The Lan-DeMets spending

function of the O'Brien-Fleming type will be used to control the overall one-sided Type I error rate at 0.025. The following significance level will be used:

- Superiority interim analysis (85% information for primary endpoint): one-sided alpha of 0.015
- Final analysis (100% information for primary endpoint): one-sided alpha of 0.021

Analyses will be performed to compare treatment within the stratification subgroups.

The final analysis will be performed when all randomized 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 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 (MDS)

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 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 QoL (Balducci, 2010; Chan, 2014; Hellstrom-Lindberg, 2013; Kao, 2008; Malcovati, 2005; Platzbecker, 2012).

Patients with MDS can be categorized into 1 of 5 risk groups according to the International Prognostic Scoring System - Revised (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 (Greenberg, 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 quality-of-life (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.

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 (ESAs) 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], 2017; European Society for Medical Oncology [ESMO], 2014 [Fenaux, 2014]; European LeukemiaNet [ELN], 2014 [Malcovati, 2013]).

1.1.1.1 Erythropoiesis Stimulating Agents (ESAs)

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 and United States (US) 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]).

The European 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]). 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 sEPO, normal blast counts and lower IPSS/World Health Organization (WHO) Prognostic Scoring System (WPSS) scores (Hellstrom-Lindberg, 2003; Santini, 2011).

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

In the EPOANE3021 Phase 3 study, a total of 130 subjects with IPSS low or intermediate-1 risk MDS and Hgb ≤ 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 450 IU/kg/week or matching placebo for 24 weeks, followed by treatment extension in responders. 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 International Working Group (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 (two subjects with prior transfusion reached 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) (Fenaux, 2017; Fenaux, 2018a). 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). 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 intermediate-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 hematologic improvement – erythroid response (HI-E) 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 patients with HI-E (n=11) in the double-blind period had a baseline sEPO ≤ 100 U/L. 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 5-24 became the primary endpoint and HI-E a secondary endpoint (Platzbecker, 2017c).

EPREX®/ERYPO® (epoetin alfa, Janssen) has recently been authorized via mutual recognition procedure (MRP) by a number of European Union (EU) member states for the treatment of symptomatic anemia (hemoglobin concentration of ≤ 10 g/dL) in adults with low- or intermediate-1-risk primary myelodysplastic syndromes (MDS) who have low serum erythropoietin (< 200 U/L).

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 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 the US for the treatment of patients with transfusion-dependent anemia due to low- or intermediate (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 RBC transfusion independence (8 weeks) for 67% of the patient population for a median duration of transfusion independence of 44 weeks.

1.1.1.4 Hypomethylating Agents

There are two hypomethylating agents (HMAs) currently approved for the treatment of various subtypes of MDS, azacitidine and decitabine.

Azacitidine for injection (Vidaza®) 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 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, and AML with > 30% marrow blasts according to WHO classification. In addition to the US and EU, azacitidine is currently approved in 30 other countries, including Canada, Switzerland, Australia and Japan, for the treatment of MDS (approvals for specific subtypes vary by country).

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

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

1.1.1.5 Iron Chelation Therapy

Iron accumulation in MDS patients is an ongoing process as ineffective erythropoiesis provides a signal that stimulates intestinal iron absorption. There is now evidence that ineffective erythropoiesis is associated with increased secretion of growth differentiation factor 15 (GDF15) and/or a molecule named twisted gastrulation 1 (TWSG1) (Tanno, 2007; Tanno, 2009) by maturing erythroblasts, leading to suppressed hepcidin production in the liver (Winder, 2008). Since hepcidin downregulates iron absorption in the duodenum, lack of hepcidin causes unrestrained intestinal iron uptake. Although this mechanism contributes to iron overload in MDS,

it is not the main cause, and rarely leads to serum ferritin levels above 1000 ng/ml at diagnosis. The main cause of iron overload in MDS is chronic transfusion therapy (Gattermann, 2011).

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

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

Furthermore Sanz, et al reported that transfusion dependence (HR = 8.8; $p < 0.0001$) and iron overload (HR = 52.4; $p < 0.0001$) are independent risk factors for overall survival and leukemic progression (Sanz, 2008) demonstrating that the longer patients can remain transfusion independent, the better their overall survival. Hence, therapeutic options that would achieve transfusion independence (TI) or reduce transfusion intensity in patients with lower-risk MDS for a significant amount of time would be highly desirable in terms of reduced requirements for iron chelation therapy.

1.2 Luspatercept Background

1.2.1 Mechanism of Action

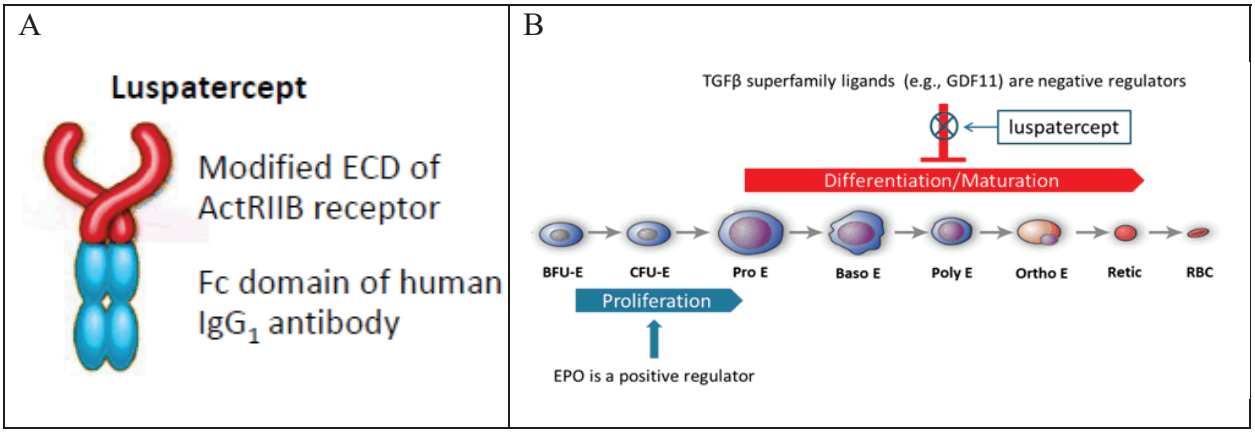
Luspatercept (ACE-536), an erythroid maturation agent, is a recombinant fusion protein consisting of a modified form of the extracellular domain (ECD) of the human activin receptor type IIB (ActRIIB) linked to the IgG1 Fc domain (Figure 1A). The ActRIIB receptor and its ligands are members of the transforming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

Members of the TGF-β 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 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 (AE) profile of luspatercept.

1.2.2 Summary of Clinical Experience

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

Across the Phase 2 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 a Phase 2 study for subjects with lower-risk MDS and anemia. Data is available for 88 subjects treated with doses of ≥ 0.75 mg/kg. Subjects had HI-E response rates of 55% 11/20 (sEPO 200-500 U/L) and 63% (27/43) (sEPO < 200 U/L) and rates of red blood cell transfusion independence (RBC-TI, 8 weeks) of 46% (6/13) (sEPO 200-500 U/L) and 56% (14/25) (sEPO < 200 U/L). The subgroup of subjects with no ring sideroblasts (RS-) and with sEPO ≤ 500 U/L had HI-E response rates of 50% (8/16) and rates of RBC-TI (8 weeks) of

44% (4/9) (Platzbecker, 2017a). For subjects achieving RBC-TI (8 weeks) criteria, the median duration of treatment is 14.7 months (range 2.8-32.4 months, as of 13 April 2017); however, this figure is expected to increase as the current Phase 2 study is in progress.

Additionally, luspatercept is currently being assessed in two 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, a 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 is ongoing.

Luspatercept was assessed in the Medalist trial (Fenaux, 2018b): A Phase 3, randomized, double-blind study in subjects with very low- to intermediate-risk MDS (IPSS-R) with ring sideroblasts 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 (mHI-E), 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.

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

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 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 ≤ 500 U/L according to treatment guidelines (NCCN, 2017; ESMO, 2014 [Fenaux, 2014]; ELN, 2014 [Malcovati, 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). Epoetin alfa has been recently been approved via the MRP in Europe in patients with low- or intermediate-1-risk primary MDS (according to IPSS) who have low serum erythropoietin (< 200 U/L).

Therefore, a new therapeutic option that would increase the frequency of response as well as the duration of RBC-TI for a sustained period of time in patients with lower-risk MDS for a sustained period of time 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 who are ESA naïve and require RBC transfusions. Preliminary Phase 2 results for luspatercept demonstrate promising results for erythroid response (HI-E), transfusion independence and duration of response for subject with endogenous sEPO level up to 500 U/L and for subject with and without ring sideroblasts.

A direct comparison of epoetin alfa and luspatercept in a Phase 3 study in lower-risk MDS is therefore justified in subjects with endogenous sEPO ≤ 500 U/L.

1.3.2 Rationale for the Study Design

ACE-536-MDS-002 is a Phase 3, multicenter, randomized, open-label, active controlled study. The primary objective of the study is to evaluate RBC-TI in the two treatment arms, luspatercept compared with epoetin alfa, for the treatment of anemia due to IPSS-R very low, low, or intermediate risk MDS in subjects who require RBC transfusions.

The design of this study (ie, randomized, prospectively stratified [see stratification factors in Section 1.3.2.2 below], with an active-control arm, and parallel-group design) will control potential bias in assignment of the IP or in data interpretation. The multicenter nature of the study will provide assurance that the results are likely to have general applicability. In addition, to avoid bias and to ensure comparability of the frequency and units of RBC transfusions administered in both treatment arms, for each subject a "pre-transfusion hemoglobin threshold" for requiring transfusion during the study will be determined based on transfusion history in the 8 weeks prior to the first dose of IP. This "pre-transfusion hemoglobin threshold" should be maintained throughout the Treatment Period when administering RBC transfusions (for details see Section 8.1.1).

1.3.2.1 Rationale for the Study Population

This study targets subjects who have received RBC transfusions (ie, 2 to 6 packed red blood cell [pRBC] units in the 8 weeks before randomization). This subject population represents a subset of subjects with IPSS-R lower-risk MDS who have anemia, requiring RBC transfusions and have limited treatment options in managing their anemia.

The IPSS-R classification has been chosen to define this Phase 3 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 the 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 reduce or eliminate transfusion dependence, which is evaluated in this study.

1.3.2.2 Rationale for Stratification Factors

A stratified randomization scheme will be used based on RBC transfusion burden at baseline, ring sideroblast (RS) status at baseline and endogenous sEPO at baseline to control heterogeneity and to balance key factors impacting study endpoints over the two treatment arms.

RBC transfusion burden at baseline: < 4 pRBC units/ 8 weeks versus ≥ 4 pRBC units/ 8 weeks

Lower-risk MDS patients often become dependent on frequent RBC transfusions, which leads to increased morbidity and mortality and decreased HRQoL (Hellstrom-Lindberg, 2003; Malcovati, 2005). In this proposed study, subjects who receive 2 to 3 pRBC units during the 8-week period prior to randomization will be balanced with subjects who receive 4 to 6 pRBC units during the 8-week period prior to randomization. This RBC transfusion burden stratification is considered important due to the likelihood of transfusion independence being correlated with the degree of transfusion burden.

Ring sideroblast (RS) status at baseline: RS+ versus RS- (with RS+ defined as Ring sideroblast ≥ 15% of erythroid precursors in bone marrow or ≥ 5% (but < 15%) if SF3B1 mutation is present)

The ongoing Phase 3 study in lower risk MDS in ESA ineligible subjects (ACE-536-MDS-001) is restricted to subjects who are RS+. However, in the population of this proposed study both RS+ and RS- patients are included and will be stratified according to RS status (RS+/RS-) at baseline. Stratifying subjects based on RS status will balance the distribution of RS+ and RS- subjects between the two treatment arms as well as any associated potential prognostic differences between the two groups. Of note, IWG HI-E response rates have been shown to be similar in RS+ and RS- subjects at endogenous sEPO levels ≤ 500 U/L in Phase 2 studies with luspatercept (A536-03, A536-05) (Platzbecker, 2017b), however, limited data is available, thus this stratification factor is a precautionary measure.

Endogenous serum erythropoietin (sEPO) level at baseline: ≤ 200 U/L versus > 200 U/L

In this proposed study, subjects who have an endogenous sEPO level ≤ 200 U/L at randomization will be balanced with subjects who have an endogenous sEPO level of > 200 U/L at randomization. This stratification will balance the impact of endogenous sEPO levels on the study endpoints over the two treatment arms.

1.3.2.3 Rationale for Study Endpoints

The primary endpoint of RBC-TI for 12 weeks (84 days) with a mean hemoglobin increase ≥ 1.5 g/dL is defined as proportion of subjects who are RBC transfusion-free for any 12-week period during the first 24-week period of study treatment associated with a concurrent mean hemoglobin increase ≥ 1.5 g/dL compared to baseline and reflects an important direct clinical benefit of the treatment.

Lower 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 (Zeidan, 2013). In addition, long-term RBC transfusion dependence has other clinical and economic consequences, including a potentially negative impact on HRQoL, iron overload and its associated complications, immunorelated disorders, and increased risk of infections (Hellstrom-Lindberg, 2003; Jansen, 2003; Thomas, 2007). Therefore, treatment of anemia leading to transfusion independency would benefit these patients. In this study, a prolonged period of 12 weeks of transfusion independence (instead of 8 weeks as per IWG criteria [Cheson, 2006]) would illustrate an important direct clinical benefit and therefore would be considered clinically relevant. The additional requirement of a mean increase of Hgb of ≥ 1.5 g/dL compared to baseline represents a substantial and clinically meaningful Hgb increase and will increase the robustness and objectivity of the endpoint.

Preliminary data from the Phase 2 A536-03 and A536-05 studies in MDS show an RBC-TI over a 24-week period of 78% (7/9) in subjects with baseline sEPO ≤ 500 U/L and 2 to 6 pRBC units/8 weeks.

Secondary objectives include evaluation of efficacy (eg, RBC-TI for 24 weeks over the first 24-week period of study treatment, RBC-TI for ≥ 12 weeks (84 days), duration and time to RBC-TI for ≥ 12 weeks (84 days), HRQoL) as well as safety and tolerability. 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).

1.3.2.4 Rationale for Open-label Design

Epoetin alfa and luspatercept are two distinct treatment modalities and are not only different in the frequency of application (weekly versus 3-weekly) but also in terms of dose modification, dose delay and stopping rules, which have been established and need to be applied separately to allow for a fair comparison. A double blind, double dummy design would increase patient burden significantly as the number of injections for subjects on the luspatercept arm would be tripled. In addition, epoetin alfa (EPREX®/ERYPO®) is supplied in prefilled syringes of various sizes (depending on the number of units) in the majority to the participating countries rendering blinding operationally unfeasible.

1.3.3 Rationale for Dose, Schedule and Regimen Selection

For luspatercept, the starting dose level of 1.0 mg/kg and the maximum dose level of 1.75 mg/kg are based on clinical data from the ongoing Phase 2 A536-03 and A536-05 studies in MDS. Preliminary results indicate that the dose levels up to 1.75 mg/kg have been generally safe and well-tolerated to date. A higher response rate, including HI-E and RBC-TI (8 weeks), was observed in the higher dose groups (0.75-to 1.75 mg/kg subcutaneous every 3 weeks [Q3W]) compared to the lower dose groups (0.125-0.5 mg/kg subcutaneous Q3W). Selection of the dosing schedule (every 3 weeks, Q3W) was based on the duration of the luspatercept responses as well as pharmacokinetic parameters for luspatercept in MDS patients. The transfusion-reducing effect of luspatercept relies on its ability to increase hemoglobin; in the Phase 2 studies, the clinically

significant increase in hemoglobin was maintained with the Q3W dosing schedule. Additional information regarding these clinical studies is summarized in the current version of the luspatercept IB.

Epoetin alfa dosing is based on the label approved via the mutual recognition procedure in a number of EU member states for the treatment of symptomatic anemia (hemoglobin concentration of ≤ 10 g/dL) in adults with low- or intermediate-1-risk primary MDS who have low serum erythropoietin (< 200 U/L) and is based on the EPOANE3021 study.

1.3.4 Rationale for Choice of Comparator Compound

The choice of the active comparator epoetin alfa will ensure that all subjects on the control arm are treated according to standard of care as per international treatment guidelines (NCCN, 2017; ELN, 2014 [Malcovati, 2013]). Epoetin alfa has been authorized via the MRP by a number of EU member states for the treatment of symptomatic anemia (hemoglobin concentration of ≤ 10 g/dL) in adults with low- or intermediate-1-risk primary MDS who have low serum erythropoietin (< 200 U/L).

While darbepoetin alfa is also part of the treatment guidelines, and efficacy in treatment of lower-risk MDS has been demonstrated in a Phase 3 study (ARCADE), darbepoetin alfa is not expected to have received regulatory approval at the time ACE-536-MDS-002 study initiation.

1.3.5 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 (GDF11) and Activin B are present in serum and bone marrow and nonclinical studies have demonstrated increased circulating GDF11 levels in a murine model of MDS. It is also 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 (47) 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 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, 2017b).

In this study, we will build on these data 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. Biomarker assessments will be performed on subjects in both the control arm (epoetin alfa) and the investigational arm (luspatercept), thus a distinction between the prognostic (disease outcome in the absence of therapy) and/or predictive (disease outcome in the presence of therapy) nature of the marker(s) will be determined. 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 can compare this phenotypic profile to response and determine whether there is a correlation between erythroid differentiation state and response to luspatercept and/or EPO. We can also evaluate the profile after treatment to determine which erythroid populations are modified following administration of luspatercept.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

Subjects who have evidence of a prior infection with 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 or impact interpretation of study events or results.

1.4 Risk/ Benefit Assessment

1.4.1 Risk Assessment

1.4.1.1 Study Intervention: Luspatercept

1.4.1.1.1 Non-clinical Risks

Kidney findings: In monkey studies kidney findings included glomerulonephritis, accumulation of tubular protein, mixed inflammatory cell infiltrates, and degeneration/atrophy of tubules. Although the presence of immunoglobulin is suggestive of immune complexes in renal tissue, presence of these immune complexes could not be demonstrated, and a direct drug effect on the

kidney could not be excluded. However, clinical experience of luspatercept in subjects without severe renal dysfunction at baseline has not resulted in identification of a drug-related renal toxicity signal. Therefore, to exclude subjects with severe renal dysfunction in whom the safety has not yet been characterized, subjects with an estimated glomerular filtration rate (eGFR) of < 40 mL/min/1.73m^2 will be excluded from the study.

Maternal health and fetal development: 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 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: 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. Dose modification guidelines include monitoring of increased white blood cell (WBC) counts as well as the presence of blasts in peripheral blood. In addition, participating subjects will be followed long term as specified in Section 6.3.2 for evidence of tumor formation.

1.4.1.1.2 Clinical risks

Increases in hematologic parameters and blood pressure: 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: 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.

Antidrug antibodies (ADA): As with all biologics, there is the potential for ADA that can be associated with increased drug clearance and hypersensitivity reactions. Data from current sponsored luspatercept studies in MDS indicate that 8.8% of subjects do develop treatment-emergent ADAs [redacted]. However, analyses of the impact of these ADAs on safety and efficacy of luspatercept in these subjects have concluded that subjects who develop ADAs on treatment with luspatercept experience neither clinically significant allergic responses nor decrements in efficacy as assessed by hemoglobin increase and transfusion reduction compared with subjects who do not develop ADAs. Nevertheless, antidrug antibody formation against luspatercept as well as human ActRIIB protein will be monitored.

Thromboembolic events: Emerging data in β-thalassemia subjects treated with luspatercept from the Phase 3 study ACE-536-B-THAL-001 reveals an imbalance in the rate of thromboembolic events in the luspatercept arm versus the placebo arm (3.6% versus 0.9%, in the luspatercept and placebo arms, respectively. All subjects with thromboembolic events had a least two pre-existing risk factors for thromboembolic events: they were all splenectomized and had at least one other risk factor including hormonal replacement or contraception, thrombocytosis, smoking, obesity, cardiac disease, hypertension, previous thromboembolic event, or diabetes. The incidence rate observed in the luspatercept arm is consistent with the expected event rate for β-thalassemia subjects, ranging from 3.3% and 6.3% (Taher, 2010; Borgna Pignatti, 1998; Moratelli, 1998; Michaeli, 1992). Of note, in the MDS population, no imbalance in thromboembolic events was observed in the Phase 3 study ACE-536-MDS-001, which evaluated the efficacy and safety of luspatercept versus placebo in subjects with IPSS-R very low, low or intermediate risk MDS with chronic anemia and refractory to, intolerant of, or ineligible for treatment with an erythropoietin-stimulating agent (ESA), ring sideroblast-positive and require frequent RBC transfusions.

Safety effects will be monitored closely through AE reporting, clinical laboratory tests, vital signs, and physical examinations.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of luspatercept may be found in the Investigator's Brochure.

1.4.1.2 Study Procedures

Blood drawing: Needle sticks carry some risks such as fainting, bleeding, bruising, discomfort, dizziness, infection and/or pain at the puncture site.

Bone marrow aspirate/ biopsy collection: Bone marrow is collected using a needle under local anesthesia to aspirate (draw out) marrow tissue from the inside of the pelvic or hipbone. The risks on bone marrow biopsy and aspirate include pain, bleeding, bruising, and/or discomfort at the biopsy site. Infection is also possible, but rare.

Trained medical personnel will perform the blood and bone marrow aspirate/bone marrow biopsy (BMA/BMB) collection procedures and will make every effort to minimize any discomforts. Risks from the needle sticks can be mitigated by applying adequate pressure to the puncture site for adequate time (10–20 min).

Electrocardiogram (ECG): The ECG involves placing adhesive patches on the skin. A slight redness or inflammation may appear due to an allergic reaction to the adhesive used to attach the patches. Those are minor and do not require any intervention.

1.4.1.3 Other: Comparator Epoetin alfa (EPREX®/ERYPO® or PROCRIT®)

Hypertension: Hypertensive crisis with encephalopathy and seizures, requiring the immediate attention of a physician and intensive medical care, have occurred during epoetin alfa treatment in patients with previously normal or low blood pressure. Hypertension will be controlled prior to treatment initiation and during treatment.

Increased mortality, myocardial infarction, stroke, and thromboembolism: Using ESAs to target a Hgb level of > 11 g/dL increases the risk of serious adverse cardiovascular reactions and has not been shown to provide additional benefit. For subjects with a predose Hgb of ≥ 12.0 g/dL (7.5 mmol/L), dosing of epoetin alfa will be delayed until Hgb < 11.0 g/dL (6.8 mmol/L). Patients with high risk of cardiovascular diseases, stroke, and thromboembolism are excluded from study participation.

Increased mortality and/ or increased risk of tumor progression or recurrence in patients with cancer: Subject with a prior history of malignancies other than MDS, unless the subject has been free of the disease for ≥ 5 years, are not eligible for study participation. During the study, subjects will be assessed for MDS disease progression every 24 weeks.

Seizures: Epoetin alfa should be used with caution in patients with epilepsy, history of seizures, or medical conditions associated with a predisposition to seizure activity such as central nervous system infections and brain metastases. Patients with new-onset seizures or poorly controlled seizures within 12 weeks prior to randomization are excluded from study participation.

Rise in the platelet counts: There may be a moderate dose-dependent rise in the platelet count within the normal range during treatment with epoetin alfa. This regresses during the course of continued therapy. In addition, thrombocythemia above the normal range has been reported. The platelet count will be monitored regularly.

Serious allergic reactions: Serious allergic reactions, including anaphylactic reactions, angioedema, bronchospasm, skin rash, and urticaria may occur. The needle cover on the EPREX®/ERYPO® pre-filled syringe contains dry natural rubber (a derivative of latex), which may cause severe allergic reactions in individuals sensitive to latex. Epoetin alfa will be discontinued immediately and permanently, and appropriate therapy will be administered.

Severe cutaneous reactions: Blistering and skin exfoliation reactions including erythema multiforme and Stevens-Johnson Syndrome /toxic epidermal necrolysis, have been reported. Epoetin alfa will be discontinued, and reactions will be managed.

Other frequently reported adverse reactions: Other frequently reported adverse reactions in ≥ 5% of epoetin alfa-treated patients in clinical studies are nausea, vomiting, myalgia, arthralgia, stomatitis, cough, weight decrease, leukopenia, bone pain, rash, hyperglycemia, insomnia, headache, depression, dysphagia, and hypokalemia.

Safety effects will be monitored closely through AE reporting, clinical laboratory tests, vital signs, and physical examinations.

Information provided in this section is based on the UK Summary of Product Characteristics (SmPC) for EPREX® and the prescribing information for PROCRIT®. For additional information please refer to the full documents, respectively.

1.4.2 Benefit Assessment

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 who are ESA naïve and require RBC transfusions. Preliminary Phase 2 results for luspatercept demonstrate promising results for erythroid response (HI-E), transfusion independence and duration of response for subjects with endogenous sEPO level up to 500 U/L and for subjects with and without ring sideroblasts. A direct comparison of epoetin alfa and luspatercept in a Phase 3 study in lower risk MDS is therefore justified in subjects with endogenous sEPO ≤ 500 U/L.

Overall, based on the assessment of available safety information collected during the overall cumulative experience to date, the benefit-risk balance for the use of luspatercept in the populations under study as well as in the currently approved indications remains favorable.

1.4.3 Overall Benefit Risk Conclusion

Current available information based on non-clinical and clinical data support an acceptable benefit-risk profile for luspatercept in subjects with very low, low or intermediate risk MDS who are ESA naïve and require red blood cell transfusions, when used in accordance with the precautions, dosing, and safety monitoring outlined in this study protocol and the routine pharmacovigilance practices.

Luspatercept may have the potential to provide hematologic improvement in erythroid response involving stimulation of the maturation phase of erythroblast differentiation and maturation in the bone marrow compared to epoetin alfa, which stimulates proliferation and differentiation of early erythroid progenitors. Furthermore, luspatercept could have the potential therapeutic benefit to achieve transfusion independence for a sustained period of time and could be an important treatment option for an unmet medical need.

Considering the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with luspatercept are justified by the anticipated benefits that may be afforded to participants with lower risk MDS.

2 STUDY OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives

Primary Objective
The primary objective of the study is to evaluate the efficacy of luspatercept on red blood cell transfusion independence (RBC-TI; for 12 weeks [84 days] with an associated concurrent mean hemoglobin increase ≥ 1.5 g/dL) compared with epoetin alfa for the 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 erythropoiesis stimulating agent (ESA) naïve subjects who require RBC transfusions.
Secondary Objective(s)
The secondary objectives are: • To assess the safety and efficacy of luspatercept compared to epoetin alfa • To assess health-related quality of life (HRQoL) and anemia outcome measures (ie, the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire [EORTC QLQ-C30] and the Functional Assessment of Cancer Therapy - Anemia (FACT-An) questionnaire for subjects treated with luspatercept compared to epoetin alfa • To evaluate pharmacokinetics for luspatercept in MDS subjects
Exploratory Objective(s)
The exploratory objectives are: • To evaluate the impact of luspatercept therapy on healthcare resource utilization and treatment satisfaction in both treatment arms • To evaluate overall MDS treatment satisfaction in both treatment arms • To evaluate 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 evaluate 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 evaluate exposure-response relationships for luspatercept in MDS subjects • To evaluate the safety of luspatercept in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibody positive subjects and to support potential health authority requests

Table 2: Study Endpoints

Endpoint	Name	Description	Timeframe
Primary	Red blood cell transfusion independence (RBC-TI) for 12 weeks (84 days) with a mean hemoglobin increase ≥ 1.5 g/dL	Proportion of subjects who are RBC transfusion-free for any 12-week period associated with a concurrent mean hemoglobin increase ≥ 1.5 g/dL compared to baseline	Week 1 through Week 24
Secondary	Red blood cell transfusion independence (RBC-TI) for 24 weeks	Proportion of subjects who are RBC transfusion-free from Week 1 through Week 24	Week 1 through Week 24
	Mean hemoglobin change over 24 weeks	Mean hemoglobin change over the 24-week period of Week 1 through Week 24 compared to baseline	Week 1 through Week 24
	Hematologic improvement – erythroid response (HI-E) per IWG (Cheson, 2006)	Proportion of subjects achieving HI-E over any consecutive 56-day period	Week 1 through Week 24
	Time to HI-E	Time from first dose to first onset of achieving HI-E	Week 1 through Week 24
	RBC-TI for ≥ 12 weeks (84 days)	Proportion of subjects who are RBC transfusion-free over a consecutive 84-day period	Week 1 through Week 24
	Duration of RBC-TI ≥ 12 weeks (84 days)	Maximum duration of RBC transfusion independence for subjects who achieve RBC-TI ≥ 84 days	Week 1 through End of Treatment
	Time to RBC-TI ≥ 12 weeks (84 days)	Time from first dose to first onset of transfusion independence ≥ 84 days	Week 1 through Week 24
	Time to first RBC transfusion	Time from first dose to first transfusion on treatment	Week 1 through End of Treatment
	RBC transfusion burden on treatment	Total number of RBC units transfused on treatment	Week 1 through Week 24
	RBC-TI for ≥ 56 days (8 weeks)	Proportion of subjects who are RBC transfusion-free over a consecutive 56-day period	Week 1 through Week 24
	RBC-TI for a consecutive 24-week period	Proportion of subjects who are RBC transfusion-free for a consecutive 24-week period in the first 48 weeks from first dose	Week 1 through Week 48
	Health-related quality-of-life (HRQoL)	Evaluation of EORTC QLQ-C30 score and FACT-An	Screening through Week 24
	Safety	Type, frequency, severity of AEs and relationship of AEs to luspatercept/epoetin alfa	Screening through 42 days post last dose; Randomization through Week 48

Table 2: Study Endpoints

Endpoint	Name	Description	Timeframe
Secondary (continued)	PK parameters	Serum luspatercept concentrations and PK parameters	Randomization through 1 year post first dose
	Antidrug antibodies (ADA)	Frequency of antidrug antibodies	Randomization through 1 year post first dose
	Progression to AML	Number and percentage of subjects progressing to AML; time to AML progression	Randomization through 5 years from first dose or 3 years from last dose (whichever occurs later)
	Overall survival	Time from date of randomization to death due to any cause	Randomization 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, drug MOA and prognostication of MDS.	Baseline through End of Treatment
	Healthcare resource utilization	Evaluation of healthcare resource use (eg, hospitalization) associated with investigational product (IP) during study	Screening through Week 24
	Health-related quality-of-life (HRQoL)	Description of QUALMS-P and Treatment Satisfaction	Screening through Week 24
	Exposure-response relationship.	Exposure-response relationship for selected endpoints of efficacy and safety.	Randomization through 1 year post first dose
	SARS-CoV-2 serology	Exploratory measurements of SARS-CoV-2 serology (anti-SARS-CoV-2 IgG or total antibody), from serum samples collected at baseline, D169, D337 and EOT, and impact on safety profile of luspatercept.	Screening through 42 days post last dose

Abbreviations: ADA = antidrug antibodies; AE = adverse event; AML = acute myeloid leukemia; D = Day; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire; EOT = end of treatment; FACT-An = Functional Assessment of Cancer Therapy – Anemia; HI-E = hematologic improvement – erythroid response; IgG = immunoglobulin G; IWG = International Working Group; MDS = myelodysplastic syndromes; MOA = mechanism of action; PK = Pharmacokinetics; QUALMS-P = Quality of Life in Myelodysplasia Scale - Physical Burden; RBC = red blood cell; RBC-TI = red blood cell transfusion independence; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

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 an interventional active-controlled, open-label, randomized Phase 3 study to compare the efficacy and safety of luspatercept (ACE-536) versus epoetin alfa for the treatment of anemia due to IPSS-R very low, low or intermediate risk MDS in ESA naïve subjects who require RBC transfusions.

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 randomization. During the Screening Period, the subject will undergo safety and other assessments to determine eligibility for the randomized study.

Central review of bone marrow aspirate smear, peripheral blood smear and cytogenetics 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.

Transfusion history must be available for at least 16 weeks immediately preceding and including the date of randomization. Refer to Table 3 for a full list of study procedures/assessments.

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 randomization of a subject.

Randomization

Approximately 350 eligible subjects will be randomized by a central randomization procedure using integrated response technology (IRT) at a 1:1 ratio to one of the below treatment arms:

- Experimental Arm: 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. See Section 7.2.1 for details.
- Control Arm: epoetin alfa (EPREX®/ERYPO® or PROCRIT®): starting dose of 450 IU/kg (maximum total starting dose is 40,000 IU) subcutaneous injection once every week (7 days; QW). Dose levels can be increased in a stepwise manner beyond the starting dose to 787.5 IU/kg, and up to a maximum of 1,050 IU/kg (with a maximum

total dose of 80,000 IU). Individual epoetin alfa doses according to body weight will be rounded as described in Section 7.2.2 in more detail.

Randomization will be stratified based on the following factors:

- RBC transfusion burden at baseline
  - < 4 pRBC units/ 8 weeks
  - ≥ 4 pRBC units/ 8 weeks
- Ring sideroblast (RS) status at baseline (with RS+ defined as Ring sideroblast ≥ 15% of erythroid precursors in bone marrow or ≥ 5% (but < 15%) if SF3B1 mutation is present).
  - RS+
  - RS-
- Endogenous Serum Erythropoietin (sEPO) level at baseline.
  - ≤ 200 U/L
  - > 200 U/L

Crossover between treatment arms is not permitted during the Study Treatment Period.

Treatment Period

The first dose of investigational product (IP) should be administered on the same day after randomization, but at the latest within 3 days of randomization. More details will be provided in the IRT manual for additional information on randomization utilizing IRT.

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

Subjects on the epoetin alfa arm will receive IP every week (7 days) (ie, at the W1D1 Visit, W2D1 Visit; W3D1 Visit, etc.).

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

In both treatment arms, best supportive care (BSC) may be used in combination with study treatment when clinically indicated per investigator. Best supportive care includes, but is not limited to, treatment with transfusions, antibiotic, antiviral and/or antifungal therapy, and nutritional support as needed. Best supportive care for this study excludes the use of ESAs outside of the study treatment. 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.]); Section 6.4.2) 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:

- Evidence of clinical benefit defined as a transfusion reduction of ≥ 2 pRBC units/8 weeks compared to the baseline (for any consecutive 8-week period within the 12 weeks immediately preceding Day 169 and every 24 weeks thereafter [ie, Day 337, Day 505, etc.]).
- Absence of disease progression per IWG criteria for altering natural history of MDS (Cheson, 2006) 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 with their assigned IP 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 open-label 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) Visit 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).

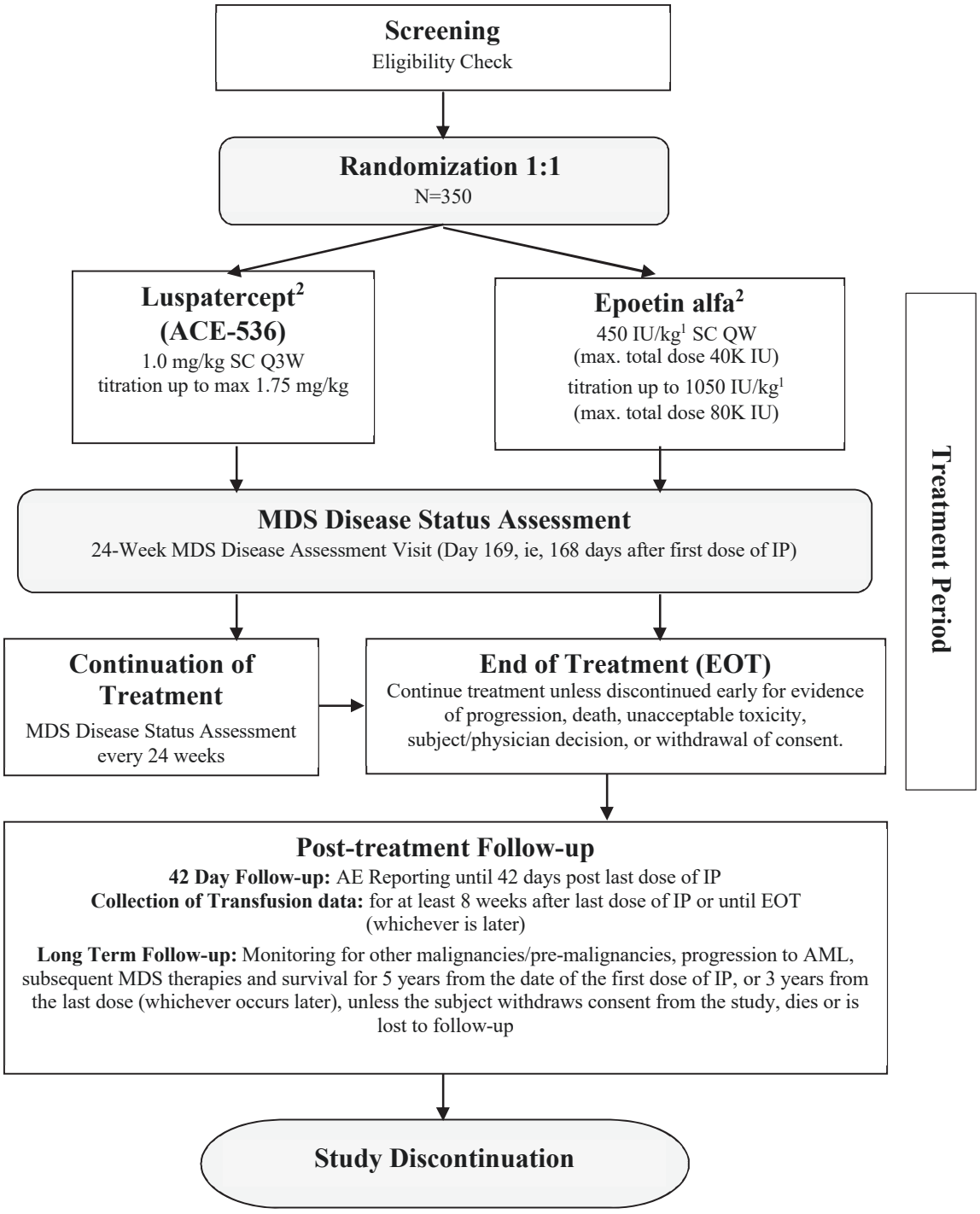
In addition, continuation of monitoring for other malignancies/pre-malignances and progression to AML will occur in the Long-term Post-treatment Follow-up Period along with data collection of subsequent MDS therapies, and overall survival for 5 years from the date of the first dose of IP, or 3 years 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 assigned to the luspatercept arm, 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.

Data Monitoring Committee (DMC)/Steering Committee (SC)

An external, independent DMC comprised of experts in MDS not involved in the ACE-536-MDS-002 study as well as a SC comprised of study investigators and sponsor representatives will be established. For details on composition and roles please refer to Section 9.10.4 and Section 9.10.5, respectively.

Figure 2: Overall Study Design



Abbreviations: AE = adverse event; EOT = End of Treatment; IP = investigational product; MDS = Myelodysplastic syndromes; QW = once every week; Q3W = every 3 weeks; SC = subcutaneous.

[1] Individual epoetin alfa doses according to body weight will be rounded: up to the next 2,000 IU dose level for Starting Dose Level and Dose Level -1, and up to the next 4,000 IU for Dose Level +1 and Dose Level +2 for doses exceeding a calculated dosing of 56,000 IU according to body weight.

[2] Crossover between the treatment arms is not permitted during the Study Treatment Period.

3.2 Study Duration for Subjects

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

- Screening Period: up to 35 days prior to randomization
- 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).
- 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 350 subjects with anemia due to IPSS-R very low, low, or intermediate risk MDS who are ESA naïve with endogenous sEPO levels of < 500 U/L and who require RBC transfusions (ie, 2 to 6 pRBC units in the 8 weeks before randomization) will be randomized worldwide.

4.2 Inclusion Criteria

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

1) Subject is ≥ 18 years of age the time of signing the informed consent form (ICF).
2) Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.
3) 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 an endogenous serum erythropoietin (sEPO) level of < 500 U/L.
6) Subject requires RBC transfusions, as documented by the following criteria (Section 6.1.2):
   - A transfusion requirement of 2 to 6 pRBCs units/8 weeks confirmed for a minimum of 8 weeks immediately preceding randomization.
     – Hemoglobin levels at the time of or within 7 days prior to administration of a RBC transfusion must have been ≤ 9.0 g/dL (5.6 mmol/L) with symptoms of anemia (or ≤ 7 g/dL [4.3 mmol/L] in the absence of symptoms) in order for the transfusion to be counted towards meeting eligibility criteria. Red blood cell transfusions administered when Hgb levels were > 9.0 g/dL (or > 7 g/dL in the absence of symptoms) and/or RBC transfusions administered for elective surgery, infections or bleeding events will not qualify as a required transfusion for the purpose of meeting eligibility criteria or stratification.
     – The hemoglobin level after the last RBC transfusion prior to randomization must be < 11.0 g/dL (6.8 mmol/L) (centrally or locally analyzed).
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.

- 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.

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 randomization (with the randomization date defined as the date in which the subject is randomized in IRT):

1) Subject with the any of the following prior treatments:
   - Erythropoiesis-stimulating agents (ESAs)
     - Subjects may be randomized at the investigator's discretion contingent on the fact that the subject received no more than 2 doses of epoetin alfa (prior treatment with darbepoetin not acceptable for entry into the study). The last dose of epoetin alfa must be ≥ 8 weeks from the date of randomization. A blood sample to determine the endogenous sEPO level (central laboratory) for stratification must be taken within 5 days of randomization unless a prior screening sample analyzed by the central laboratory demonstrated an endogenous sEPO level ≤ 500 U/L.
   - Granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), within 8 weeks prior to randomization, unless given for treatment of febrile neutropenia
   - 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 randomization, at the investigator's discretion.
   - Hypomethylating agents
     - Subjects may be randomized at the investigator's discretion contingent that the subject received no more than 2 doses of HMA. The last dose must be ≥ 8 weeks from the date of randomization.

[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 (for example, birth control pills, injection, implant, transdermal patch, vaginal ring); intrauterine device (IUD); tubal ligation (tying your tubes); or a partner with a successful vasectomy.

- Luspatercept (ACE-536) or sotatercept (ACE-011)
- Immunosuppressive therapy for MDS
- Hematopoietic cell transplant

2) Subject with MDS associated with del(5q) cytogenetic abnormality or MDS unclassifiable (MDS-U) according to WHO 2016 classification.
3) 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.
4) 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.
5) 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).
6) Subject with known history of diagnosis of AML.
7) Subject receiving any of the following treatment within 8 weeks prior to randomization:
   - Anticancer cytotoxic chemotherapeutic agent or treatment
   - Systemic corticosteroid, except for subjects on a stable or decreasing dose for ≥ 1 week prior to randomization for medical conditions other than MDS
   - Iron-chelating agents, except for subjects on a stable or decreasing dose for at least 8 weeks prior to randomization
   - Other RBC hematopoietic growth factors (eg, Interleukin-3)
   - Androgens, unless to treat hypogonadism
   - Hydroxyurea
   - Oral retinoids (except for topical 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)
8) 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.
9) Subject with any of the following laboratory abnormalities:
   - Absolute neutrophil count (ANC) < 500/µL (0.5 x 109/L)
   - Platelet count < 50,000/µL (50 x 10^9/L)

- Estimated glomerular filtration rate (eGFR) < 40 mL/min/1.73 m2 (APPENDIX F)
- 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.

10) 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:
    - Basal or squamous cell carcinoma of the skin
    - Carcinoma in situ of the cervix
    - Carcinoma in situ of the breast
    - Incidental histologic finding of prostate cancer (T1a or T1b using the tumor, nodes, metastasis [TNM] clinical staging system)
11) Subject with major surgery within 8 weeks prior to randomization. Subjects must have completely recovered from any previous surgery prior to randomization.
12) 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 randomization
    Note: prior superficial thrombophlebitis is not an exclusion criterion.
13) New-onset seizures or poorly controlled seizures within 12 weeks prior to randomization.
14) Subject with the following cardiac conditions within 6 months prior to randomization: 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 randomization.
15) 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).
16) 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.
17) Subject with history of severe allergic or anaphylactic reactions or hypersensitivity to recombinant proteins or excipients in luspatercept (see Investigator's Brochure).
18) Subject with known hypersensitivity to the active substance or to any of the excipients in epoetin alfa.
19) Subject with history of pure red cell aplasia (PRCA) and/or antibody against erythropoietin.

20) Female subject who is pregnant or breastfeeding.
21) 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.
22) 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.
23) Subject has any condition or receives concomitant medication that confounds the ability to interpret data from the study.
24) Subject has history of active SARS-CoV-2 infection within 4 weeks prior to screening, unless the subject has adequately recovered from COVID 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 randomization.

5 TABLE OF EVENTS

Table 3: Table of Events

		Screening	Treatment Period (open-label)								Post-treatment Follow-up		
								Efficacy Assessment *Independent of any dose delays*					
	Section	**Day -35 to Random-ization**	**W1D1 Visit[c]**	**W2D1 Visit**	**W3D1 Visit**	**Add. Visits EPO** *W5/6D1 W8/9D1 etc.*	**3-wkly Visits** *W4D1 W7D1 W10D1 etc.*	**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								6.4	6.4	6.2.2/11.1	6.3.1	6.3.2	11.2
Time window				±2 days	±2 days	±2 days	±2 days	±14 days[b]	±14 days[b]		+3 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 (weekly for epoetin alfa and every three 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 randomization 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	–	–	–	–	–	–	–	–	–	–	–
Randomization[c]	6.1/9.4	X	–	–	–	–	–	–	–	–	–	–	–

Table 3: Table of Events

		Screening	Treatment Period (open-label)								Post-treatment Follow-up		
								Efficacy Assessment *Independent of any dose delays*					
	Section	**Day -35 to Randomization**	**W1D1 Visit[c]**	**W2D1 Visit**	**W3D1 Visit**	**Add. Visits EPO** *W5/6D1 W8/9D1 etc.*	**3-wkly Visits** *W4D1 W7D1 W10D1 etc.*	**24-Wk MDS Assessment Visit** *D169*	**Every 24 wks** *D337 D505 etc.*	**EOT Visit[a]**	**42-Day Follow-up**	**Long Term Follow-up**	**End of Study**
Section								6.4	6.4	6.2.2/11.1	6.3.1	6.3.2	11.2
Time window				±2 days	±2 days	±2 days	±2 days	±14 days[b]	±14 days[b]		+3 days	±7 days	
INVESTIGATIONAL PRODUCT (IP)													
IP Administration and Accountability Luspatercept	7	–	X	–	–	–	X	–	–	–	–	–	–
IP Administration and Accountability Epoetin alfa[h]	7	–	X	X	X	X[d]	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[i]	6.1.14	X	X	–	–	–	X	–	–	X	X	X[k]	–
Adverse events	6.1.18 10	Continuous, after signing informed consent until 42 days after last IP administration										–	–

Table 3: Table of Events

		Screening	Treatment Period (open-label)								Post-treatment Follow-up		
								Efficacy Assessment *Independent of any dose delays*					
	Section	**Day -35 to Randomization**	**W1D1 Visit[c]**	**W2D1 Visit**	**W3D1 Visit**	**Add. Visits EPO** *W5/6D1 W8/9D1 etc.*	**3-wkly Visits** *W4D1 W7D1 W10D1 etc.*	**24-Wk MDS Assessment Visit** *D169*	**Every 24 wks** *D337 D505 etc.*	**EOT Visit[a]**	**42-Day Follow-up**	**Long Term Follow-up**	**End of Study**
Section								6.4	6.4	6.2.2/11.1	6.3.1	6.3.2	11.2
Time window				±2 days	±2 days	±2 days	±2 days	±14 days[b]	±14 days[b]		+3 days	±7 days	
Prior and Concomitant medications/ procedures	6.1.178	Continuous, 8 weeks prior to randomization 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[d] blood pressure only	X	X	X	X	–	–	–
Serum Chemistry	6.1.10	X	X	–	–	–	X	X	X	X	–	–	–
EFFICACY ASSESSMENTS													
Hematology	6.1.9	X	X	X	X	X[d] local Hgb only	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	–	–	–

Table 3: Table of Events

		Screening	Treatment Period (open-label)								Post-treatment Follow-up		
								Efficacy Assessment *Independent of any dose delays*					
	Section	**Day -35 to Random-ization**	**W1D1 Visit[c]**	**W2D1 Visit**	**W3D1 Visit**	**Add. Visits EPO** *W5/6D1 W8/9D1 etc.*	**3-wkly Visits** *W4D1 W7D1 W10D1 etc.*	**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								6.4	6.4	6.2.2/11.1	6.3.1	6.3.2	11.2
Time window				±2 days	±2 days	±2 days	±2 days	±14 days[b]	±14 days[b]		+3 days	±7 days	
Transfusion Data Collection and Assessment	6.1.2 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 EOT 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 transfusions received at institutions outside of the study site 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 patient.											–
MDS Disease Assessment	6.4.2	–	–	–	–	–	–	X	X		–	–	–
BMA and PB for Cytomorphology and Cytogenetic testing (including RS status)[e]	6.1.1	X	–	–	–	–	–	X	X	X	–	–	–
EXPLORATORY/BIOMARKER ASSESSMENTS													
PB for Exploratory Biomarkers (eg, TGF-ß superfamily, MDS-associated molecular mutations and other markers of drug MOA)	6.1.1 6.7	X	–	–	X	–	W10D1 W34D1 only	X	X	X	–	–	–

Table 3: Table of Events

		Screening	Treatment Period (open-label)								Post-treatment Follow-up		
								Efficacy Assessment *Independent of any dose delays*					
	Section	**Day -35 to Randomization**	**W1D1 Visit[c]**	**W2D1 Visit**	**W3D1 Visit**	**Add. Visits EPO** *W5/6D1 W8/9D1 etc.*	**3-wkly Visits** *W4D1 W7D1 W10D1 etc.*	**24-Wk MDS Assessment Visit** *D169*	**Every 24 wks** *D337 D505 etc.*	**EOT Visit[a]**	**42-Day Follow-up**	**Long Term Follow-up**	**End of Study**
Section								6.4	6.4	6.2.2/11.1	6.3.1	6.3.2	11.2
Time window				±2 days	±2 days	±2 days	±2 days	±14 days[b]	±14 days[b]		+3 days	±7 days	
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	6.7	X	–	–	–	–	–	X	D337 only	X	–	–	–
PK/ADA ASSESSMENTS													
PK Sample Collection (Luspatercept arm only) *Should be collected prior to IP dosing on a dosing day*	6.5	–	X	X	X	–	W4D1 W10D1 W16D1 W22D1 only	X	And every 12 weeks (± 14 days) from the 24-Week MDS Assessment visit for up to one 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.				–

Table 3: Table of Events

		Screening	Treatment Period (open-label)								Post-treatment Follow-up		
								Efficacy Assessment *Independent of any dose delays*					
	Section	**Day -35 to Random-ization**	**W1D1 Visit[c]**	**W2D1 Visit**	**W3D1 Visit**	**Add. Visits EPO** *W5/6D1 W8/9D1 etc.*	**3-wkly Visits** *W4D1 W7D1 W10D1 etc.*	**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								6.4	6.4	6.2.2/11.1	6.3.1	6.3.2	11.2
Time window				±2 days	±2 days	±2 days	±2 days	±14 days[b]	±14 days[b]		+3 days	±7 days	
ADA Sample Collection (Luspatercept arm only) *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 one year from the first dose. If the subject was discontinued from study treatment earlier than one year from the first dose, additional samples will be collected if last ADA is positive.				–
QUALITY-OF-LIFE													
EORTC QLQ-C30[g]	6.8	X	X	–	–	–	X 6-wkly only *W7D1 W13D1 etc.*	X	X D337 only	X	–	–	–
FACT-An[g]	6.8	X	X	X	X	–	X	X	X D337 only	X	–	–	–
QUALMS-P[g]	6.8	X	–	–	–	–	–	X	–	–	–	–	–

Table 3: Table of Events

		Screening	Treatment Period (open-label)								Post-treatment Follow-up		
								Efficacy Assessment *Independent of any dose delays*					
	Section	**Day -35 to Randomization**	**W1D1 Visit[c]**	**W2D1 Visit**	**W3D1 Visit**	**Add. Visits EPO** *W5/6D1 W8/9D1 etc.*	**3-wkly Visits** *W4D1 W7D1 W10D1 etc.*	**24-Wk MDS Assessment Visit** *D169*	**Every 24 wks** *D337 D505 etc.*	**EOT Visit[a]**	**42-Day Follow-up**	**Long Term Follow-up**	**End of Study**
Section								6.4	6.4	6.2.2/11.1	6.3.1	6.3.2	11.2
Time window				±2 days	±2 days	±2 days	±2 days	±14 days[b]	±14 days[b]		+3 days	±7 days	
Patient Treatment Satisfaction Survey[g]	6.8	X	X	–	–	–	6-wkly only *W7D1 W13D1 etc.*	X	X D337 only	X	–	–	–
Healthcare Resource Utilization	6.9	After signing ICF and until 42 days after the last IP dose or End of Treatment Visit, whichever period is longer										–	–
FOLLOW-UP													
Monitoring for progression to AML and other malignancies/pre-malignancies	6.1.19 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											
Post-treatment MDS therapies	6.3.2	–	–	–	–	–	–	–	–	–	X	X	X
Survival Follow-up	6.3.2	–	–	–	–	–	–	–	–	–	X	X	X

Abbreviations: ADA = antidrug antibodies; AML = acute myeloid leukemia; BMA = bone marrow aspirate; BMB = bone marrow biopsy; D = Day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire; EOT = End of Treatment; EPO = erythropoietin; FACT-An = Functional Assessment of Cancer Therapy – Anemia; FCBP = female of childbearing potential; Hep = hepatitis; Hgb = hemoglobin; HIV = human immunodeficiency virus; ICF = informed consent form; IP = investigational product; IRT = integrated response technology; MDS = myelodysplastic syndromes; MOA = mechanism of action; PB = peripheral blood; PK = pharmacokinetics; QUALMS-P = Quality of Life in Myelodysplasia Scale - Physical Burden; RBC = red blood cell; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2; TGF-β = transforming growth factor-beta; W/wk = 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] Randomization via IRT. The first dose of IP should be administered after, but within 3 days of randomization and can be on the same day as randomization.

[d] On days where subject dosing occurs at home (if in line with local practice) and not at the site: blood pressure measurement and Hgb value collection are not applicable (Section 7.2.2).

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

[h] In the event epoetin alfa will be home-administered, compliance will be monitored using a medication diary card or other local procedures in place at the investigational site.

[i] In the event of dose delays, counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted monthly.

[k] An additional pregnancy test is to be performed 12 weeks (±7 days) from the date of last dose of IP for FCBP.

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 randomization unless noted otherwise below. All eligibility criteria must be met in order for subjects to be randomized 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 randomization. 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 randomization 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 prior to randomization. Samples should be collected, if possible, no later than 14 days prior to the planned randomization 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 randomization. If the central reviewer and local pathologist disagree on the diagnosis of a subject, a third reviewer at the central laboratory may be consulted to provide an adjudication assessment, which will be considered the final assessment. Only slides of the most recent BM sample should be used for adjudication. The central laboratory may also request the site to send in samples reviewed by the local pathologist for further assessment.

- Cytogenetics Analysis:

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

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 randomization, local cytomorphology/cytogenetic analysis may suffice for randomization 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 randomization.

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 randomizing a subject using cytogenetic results from a local laboratory.

Results from central laboratory analysis should be used to determine the baseline IPSS-R category (Greenberg, 2012) (APPENDIX C). In the event historical local BM samples/reports are being used for "over read", local lab 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 to be prepared. In the event analysis of the samples sent to the central lab is technical failing, local cytomorphology/cytogenetics report, slides and/or photographs may be used for "over read" by the central lab.

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 immediately preceding and including the date of randomization. Red blood cell transfusion data during the 8 weeks immediately preceding randomization will be used to determine the baseline RBC transfusion requirement for an individual study subject. Thus, this information must be collected during the Screening window (prior to randomization) (including any transfusions received at institutions outside of the study site).

In the event a subject requires RBC transfusions during Screening, the Screening Hematology sample should be taken prior to the administration of the RBC transfusion or ≥ 7 days after the RBC transfusion to minimize risk of confounding the baseline IPSS-R score. 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

If known, 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 subjects on the epoetin alfa arm, weight will be assessed at every third

dosing visit only). For more details and exceptions please refer to Section 7.2.1.1 and Section 7.2.2.1 for luspatercept and epoetin alfa treatment, respectively.

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 E.

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 (ie, RBC count, complete blood count [CBC], 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).

Please note that for subjects on the epoetin alfa arm, on visit days in-between 3-weekly visits (ie, W5D1, W6D1, W8D1, W9D1, W11D1, W12D1, etc.) only local pre-dosing Hgb values are required (when dosing occurs at the site; in the event of home dosing no Hgb assessment is performed).

In the event a subject requires RBC transfusions during Screening, the Screening Hematology sample should be taken prior to the administration of the RBC transfusion or ≥ 7 days after the RBC transfusion to minimize risk of confounding the baseline IPSS-R score. 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 and Section 7.2.2 for luspatercept and epoetin alfa, respectively.

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. Serum EPO collected during the Screening Period should be collected on the same day as a planned RBC transfusion, prior to the transfusion, or 7 days after any RBC transfusion due to possible reduction of the serum level related to the hemoglobin level achieved after the last transfusion. 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, 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 and in the Post-treatment Follow-up 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 and Section 6.3.2 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 Subject Reported Quality-of-life and Healthcare Resource Utilization

Refer to Section 6.8 and Section 6.9 for more information.

6.1.17 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 randomization. Any prior anticancer treatments should be recorded on the appropriate eCRF(s).

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

6.1.18 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.

6.1.19 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 after 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 first dose of IP, or 3 years from 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 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.

6.1.20 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 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 randomization at the latest and can be on the same day as randomization. For all subsequent visits, an administrative time window of ± 2 days is permitted if not indicated otherwise. If screening assessments are performed within 72 hours of Week 1 Day 1 (W1D1), safety laboratory and physical examinations need not be repeated at W1D1.

Subjects on the luspatercept arm will receive IP every 3 weeks (21 days) (ie, at the W1D1 Visit, W4D1 Visit; W7D1 Visit, etc.). Subjects on the epoetin alfa arm will receive IP every week (7 days) (ie, at the W1D1 Visit, W2D1 Visit; W3D1 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)
- Exploratory Biomarker sample collection (as detailed in Section 6.7)
- Pharmacokinetic (PK) and ADA sample collection (as detailed in Section 6.5 and Section 6.6, respectively.
- Subject reported quality-of-life and healthcare resource utilization (see Section 6.8 and Section 6.9 for more details)
- Monitoring for progression to AML and other malignancies/pre-malignancies (as detailed in Section 6.1.19)

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 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 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 randomized 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. An administrative time window of +3 days is permitted.

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

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 assigned to the luspatercept arm, 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).

An additional pregnancy test is to be performed 12 weeks (±7 days) from the date of last dose of IP for FCBP (Section 6.1.14).

All subjects discontinued from protocol-prescribed therapy for any reason should be followed for the below events/therapies for 5 years after 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 6.1.19 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 after 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) (APPENDIX D), 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, healthcare resource utilization.

The timing of efficacy assessments (MDS disease assessments, health-related quality-of-life, and healthcare resource utilization) 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

The RBC transfusion data during the 8 weeks immediately preceding randomization will be used to determine the baseline RBC transfusion requirement for an individual study subject.

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 transfusions received at institutions outside of the study site 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 patient.

Red blood cell transfusions administered for elective surgery, infections or bleeding events will not count toward baseline requirement, efficacy assessment, or progressive disease status but should still be recorded in the eCRF.

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 first dose of IP, 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 first dose of IP 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 institutions outside of the study site) 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:

- Evidence of clinical benefit defined as a transfusion reduction of ≥ 2 pRBC units/8 weeks compared to the baseline (for any consecutive 8-week period within the 12 weeks immediately preceding Day 169 and every 24 weeks thereafter [ie, Day 337, Day 505, etc.]).
- Absence of disease progression per IWG criteria for altering natural history of MDS (Cheson, 2006) 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 with their assigned IP 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 assessment of cytomorphology/cytogenetics results within 4 weeks of the MDS Disease Assessment Visit at the

latest (ie, Day 169, Day 337, Day 505, etc. for the MDS disease assessments every 24 weeks thereafter) to continue dosing beyond these 4 weeks.

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 subjects treated with luspatercept. 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):

- 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

If a PK sample is drawn on a dosing day, the PK sample should be drawn prior to luspatercept dosing. The maximum PK sampling period will not exceed one year from the first dose of luspatercept, unless justified by safety reasons. Pharmacokinetic sampling per investigator's or sponsor's discretion is allowed and should be recorded as an unscheduled visit. 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 in subjects treated with luspatercept. 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 is positive at end of treatment, 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 one year from the first luspatercept dose unless justified by safety reasons. Antidrug antibodies 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 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 remaining bone marrow aspirate (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 study's Central Laboratory Manual for additional information related to sample collection.

Activin Receptor IIB ligands and other exploratory biomarkers

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

Serum will be collected at baseline, D169, D337 and EOT for possible measurements of SARS-CoV-2 serology (anti-SARS-CoV-2 IgG or total antibody).

6.8 Patient Reported Outcomes

The European Organization for Research and Treatment of Cancer Quality-of-Life questionnaire (EORTC QLQ-C30) (Aaronson, 1993) (APPENDIX G) is a validated HRQoL measure applicable to subjects with any cancer diagnosis. It is composed of 30 items that address general physical symptoms, physical functioning, fatigue and malaise, and social and emotional functioning. Subscale scores are transformed to a 0 to 100 scale, with higher scores on functional scales

indicating better function and higher score on symptom scales indicating worse symptoms. The EORTC QLQ-C30 is available in many languages. This instrument takes 10 to 15 minutes to administer.

The Functional Assessment of Cancer Therapy-Anemia Version 4 (FACT-An) questionnaire (Yellen, 1997) (APPENDIX H) is a validated instrument specific in measuring HRQoL related anemia. The 47-item FACT-An scale measures cancer-related symptoms with 13 items that measure fatigue (the FACIT-Fatigue subscale) and an additional 7 items that measure items pertinent to anemia. The 47-item FACT-An scale is formatted for self-administration on one page, and uses a 5-point Likert-type scale (0 = Not at all; 1 = A little bit; 2 = Somewhat; 3 = Quite a bit; and 4 = Very Much). As each items of the FACT-An scale ranges from 0-4, and to obtain the score each negatively-worded item response is recoded so that 0 is consider worse quality of life and 4 is good response. The FACT-An is available in many languages and this instrument takes no more than 15 minutes to administer.

The Quality of Life in Myelodysplasia Scale (QUALMS) (Abel, 2016) is a novel QoL tool with a 38-item assessment for patients with MDS (APPENDIX I). To score the QUALMS, each question (all have 5-point Likert-type answers) were assigned a value with a potential range of 0 (worst) to 100 (best) as follows: Never = 100; Rarely = 75; Sometimes = 50; Often = 25 and Always = 0. Four items were scored in the opposite direction such that Always = 100 and Never = 0. The QUALMS total score was calculated by averaging the scores, so the potential range of scores was 0 (worst) to 100 (best). Higher scores mean better QoL. Recognizing the value of the QUALMS and its limitation, QUALMS - Physical Burden (QUALMS-P), a 14-item subscale focused on physical factors (which had excellent internal consistency and performed well, distinguishing between clinical known groups), will be implemented on a limited basis as an exploratory endpoint. QUALMS-P will be measured at Screening and the 24-Week MDS Assessment Visit in countries where the tool has been linguistically and culturally validated. The instrument is available in several languages and takes about 10 minutes to administer.

The Patient Treatment Satisfaction Survey (APPENDIX J) is designed to understand overall MDS treatment satisfaction. The survey composed of 3 questions that measure patients' transfusion burden, treatment satisfaction and ease of administration. The survey will be analyzed by descriptive statistics.

All eligible subjects will complete the EORTC QLQ-C30, FACT-An, QUALMS-P and the Patient Treatment Satisfaction Survey at the frequency noted in the Table of Events (Table 3).

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

It is important that every subject completes all of the EORTC QLQ-C30, FACT-An, QUALMS-P and Patient Treatment Satisfaction Survey assessments at every specified time point to minimize the amount of missing data.

6.9 Healthcare Resource Utilization

The economic objective of this study is to characterize certain aspects of medical resource utilization among subjects treated with luspatercept as compared to subjects receiving epoetin alfa

treatment. To facilitate this aim, certain medical resource utilization data will be collected. Information on hospitalizations will be collected utilizing a case report form designed for this purpose that collects information on reason for hospitalization (eg, disease progression, MDS-related illness, treatment-related adverse event), and days of hospitalization by treatment setting (regular hospital ward versus intensive care unit). Other disease- and treatment-related forms of healthcare utilization will be collected through routine study activities. These may include RBC transfusions, emergency room visits, or significant diagnostic procedures. Additionally, information on concomitant medications (eg, antibiotics, antiviral medications, iron chelation therapies) and resource use associated with treatment administration for MDS will be collected (Table 3).

7 DESCRIPTION OF STUDY TREATMENTS

7.1 Description of Investigational Products

7.1.1 Luspatercept

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] 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.

7.1.2 Epoetin Alfa

Epoetin alfa (either EPREX®/ERYPO® [ex-US] or PROCRIT® [US]) will be centrally supplied or obtained according to local clinical study agreement and in accordance with local guidelines on a per country basis. Please refer to local epoetin alfa prescribing information for more details on available formulations (pre-filled syringes or vials), preparation, storage conditions, the approved indications, known precautions, warnings, and adverse reactions of epoetin alfa (see current version of Prescribing Information). The epoetin alfa dosing schedule and dose adjustments to be followed for this study are described in Section 7.2.2.

7.2 Treatment Administration and Schedule

7.2.1 Luspatercept Treatment

7.2.1.1 Luspatercept Administration and Schedule

Luspatercept will be administered as a subcutaneous injection every 3 weeks (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 7.2.1.2.

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.

The clinical site staff must also confirm (and document in the subject's source record) if any transfusions were received by the subject (including any transfusions received at institutions outside of the study site 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 patient.

7.2.1.2 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). If the Hgb levels are within 10 g/dL to 12 g/dL (6.2 mmol/L to 7.5 mmol/L) due to the influence of transfusions, the dose may still be adjusted (please consider the other three criteria noted below).
- Subject Hgb level increase compared to the Hgb sample taken prior to the previous luspatercept dose is ≤ 1 g/dL (0.6 mmol/L). If the Hgb level increase is > 1 g/dL due to the influence of transfusions, the dose may still be adjusted.
- 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[k])	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
> 2 dose reductions due to suspected related AE[a]	Discontinue treatment
ΔHgb > 2.0 g/dL (1.2 mmol/L) (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 (7.5 mmol/L)	Dose delay until Hgb < 11.0 g/dL (6.8 mmol/L)[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) **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) **OR** WBC remain above upper limit of normal[e]

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[k])	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]
Leukopenia, Neutropenia and/or Thrombocytopenia A worsening by ≥ 2 grades[i] leukopenia, neutropenia and/or thrombocytopenia to ≥ Grade 3 during treatment with luspatercept without any other likely cause (eg, infectious event, trauma, etc.). **Worsening of Anemia** A ≥ 50% increase in transfusion burden from baseline in combination with an unexplained worsening from baseline of ≥ 2 grades[i] leukopenia, neutropenia and/or thrombocytopenia.	Dose delay[c] and repeat WBC, neutrophils and platelet counts weekly **for two consecutive weeks** • If WBC, neutrophils and platelet counts improve to baseline or ≤ Grade 1, resume treatment at the same/decreased dose. • If WBC, neutrophils and platelet counts do **not** improve as defined above, collect bone marrow and peripheral blood samples to assess MDS disease status. – If disease progression per IWG response criteria for altering natural history of MDS (Cheson, 2006) is confirmed, discontinue treatment – If disease progression per IWG response criteria for altering natural history of MDS (Cheson, 2006) is **not** confirmed, discuss future dosing with Medical Monitor

Abbreviations: AE = adverse event; CBC = complete blood count; CTCAE = Common Terminology Criteria for Adverse Events; Hgb = hemoglobin; IP = investigational product; IWG = International Working Group; MDS = myelodysplastic syndromes; RBC = red blood cell; WBC = white blood cell count.

[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, 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] Thrombocytopenia, leukopenia, and neutropenia toxicity grades as defined by CTCAE criteria.

[k] 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.

7.2.2 Epoetin Alfa Treatment

7.2.2.1 Epoetin Alfa Administration and Schedule

Epoetin alfa (EPREX®/ERYPO® or PROCRIT®) will be administered as a subcutaneous injection once every week (7 days; QW) at a starting dose of 450 IU/kg (maximum total starting dose is 40,000 IU). Doses may be titrated up starting at dosing visit W7D1 (ie, Dose 7) as described in Section 7.2.2.2. Individual epoetin alfa doses according to body weight will be rounded: up to the next 2,000 IU dose level for Starting Dose Level and Dose Level -1; and up to the next 4,000 IU for Dose Level +1 and Dose Level +2 for doses exceeding a calculated dosing of 56,000 IU according to body weight (maximum total dose is 80,000 IU).

As epoetin alfa is dosed according to body weight, subject weight will be assessed at every third epoetin alfa dosing visit (ie, W1D1, W4D1, W7D1, etc.) and in the event of a dose delay at restart of treatment. Changes of body weight of ≤ ± 5% do not require a dose adjustment.

Epoetin alfa will be administered as a subcutaneous injection by the site staff. Starting with the W7D1 Visit, site visits for IP administration are only required every third dose (ie, W10D1, W13D1, W16D1, etc.) and self-administration or administration by a nursing service is permitted between dosing site visits at the discretion of the investigator (ie, W8D1 and W9D1; W11D1 and W12D1, etc.) if in line with local practice. In the event dose adjustments of epoetin alfa are required, dosing should occur at the clinical site only until the dose adjustment process has been completed.

Administration of IP will be documented in the subject's source record. Compliance of self-administration of epoetin alfa will be monitored via the use of a medication diary card or other local procedures in place at the investigational site.

Subjects must have hemoglobin and blood pressure assessed prior to each IP administration when administered at the clinical site.

In addition, the clinical site staff must also confirm (and document in the subject's source record) if any transfusions were received by the subject (including any transfusions received at institutions outside of the study site 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 patient.

7.2.2.2 Epoetin Alfa Dose Adjustment and 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 the W7D1 dosing visit (ie, Dose 7) of epoetin alfa and assessed by the investigator, subjects may have the dose level increased in a stepwise manner beyond the starting dose of 450 IU/kg to 787.5 IU/kg and 1,050 IU/kg (total dose 80,000 IU). Dose increases and decreases should be done one dosing level at a time Table 6). A minimum of 4 weeks should elapse between dose increases.

Dose delay and/or reduction or discontinuation may be required due to increased Hgb or adverse events. For details on dose modification guidance for epoetin alfa please refer to Table 7.

Table 6: Epoetin Alfa Starting Dose Level with Dose Reductions and Dose Titration

Dose Level -1	Starting Dose Level	Dose Level +1	Dose Level +2
337.5 IU/kg (maximum total dose 40,000 IU)	450 IU/kg (maximum total dose 40,000 IU)	787.5 IU/kg (maximum total dose 80,000 IU)	1,050 IU/kg (maximum total dose 80,000 IU)

Individual epoetin alfa doses according to body weight will be rounded: up to the next 2,000 IU dose level for Starting Dose Level and Dose Level -1; and up to the next 4,000 IU for Dose Level +1 and Dose Level +2 for doses exceeding a calculated dosing of 56,000 IU according to body weight.

Table 7: Epoetin Alfa 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[k])	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 6.
> 2 dose reductions due to suspected related AE[a]	Discontinue treatment.
ΔHgb > 2.0 g/dL (1.2 mmol/L) over 4 weeks (not influenced by RBC transfusions[d])	Consider dose decrease by one dose level according to Table 6.
Predose Hgb ≥ 12.0 g/dL (7.5 mmol/L)	Dose delay until Hgb < 11.0 g/dL (6.8 mmol/L)[d]. Restart on same dose level or reduce by one dose level according to Table 6 (investigator judgement).
Loss of response or Hgb drop ≥ 1 g/dL (0.6 mmol/L) upon dose reduction	Increase by one dose level according to Table 6. A minimum of 4 weeks should elapse between dose increases.
≥ 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)[i]	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

Table 7: Epoetin Alfa 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[k])	Action
	If WBC remains above upper limit of normal[e] for ≥ 2 consecutive weeks in absence of an associated condition (eg, infection or concomitant corticosteroid use); continue dose delay and collect bone marrow/peripheral blood samples to assess MDS disease status. Treatment may be resumed if: Absence of disease progression per IWG response criteria for altering natural history of MDS (Cheson, 2006) AND WBC values return below upper limit of normal Discontinue treatment if: Disease progression per IWG response criteria for altering natural history of MDS (Cheson, 2006) OR WBC remain above upper limit of normal[e]
Presence of ≥ 1% blasts in peripheral blood[i] (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 epoetin alfa administration. – If presence of ≥ 1% blasts in peripheral blood; discontinue treatment[h]

Abbreviations: AE = adverse event; CBC = complete blood count; Hgb = hemoglobin; IP = investigational product; IWG = International Working Group; MDS = myelodysplastic syndromes; RBC = red blood cell; WBC = white blood cell count.

[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, 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] Mandatory assessment only at 3-weekly visits (W4D1, W7D1, W10D1, etc.)

[k] 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

7.2.3.1 Luspatercept 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.

7.2.3.2 Epoetin Alfa Overdose

On a per dose basis, an overdose for epoetin alfa is defined as the following amount over the protocol-specified dose (applying the rounding rules as specified in Section 7.2.2.1) of epoetin alfa 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 treatment assignment (randomization) 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 randomized by a central randomization procedure 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 randomize 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.

The relationship of the randomization number to the subject identification (ID) number will be described by a randomization algorithm. The randomization algorithm will be employed by the IRT system to assign a subject to a treatment based on the prespecified rules, such as open-label study, stratified randomization with randomization ratio active versus comparator on a 1:1. Subjects will be placed into the appropriate stratum per the responses/data entered/collected for questions collecting stratification factors and based on the combination of these data points, the IRT will place the subject in the next available slot within the appropriate stratum for that subject. The IRT will be utilized to ensure an equal weight central randomization based on randomization method according to stratification factors defined in Section 3.1. The randomization number corresponds to a particular treatment arm within a stratum.

7.4 Packaging and Labeling

Where centrally supplied, 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 local 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.

For luspatercept and epoetin alfa vials (PROCRIT® [US]), unless otherwise notified, all vials, both used and unused, should be saved for drug accountability purposes. The used vials may be discarded, per the institution's standard operating procedures, after drug accountability has been completed by the monitor. For epoetin alfa prefilled syringes (EPREX®/ERYPO® [ex-US]), only unused IP must be saved for drug accountability purposes as used syringes must be discarded in sharp containers, unless otherwise notified.

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 on the luspatercept arm is therefore unnecessary.

Epoetin alfa may also be self-administered by the subject at certain timepoints if certain requirements are met as further detailed Section 7.2.2.1. Compliance of self-administration of epoetin alfa will be monitored via the use of a medication diary card or other local procedures in place at the investigational site.

The investigator or designee is responsible for accounting for all IP (luspatercept and epoetin alfa) 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 randomization until 42 days after the last dose of IP, must be reported on the eCRF. All prior procedures within the 8 weeks prior to randomization as well as concomitant procedures will be recorded on the appropriate eCRF. All transfusions will be reported on the eCRF for at least 16 weeks prior to randomization until 8 weeks after last dose of IP or the EOT Visit, whichever occurs later.

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

Prior iron chelation therapy 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 Investigator's Brochure and/or local 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.

Each subject will have a "pre-transfusion hemoglobin threshold" for requiring a transfusion during the study which will be determined based on transfusion history. Baseline pre-transfusion hemoglobin threshold will be the mean of all documented pre-transfusion hemoglobin values during the 8 weeks prior to the first dose of IP. During treatment, if the pre-transfusion hemoglobin level is increased by ≥ 1 g/dL (0.6 mmol/L) (at the time of a next anticipated transfusion event) compared to the pre-transfusion hemoglobin threshold for that subject, transfusion should be delayed by a minimum of 7 days. Subjects may be transfused at the investigator's discretion for symptoms related to anemia or other requirements (eg, infection).

8.1.2 Iron Chelation Therapy

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

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

8.1.3 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 randomization. Use of topical steroids is permitted. Occasional use of corticosteroids before transfusions to prevent allergic reactions is permitted.

8.1.4 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.

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.

8.1.5 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:

- Erythropoietin stimulating agents (ESAs) other than assigned IP and other RBC hematopoietic growth factors (eg, Interleukin-3)
- Granulocyte colony stimulating factors (ie, G-CSF, GM-CSF), except in cases of neutropenic fever.
- Cytotoxic, chemotherapeutic, targeted or investigational agents/therapies
- Azacitidine, decitabine or other hypomethylating agents
- Lenalidomide, thalidomide and other immunomodulating drugs (IMiDs)
- Hydroxyurea
- Androgens, unless to treat hypogonadism
- Oral retinoids (topical retinoids are permitted)
- Arsenic trioxide
- Interferon and interleukins

8.3 Required Concomitant Medications and Procedures

Not applicable.

9 STATISTICAL CONSIDERATIONS

9.1 Overview

This is a Phase 3, multicenter, randomized, open-label, active-controlled study. The primary objective of the study is to evaluate efficacy in the two treatment arms, luspatercept compared with epoetin alfa, for the treatment of anemia due to IPSS-R very low, low, or intermediate risk MDS in ESA naïve subjects who require RBC transfusions.

The final analysis will be performed when all randomized 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 last dose (whichever occurs later) during the Post-treatment Follow-up Period of the study.

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 randomized subjects regardless of whether or not the subject received IP.

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

HRQoL evaluable population: The HRQoL evaluable population will consist of all subjects in the ITT population who completed the respective patient reported outcomes (PRO) assessment[3] at baseline and at least one post-baseline assessment visit.

PK population: The PK population will consist of all subjects who received at least one dose of luspatercept and had measurable luspatercept serum concentrations.

Statistical methods to handle missing data will be described in the statistical analysis plan (SAP). The SAP will describe any predefined rules for including/excluding any subjects with data from any analyses (eg, time windows, visit by visit analysis, endpoint analysis, protocol violation).

9.3 Sample Size and Power Considerations

A total sample size of approximately 350 subjects (175 in the experimental arm [luspatercept (ACE-536)], 175 in the control arm [epoetin alfa]) will have 90% power to detect the difference between a RBC-TI (for 12 weeks associated with a concurrent hemoglobin increase) response rate of 36% in the experimental arm (luspatercept [ACE-536]) and a response rate of 20% in the control arm (epoetin alfa), with the first interim analysis on futility only when about 105 subjects have completed 24 weeks of treatment, or discontinued before reaching 24 weeks of treatment (30% information for primary endpoint). The Lan-DeMets (O'Brien-Fleming) spending function will

[3] Instrument-dependent.

be used as the futility boundary. The sample size calculation is based on one-sided alpha of 0.025, test statistics on odds ratio of proportions using the EAST® Version 6.4 software system.

A second interim analysis to test the superiority of the luspatercept arm does not alter the above sample size calculation. The study power remains at 90% for the final analysis with 350 subjects and the Lan-DeMets spending function of the O'Brien-Fleming type will be used to control the overall one-sided Type I error rate at 0.025.

9.4 Randomization and Stratification

Subjects will be randomized to receive luspatercept or epoetin alfa at a 1:1 ratio.

Randomization will be accomplished by an IRT to ensure timely registration and randomization. A stratified randomization schedule will be implemented. Randomization will be stratified by baseline RBC transfusion burden, RS status, and endogenous serum erythropoietin (sEPO) level at baseline:

- RBC transfusion burden at baseline
  - < 4 pRBC units/8 weeks
  - ≥ 4 pRBC units/8 weeks
- Ring sideroblast (RS) status at baseline (with RS+ defined as ring sideroblasts ≥ 15% of erythroid precursors in bone marrow or ≥ 5% (but < 15%) if SF3B1 mutation is present).
  - RS+
  - RS-
- Endogenous Serum Erythropoietin (sEPO) level at baseline.
  - ≤ 200 U/L
  - > 200 U/L

9.5 Background and Demographic Characteristics

Subjects' age, height, weight, and baseline characteristics will be summarized using descriptive statistics, while gender, race and other categorical variables will be provided using frequency tabulations by treatment arm. Prior transfusion history will be summarized. Medical history data will be summarized using frequency tabulations by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Myelodysplastic syndrome (MDS) diagnoses as well as RBC transfusion dependence will be summarized using frequency tabulations.

9.6 Subject Disposition

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

9.7 Efficacy Analysis

9.7.1 Primary Efficacy Analysis

The primary efficacy analysis will be the comparison of the response rates in the two treatment arms in the ITT population. The primary efficacy endpoint of RBC transfusion independence for 12 weeks with an associated concurrent mean increase of ≥ 1.5 g/dL Hgb increase, is defined as the absence of any RBC transfusion for any 12-week period from Week 1 to the end of Week 24 associated with a concurrent mean increase of hemoglobin of at least ≥ 1.5 g/dL compared to baseline.

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

$$H_0 : P_1 \leq P_2$$

$$H_a : P_1 > P_2$$

where P_1 denotes the true response rate in the luspatercept group, and P_2 denotes the true response rate in the epoetin alfa group. The number and percentage of subjects in the ITT population who achieve the response will be presented by treatment group. The Cochran–Mantel–Haenszel (CMH) test will be used to test the difference between the two response rates with randomization factors as strata. The one-sided significance level at the final analysis will be 0.021 with one planned interim analysis for superiority.

Additional details will be outlined in the SAP.

9.7.2 Secondary Efficacy Analyses

The secondary efficacy endpoints will be analyzed and reported at the time of the analysis of the primary efficacy endpoints.

Secondary endpoints will be analyzed descriptively, unless otherwise specified, and will be based on the ITT population. Kaplan-Meier methods will be used to estimate curves for time to event secondary variables. Count, percentages, and 95% confidence interval will be used to describe categorical secondary variables.

Gate-keeping method will be used to control the overall Type I error rate for the following secondary endpoints in the order of:

- HI-E response (Week 1 to 24)
- RBC-TI for 24 weeks (Week 1 to 24)
- RBC-TI ≥ 12 weeks (Week 1 to 24)

After the result from the primary efficacy endpoint shows statistical significance, RBC-TI for 24 weeks in Week 1 to 24 will be tested for significance at the one-sided significance level of 0.021 only if both primary endpoint and HI-E response in Week 1 to 24 are significant. RBC-TI ≥ 12 weeks in Week 1 to 24 will be tested for significance at the one-sided significance level of

0.021 only if the results for primary endpoint, HI-E in Week 1 to 24, and RBC-TI for 24 weeks in Week 1 to 24 are all significant. The testing procedure above will be implemented strictly in order to control the overall one-sided Type I error rate of 0.025 due to multiplicity.

Other secondary endpoints will be analyzed without employing methods for controlling the type one error rate. Any statistically significant treatment effect on these secondary endpoints cannot be interpreted as confirmatory, but rather informatory.

RBC transfusion independence (RBC-TI) for 24 weeks is defined as the absence of any RBC transfusion from Week 1 to the end of Week 24. Subjects discontinued from the Treatment Phase prior to finishing Week 24 will be counted as non-responders.

Mean hemoglobin change over 24 weeks is defined as the mean hemoglobin change over the 24-week period of Week 1 through Week 24 compared to baseline

Hematologic improvement – erythroid response (HI-E) per IWG (Cheson, 2006**)** is defined as proportion of subjects meeting HI-E criteria sustained over any consecutive 56-day period over the first 24 weeks from Week 1. Subjects discontinued from the Treatment Period without achieving HI-E will be counted as non-responders.

Time to HI-E will be summarized only for subjects who achieve HI-E response. It is defined as time from Week 1 to first onset of achieving HI-E. It will be summarized only for subjects who achieve HI-E within the first 24 weeks from Week 1.

RBC-TI for ≥ 12 weeks (84 days) is defined as the proportion of subjects achieving RBC-TI for ≥ 84 days during any consecutive 84-day period from Week 1 through Week 24.

Duration of RBC-TI ≥ 12 weeks (84 days) is defined as the longest RBC-TI period for subjects who achieve RBC-TI ≥ 12 weeks from Week 1 through Week 24. Subjects who maintain RBC-TI through the end of the Treatment Period or at the time of analysis will be censored at the date of treatment discontinuation, date of analysis or death, whichever occurs first.

Time to RBC-TI ≥ 12 weeks (84 days) will be summarized only for subjects who achieve RBC-TI ≥ 84 days from Week 1 through Week 24. It is defined as the time between Week 1 and the date onset of TI is first observed (ie, Day 1 of 84 days without any RBC transfusions).

Time to first RBC transfusion is defined as time from Week 1 to first RBC transfusion on treatment. Subjects who maintain RBC-TI 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.

RBC transfusion burden on treatment is defined as total number of pRBC units transfused within the first 24 weeks of treatment since Week 1.

RBC-TI for ≥ 56 days (8 weeks) is defined as the proportion of subjects achieving RBC-TI for ≥ 56 days during any consecutive 56-day period from Week 1 through Week 24.

RBC-TI for a consecutive 24-week period is defined as the proportion of subjects achieving RBC-TI for ≥ 168 days during any consecutive 168-day period from Week 1 through Week 48.

Progression to AML: time to AML progression is defined as the time between randomization and first diagnosis of AML as per WHO classification of ≥ 20% blasts in peripheral blood or bone

marrow. Subjects with diagnosis of AML will be considered to have had an event. Subjects who have not progressed to AML at the time of analysis will be censored at the last assessment date which does not indicate progression to AML.

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

Full analysis details will be included in the SAP.

9.8 Safety Analysis

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

Adverse events will be coded using MedDRA. Adverse event listings will include the verbatim term and the MedDRA preferred term. Treatment-emergent adverse events will be summarized by system organ class and preferred term. Treatment-emergent adverse events leading to death or to discontinuation from treatment, treatment-emergent adverse events (TEAEs) classified as National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (version 4.03) all grades or grade 3/4 TEAEs, related to investigational product, and serious TEAEs will be summarized separately.

Clinical laboratory results will be summarized descriptively by treatment group. Clinically significant hematologic and non-hematologic laboratory abnormalities will be listed and summarized according to the NCI CTCAE (version 4.03) by treatment group.

Physical examination data and vital sign measurements, including body weight, will be listed for each subject at each visit. Descriptive statistics for vital signs, both observed values and changes from baseline, will be summarized by treatment group.

9.9 Interim Analysis

Two interim analyses are planned. The first interim analysis (IA) is for futility and the second IA is for efficacy.

For the first IA, the primary efficacy variable, RBC transfusion independence (12 weeks with a concurrent hemoglobin increase), will be compared between the two treatment arms using the CMH test at approximately 30% information (when approximately 105 subjects have completed 24 weeks of treatment, or discontinued before reaching 24 weeks of treatment). A non-binding β-spending function of the O'Brien-Fleming type will be used to control the Type II error rate with overall one-sided $\beta = 0.10$.

At the first interim analysis, CMH statistic will be calculated and compared with the futility boundary. If the value of the CMH statistics is below the futility boundary, a recommendation to stop the study due to futility can be considered.

Equivalently, the p-value for the one-sided CMH test will be calculated and a recommendation to terminate will be made if the p-value is greater than the futility boundary. The table below gives the nominal p-value for rejecting the alternative hypothesis corresponding to the O'Brien-Fleming boundary. (The interim bound is approximate and will be re-calculated based on the amount of information available when the interim analysis is actually performed.)

Table 8: Futility Interim Boundaries for the first IA

Analysis	Futility Bound (odds ratio)	Reject Alternative Hypothesis if p greater than
Interim (30%)	0.632	0.844

Note: Nominal p-values for futility computed using the program East Version 6.4 (Cytel Statistical Software Company).

Thus, if at the first interim analysis, the p-value is greater than 0.844, then the DMC could consider stopping the trial due to futility.

A second interim analysis is planned to test the superiority of the primary endpoint at about 85% of the information (when approximately 300 subjects have completed 24 weeks of treatment or discontinued before reaching 24 weeks of treatment).

At the second interim analysis, the p-value from the one-sided CMH test for the primary endpoint will be calculated. If the one-sided p-value is less than or equal to 0.015, DMC could recommend that luspatercept is superior to epoetin alfa in terms of the primary endpoint. If the one-sided p-value is greater than 0.015, the study will continue as planned and the p-value from the one-sided CMH test at the final analysis will be compared against the significance level 0.021. The Lan-DeMets spending function of the O'Brien-Fleming type will be used to control the overall one-sided alpha level at 0.025.

At the time of second interim analysis, gate-keeping method will be used to control the Type I error rate for the following secondary endpoints in the order of:

- HI-E response (Week 1 to 24)
- RBC-TI for 24 weeks (Week 1 to 24)
- RBC-TI ≥ 12 weeks (Week 1 to 24)

After the result from the primary efficacy endpoint shows statistical significance at the level of 0.015, RBC-TI for 24 weeks in Week 1 to 24 will be tested for significance at a one-sided significance level of 0.015 only if both the primary endpoint and HI-E response in Week 1 to 24 are significant at the one-sided significance level of 0.015. RBC-TI ≥ 12 weeks in Week 1 to 24 will be tested for significance only if the results for primary endpoint, HI-E in Week 1 to 24, and RBC-TI for 24 weeks in Week 1 to 24 are all significant at the one-sided significance level of 0.015. The testing procedure above will be implemented strictly in order to control the overall one-sided Type I error rate of 0.015 at the interim analysis due to multiplicity.

Other secondary endpoints will be analyzed without employing methods for controlling the Type I error rate. Any statistically significant treatment effect on these secondary endpoints cannot be interpreted as confirmatory, but rather informatory.

The table below summarizes alpha spent at each analysis. Note that the actual alpha level used at the second interim analysis will be determined based on the actual information fraction (percent of subjects who have completed 24 weeks of treatment or discontinued before reaching 24 weeks of treatment) at the second interim analysis.

Table 9: Summary of Alpha Spending

Analysis	Enrollment	One-sided alpha	Endpoint Assessment
Futility Interim	30% information for primary endpoint (105 subjects)	N/A	Efficacy not tested
Superiority Interim	85% information for primary endpoint (300 subjects)	0.015	Testing in order of: Primary endpoint HI-E response (Week 1 to 24) RBC-TI for 24 weeks (Week 1 to 24) RBC-TI ≥ 12 weeks (Week 1 to 24)
Superiority Final	100% information for primary endpoint (350 subjects)	0.021	Testing in order of: Primary endpoint HI-E response (Week 1 to 24) RBC-TI for 24 weeks (Week 1 to 24) RBC-TI ≥ 12 weeks (Week 1 to 24)

Abbreviations: HI-E = Hematologic improvement – erythroid response; N/A = not applicable: RBC-TI = Red blood cell transfusion independence

9.10 Other Topics

9.10.1 Health-related Quality-of-life Assessment

The effect of luspatercept and epoetin alfa on patients' HRQoL based on EORTC QLQ-C30, FACT-An, QUALMS-P and the Patient Treatment Satisfaction Survey will be assessed. The intent is to summarize the descriptive statistics of observed score at each visit and change from baseline at each post-baseline visit for all domains of the QLQ-C30 and FACT-An, QUALMS-P for each treatment group. Within-treatment and between-treatment differences will be examined using a 1-sample, 2-sided t-test and a pooled 2-sample, 2-sided t-test, respectively. However, these t-tests will be descriptive (ie, non-inferential) in nature.

In addition, the least square (LS) mean (95% confidence interval [CI] and p-value) for change from baseline at each post-baseline visit for all domains within each treatment group, and the difference in the LS means (95% CI, p-value) between treatment groups at each post-baseline visit, will be

estimated using the analysis of covariance (ANCOVA) model adjusting for baseline domain scores and stratification factors (ie, transfusion burden, RS status and sEPO level) where appropriate. Various schemes will be assessed for missing data imputation. Full details will be included in an HRQoL SAP.

9.10.2 Healthcare Resource Utilization

Characterization of certain medical resource utilization among subjects treated with luspatercept as compared to subjects receiving epoetin alfa. Examples of relevant healthcare resource utilization include hospitalizations, prior concomitant therapies and surgeries, as well as RBC transfusion utilization. Data for the analysis of healthcare resource utilization will be sourced both from specific report forms or through routine study data collection.

Full details will be included in the SAP.

9.10.3 Pharmacokinetic Analysis

Population PK analysis will be performed using nonlinear mixed effect modeling. Concentration data obtained from this study and other studies may be combined to develop a population PK model that describes the PK exposure data and the associated variability. Subject-specific factors (demographics, baseline characteristics, markers for organ function, ADA against luspatercept, etc.) will be explored as covariates for their potential to influence luspatercept PK parameters. Empiric individual Bayesian estimates of PK parameters will be generated using the final population PK model and appropriate measures of luspatercept exposure (area under the concentration-time curve [AUC], maximum plasma concentration of drug [Cmax], or other exposure metrics of interest) will be computed for each subject. The relationship between serum luspatercept exposure and the primary efficacy endpoint, AEs of interest, or other selected secondary endpoints will be explored as appropriate.

Full details will be included in the PK/Pharmacodynamic (PD) Data Analysis Plan.

9.10.4 Data Monitoring Committee

An external, independent DMC will be comprised of experts in MDS not involved in the ACE-536-MDS-002 study, and an independent Statistician, and may include additional ad hoc members. Representatives of the sponsor may attend the open session of DMC meeting but will not be present during the closed sessions of DMC meetings.

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

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

9.10.5 Steering Committee

A SC will be established by charter for this study. The Steering Committee will be comprised of study investigators, sponsor representatives, and may include additional ad hoc members. The SC will serve in an advisory capacity to the sponsor. Operational details for the SC will be detailed in a separate SC charter.

Note: The SC is separate from the DMC.

9.10.6 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 test will be applied for these parameters if applicable. Full details will be included in the SAP.

9.10.7 Subgroup Analysis

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

10 ADVERSE EVENTS

10.1 Monitoring, Recording and Reporting of Adverse Events

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

Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose eCRF (See Section 7.2.3 for the definition of overdose). Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE on the AE eCRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE eCRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and eCRF but should not be reported as an SAE itself.

In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary.

- Luspatercept: 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 hemoglobin levels occur.
- Epoetin alfa: The therapeutic margin of epoetin alfa is very wide. Overdosage of epoetin alfa may produce effects that are extensions of the pharmacological effects of the hormone. Phlebotomy may be performed if excessively high hemoglobin levels occur. Additional supportive care should be provided as necessary.

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

All AEs will be recorded by the investigator from the time the subject signs informed consent until 42 days after the last dose of IP as well as those SAEs made known to the investigator at any time thereafter that are suspected of being related to IP. Adverse events (AEs) and SAEs will be recorded on the AE page of the eCRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours of the investigator's knowledge of the event by facsimile, or other appropriate method.

10.2 Evaluation of Adverse Events

A qualified investigator will evaluate all adverse events as to:

10.2.1 Seriousness

An SAE is any AE occurring at any dose that:

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

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

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

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

- emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

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

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

10.2.2 Severity/Intensity

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

The severity/intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of the Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0); http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ ctc.htm# ctc _40

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/SAE as Not Suspected or Suspected as defined below:

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

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

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

10.2.4 Duration

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

10.2.5 Action Taken

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

10.2.6 Outcome

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

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered (returned to baseline 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 on the AE page/screen of the eCRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

10.4 Pregnancy

All pregnancies or suspected pregnancies occurring in either a female subject of childbearing potential or 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 by facsimile, or other appropriate method, within 24 hours of the investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

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

10.4.2 Male Subjects

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

10.5 Other Malignancies/Pre-malignancies

Events of new malignancy, pre-malignant lesions (excluding benign tumors or benign neoplasia) are to be reported to Celgene Drug Safety within 24 hours of the investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. All SAE criteria (eg, hospitalization) should be marked if applicable, and all events must be marked as an "Important Medical Event" even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the CRF and subject's source documents. Documentation related to the diagnosis of malignancy must be provided at the time of reporting as a serious adverse event (eg, any confirmatory histology or cytology results, X-rays, 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 criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the eCRF. All SAEs must be reported to Celgene Drug Safety within 24 hours of the investigator's knowledge of the event by facsimile, or other appropriate method (eg, via email), using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent until 42 days after the last dose of IP) or any SAE

made known to the investigator at any time thereafter that are suspected of being related to IP. Serious adverse events occurring prior to treatment (after signing the ICF) will be captured.

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

Where required by local legislation, the investigator is responsible for informing the Institutional Review Board/Ethics Committee (IRB/EC) of the SAE and providing them with all relevant initial and follow-up information about the event. The investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

10.6.1 Safety Queries

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

10.7 Expedited Reporting of Adverse Events

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

In the United States, expedited reports sent to the Food and Drug Administration (FDA) by the sponsor based on the reasonable possibility threshold are known as 'Investigational New Drug (IND) safety reports' and will be reported in accordance with 21 CFR 312.32.

For reporting to the FDA, events that are not suspected to be causally related to luspatercept by the sponsor will not be considered adverse reactions. As per FDA regulations, events that are anticipated in the study population, as detailed in the IB, will not be considered adverse reactions on individual assessment and will be reviewed on an aggregate basis for assessment of frequency.

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

For the purpose of regulatory reporting in the EEA, Celgene Drug Safety will determine the expectedness of events suspected of being related to the other IP, epoetin alfa, based on the UK Summary of Product Characteristics (SmPC).

In addition, if requested, any report of progression to high risk MDS or AML in both the luspatercept and epoetin alfa arm, regardless of causality, will be reported as an expedited safety report to individual health authorities.

Celgene or its authorized representative shall notify the investigator of the following information (In Japan, Celgene KK shall notify the heads of the institutes in addition to the investigators):

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

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

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

Celgene Drug Safety Contact Information:

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

10.8 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(s):

- 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 7.2.1.2 and Section 7.2.2.2 for luspatercept and epoetin alfa, respectively.
- Disease Progression as per IWG criteria for altering natural history of MDS (Cheson, 2006) (APPENDIX D)
  - For subjects with 5-10% 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
- 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 an open-label study; therefore, IP will be identified on the package labeling.

13 REGULATORY CONSIDERATIONS

13.1 Good Clinical Practice

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

13.2 Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for 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 five (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 will include on-site visits with the investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, investigational product storage area, eCRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative in accordance with the Study Monitoring Plan.

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

15.2 Audits and Inspections

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

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

15.3 Product Quality Complaint

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

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

16 PUBLICATIONS

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

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

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

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

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18 APPENDICES

APPENDIX A TABLE OF ABBREVIATIONS

Table 10: 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
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the concentration-time curve
β-hCG	β-subunit of human chorionic gonadotropin
BM	Bone marrow
BMA	Bone marrow aspirate
BMB	Bone marrow biopsy
BMP6	Bone morphogenetic protein 6
BMP9	Bone morphogenetic protein 9
BSC	Best supportive care
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of Federal Regulation
CI	Confidence interval
C_{max}	Maximum plasma concentration of drug
CMH	Cochran–Mantel–Haenszel
CMML	Chronic myelomonocytic leukemia
COVID-19	Coronavirus disease 2019
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DAR	Darbepoetin
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee

Table 10: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
DNA	Deoxyribonucleic acid
DVT	Deep venous thrombosis
EC	Ethics Committee
ECD	Extracellular domain
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EEA	European Economic Area
eGFR	Estimated glomerular filtration rate
ELN	European Leukemia Net
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire
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
FACT-An	Functional Assessment of Cancer Therapy - Anemia
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
GCP	Good clinical practice
G-CSF	Granulocyte-colony stimulating factor
GDF11	Growth differentiation factor 11
GDF15	Growth differentiation factor 15
GM-CSF	Granulocyte-macrophage colony-stimulating factor
Hep	Hepatitis
Hgb	Hemoglobin
HI-E	Hematologic improvement – erythroid response
HIV	Human immunodeficiency virus

Table 10: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
HMA	Hypomethylating agent
HR	Heart rate
HRQoL	Health-related quality-of-life
IA	Interim analysis
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ID	Subject identification
IgG1-Fc	Immunoglobulin G1 - Fragment crystallizable
IMiD	Immune-modulatory drug
IND	Investigational new drug
Int-1	Intermediate-1
IP	Investigational product
IPSS	International prognostic scoring system
IPSS-R	Revised international prognostic scoring system
IRB	Institutional review board
IRT	Integrated response technology
ITT	Intent-to-treat
IU	International unit
IUD	Intrauterine device
IWG	International Working Group
JMML	Juvenile myelomonocytic leukemia
LDH	Lactate dehydrogenase
LS	Least square
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-U	Myelodysplastic syndromes - unclassifiable
MDS/MPN	Myelodysplastic/myeloproliferative neoplasms

Table 10: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
MOA	Mechanism of action
MRP	Mutual recognition procedure
MUGA	Multi-gated acquisition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
nRBC	Nucleated red blood cells
NYHA	New York Heart Association
OR	Odds ratio
OS	Overall survival
PBO	Placebo
PD	Pharmacodynamic
PK	Pharmacokinetics
PQC	Product Quality Complaint
pRBCs	Packed red blood cells
PRCA	Pure red cell aplasia
Q3W	Every 3 weeks
QoL	Quality-of-life
QUALMS	Quality of Life in Myelodysplasia Scale
QUALMS-P	Quality of Life in Myelodysplasia Scale - Physical Burden
QW	Once every week
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

Table 10: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SBP	Systolic blood pressure
sEPO	Endogenous serum erythropoietin
SC	Steering committee
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SmPC	Summary of Product Characteristics
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
TNM	Tumor nodes metastasis
TWSG1	Twisted gastrulation 1
UK	United Kingdom
ULN	Upper limit of normal
US	United States of America
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[a]

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

[a] 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.

[b] Medians, years.

[c] 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 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-002 subject population.

APPENDIX D. INTERNATIONAL WORKING GROUP RESPONSE CRITERIA FOR MYELODYSPLASTIC SYNDROMES (CONT.)

[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 Jul 15;108 (2):419-25.

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

Hgb = hemoglobin; HI-E = hematologic improvement erythroid response; HI-N = hematologic improvement neutrophil response; HI-P = hematologic improvement platelet response; IWG = International Working Group; pRBC = packed red blood cells; RBC = red blood cell.; wk = week.

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

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

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

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

The following **study-specific modifications will be applied**: To accommodate the varying baseline transfusion burden of the ACE-536-MDS-002 subject population HI-E will be defined as follows:

- Subjects with baseline transfusion burden of < 4 pRBC units/8 weeks preceding first dose of investigational product: Hgb increase of ≥ 1.5 g/dL in the absence of transfusions.
- Subjects with baseline transfusion burden of ≥ 4 pRBC units/8 weeks: a relevant reduction of pRBC units by an absolute number of at least 4 pRBC units/8 weeks compared to the baseline transfusion burden in the 8 weeks preceding first dose of investigational product.

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 Jul 15;108 (2):419-25.

APPENDIX E 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 F 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)

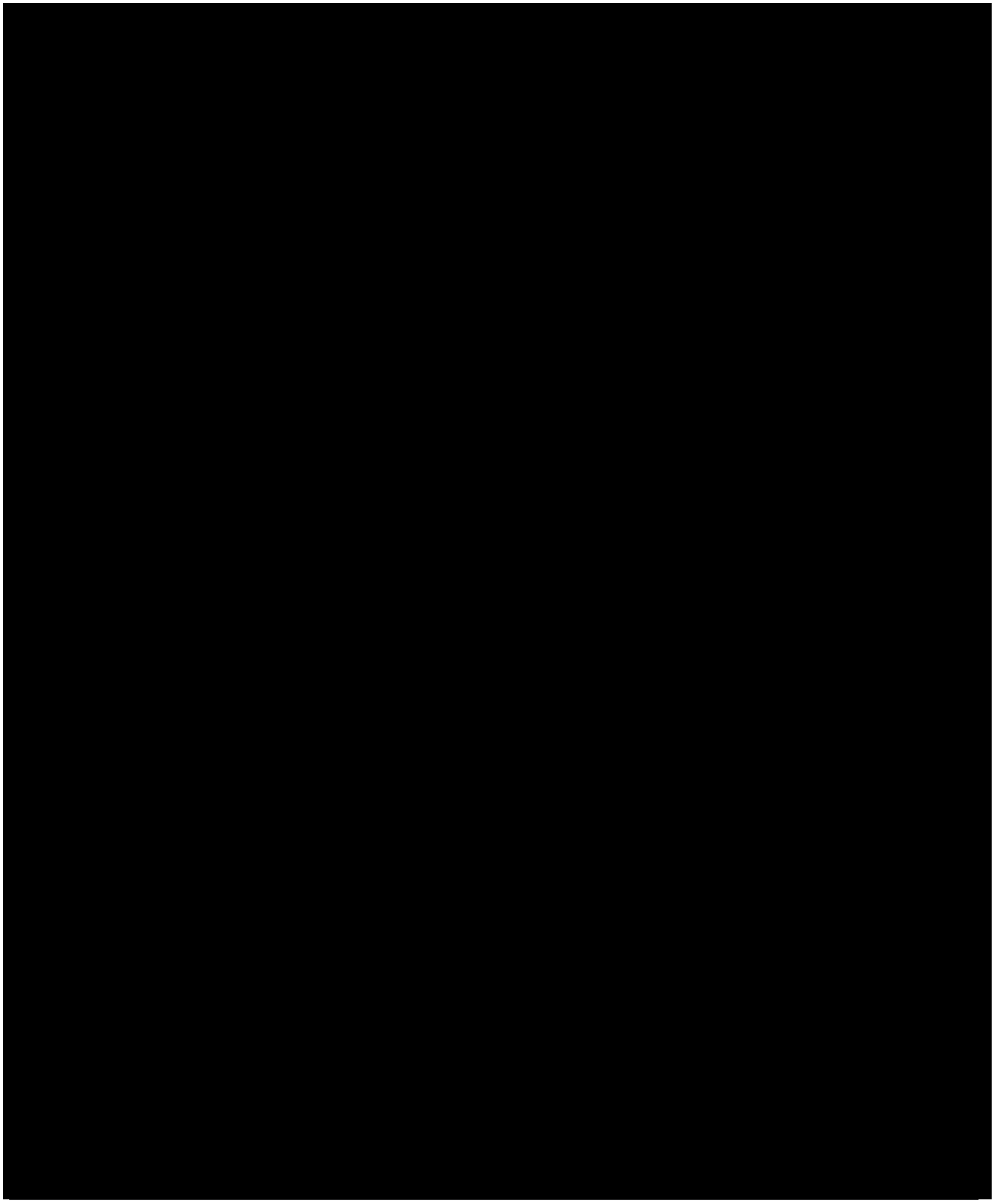
Creatinine levels in µmol/L can be converted to mg/dL by dividing them by 88.4

Source:

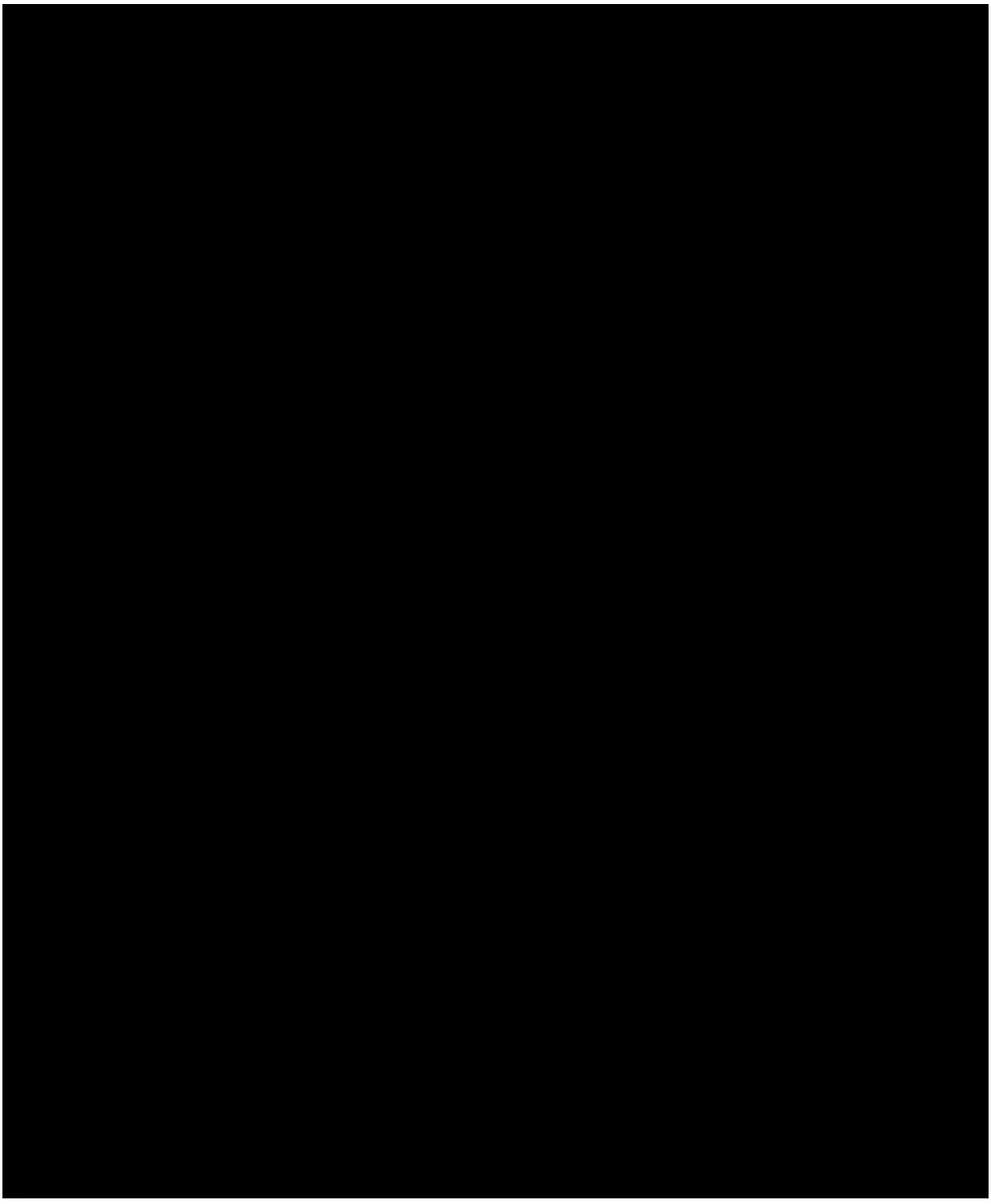
Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.

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.

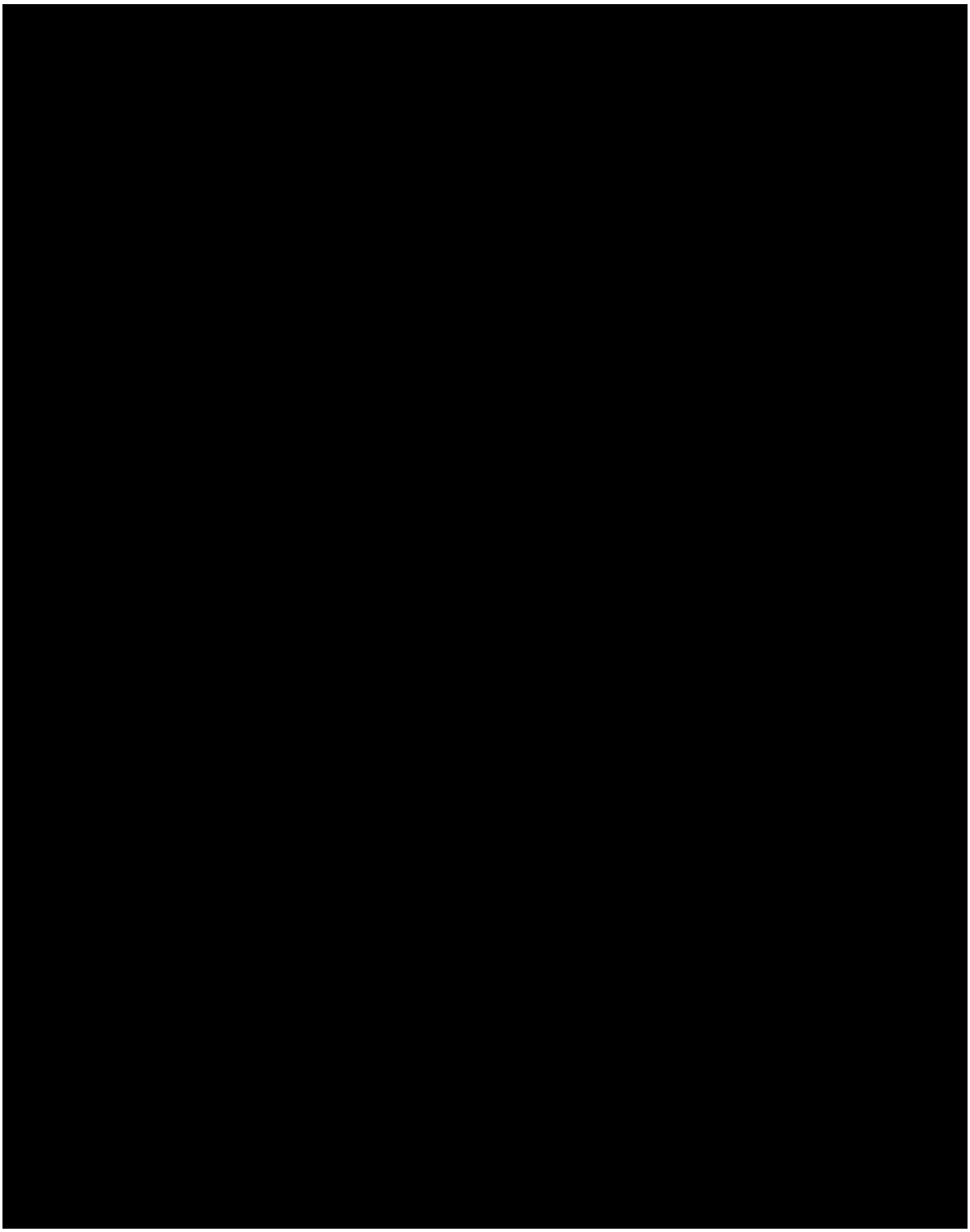
APPENDIX G EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER QUALITY-OF-LIFE QUESTIONNAIRE (VERSION 3.0)



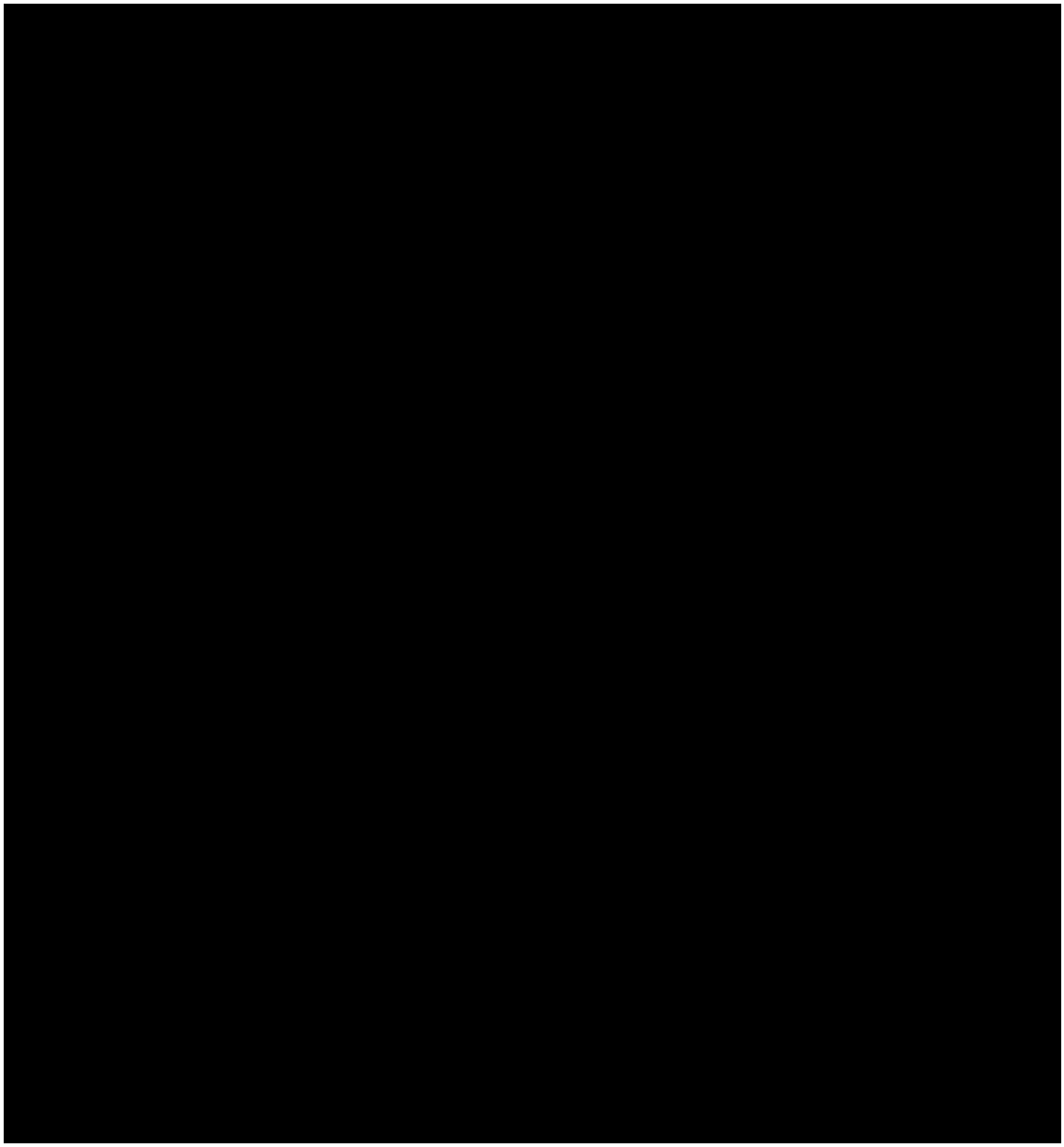
APPENDIX G. EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER QUALITY-OF-LIFE QUESTIONNAIRE (VERSION 3.0) (CONTINUED)



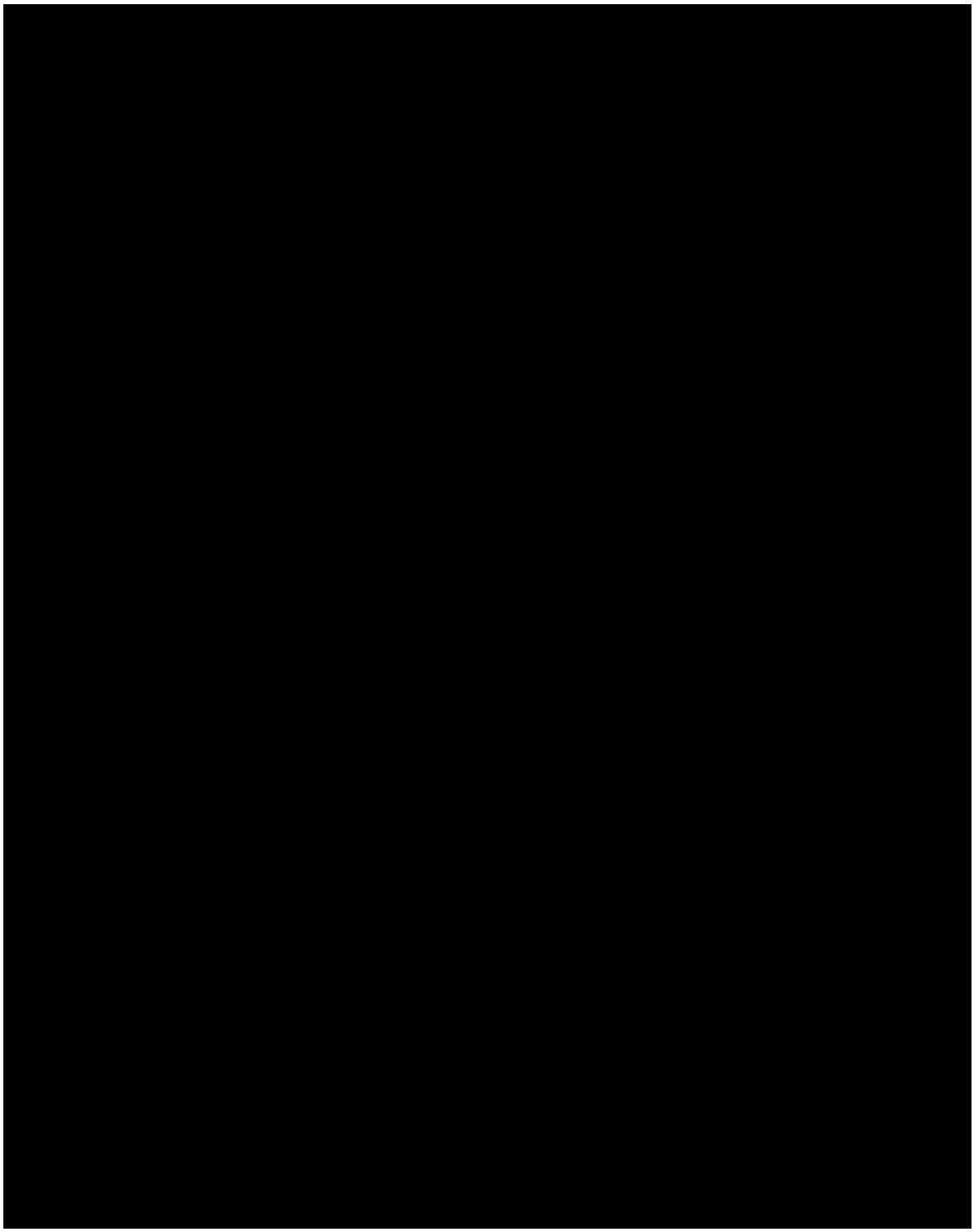
APPENDIX H FUNCTIONAL ASSESSMENT OF CANCER THERAPY-ANEMIA (FACT-AN) QUESTIONNAIRE (VERSION 4.0)



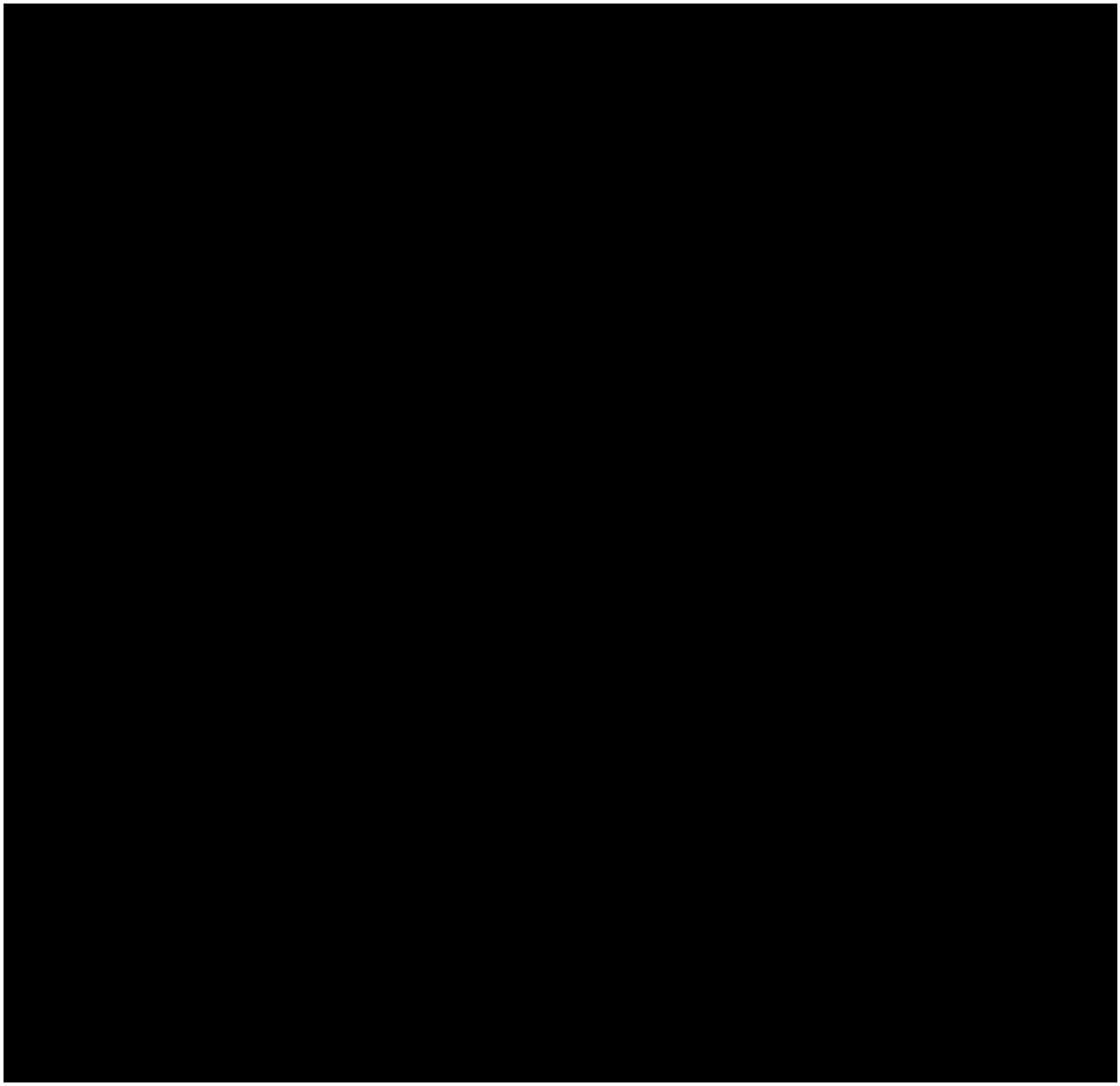
APPENDIX H. FUNCTIONAL ASSESSMENT OF CANCER THERAPY-ANEMIA (FACT-AN) QUESTIONNAIRE (VERSION 4.0) (CONTINUED)



APPENDIX H. FUNCTIONAL ASSESSMENT OF CANCER THERAPY-ANEMIA (FACT-AN) QUESTIONNAIRE (VERSION 4.0) (CONTINUED)



APPENDIX I QUALITY-OF-LIFE IN MYELODYSPLASIA SCALE - PHYSICAL BURDEN (QUALMS-P)



APPENDIX J PATIENT TREATMENT SATISFACTION SURVEY

1. **How burdensome (e.g., inconvenient, worrisome, painful) are the transfusions that you receive for your anemia?**
   - ☐ Not at all
   - ☐ A little
   - ☐ Somewhat
   - ☐ A lot
   - ☐ Extremely
   - ☐ I am not receiving transfusions

2. **In general, how satisfied are you with the study medication that you are receiving for your anemia?**
   - ☐ Very satisfied
   - ☐ Satisfied
   - ☐ Neither satisfied nor dissatisfied
   - ☐ Dissatisfied
   - ☐ Very dissatisfied
   - ☐ Not applicable (I haven't start any treatment yet)

3. **How easy or difficult is it to plan (e.g., administration, schedule) for your anemia treatment?**
   - ☐ Very easy
   - ☐ Easy
   - ☐ Neither easy nor difficult
   - ☐ Difficult
   - ☐ Very Difficult