DISCLOSURE

REDACTED STATISTICAL ANALYSIS PLAN

ACE-536-MDS-001

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

The "MEDALIST" Trial

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STATISTICAL ANALYSIS PLAN

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

STUDY DRUG:	**Luspatercept (ACE-536)**
PROTOCOL NUMBER:	**ACE-536-MDS-001**
DATE FINAL:	**May 31, 2018**

Prepared by:

Celgene Corporation

86 Morris Avenue

Summit, NJ 07901

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SAP VERSION, DATE	Final Draft, 30-May-2018
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PROTOCOL TITLE	A Phase 3, Double-blind, Randomized Study to Compare the Efficacy and Safety of Luspatercept (ACE-536) Versus Placebo for the Treatment of Anemia Due to IPSS-R Very Low, Low, or Intermediate Risk Myelodysplastic Syndromes in Subjects with Ring Sideroblasts Who Require Red Blood Cell Transfusions
INVESTIGATIONAL PRODUCT	Luspatercept (ACE-536)
PROTOCOL NUMBER	ACE-536-MDS-001
PROTOCOL VERSION, DATE	Amendment 2.0, 09-May-2017
SIGNATURE STATEMENT	By my signature, I indicate I have reviewed this SAP and find its contents to be acceptable.

Statistical Therapeutic Area Head

Signature _____

Printed Name PPD

_____ Date _____

Lead Clinical Research Physician / Clinical Research Physician

Signature _____

Printed Name PPD Date _____

Lead Product Safety Physician

Signature _____

Printed Name PPD Date _____

1. LIST OF ABBREVIATIONS

Table 1: Abbreviations and Specialist Terms

ADA	Antidrug antibodies
AE	Adverse event
AML	Acute myelogenous leukemia
ANCOVA	Analysis of covariance
ATC	Anatomical therapeutic chemical
BMA	Bone marrow aspirate
BMB	Bone marrow biopsy
BMI	Body mass index
BSC	Best supportive care
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
CMH	Cochran Mantel Haenszel
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EPO	Erythropoietin
EOT	End of treatment
eCRF	Electronic case report form
ESA	Erythropoiesis-stimulating agents
FCBP	Female of childbearing potential
HI-E	Hematologic improvement-erythroid
HI-N	Hematologic improvement-neutrophils
HI-P	Hematologic improvement-platelets
HIV	Human Immunodeficiency Virus
HRQoL	Health-related quality of life
ICF	Informed consent form
ICT	Iron chelation therapy
IP	Investigational Product
IPSS-R	International Prognostic Scoring System-Revised
ITT	Intent to treat
IVRS	Interactive voice response system
IWG	International Working Group
KM	Kaplan-Meier
MDS	Myelodysplastic syndromes
MedDRA®	Medical Dictionary for Regulatory Activities
mHI-E	Modified hematologic improvement-erythroid
NCI	National Cancer Institute
OS	Overall survival
PK	Pharmacokinetics
PT	Preferred term
QTcF	Heart-rate corrected QT with Fredericia's correction
RBC	Red blood cell
RBC-TI	Red blood cell transfusion independence

RS	Ring Sideroblasts
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis software
SF3B1	Splicing factor 3B subunit 1
SOC	System organ class
SD	Standard deviation
TEAE	Treatment-emergent adverse event
TGF	Transforming growth factor
WBC	White blood cell
WHO	World Health Organization

2. INTRODUCTION

This statistical analysis plan (SAP) describes the analyses and data presentations for Celgene's protocol [ACE-536-MDS-001] "A Phase 3, Double-blind, Randomized Study to Compare the Efficacy and Safety of Luspatercept (ACE-536) Versus Placebo for the Treatment of Anemia Due to IPSS-R Very Low, Low, or Intermediate Risk Myelodysplastic Syndromes in Subjects with Ring Sideroblasts Who Require Red Blood Cell Transfusions". It contains definitions of analysis populations, derived variables and statistical methods for the analysis of efficacy and safety.

These analyses include one interim analysis and one final analysis. Throughout this SAP, the treatment arms will be referred to as luspatercept (ACE-536) and placebo. The purpose of the SAP is to ensure the credibility of the study findings by specifying the statistical approaches to the analysis of study data prior to database lock for the interim/final analysis. This SAP will be finalized and signed prior to the clinical database lock. All statistical analyses detailed in this SAP will be conducted using Statistical Analysis Software (SAS)® Version 9.2 or higher.

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective is to evaluate red blood cell transfusion independence (RBC-TI) of luspatercept compared with placebo for the treatment of anemia due to the revised International Prognostic Scoring System (IPSS-R) very low, low, or intermediate risk Myelodysplastic Syndromes (MDS) in subjects with ring sideroblasts who require RBC transfusions.

3.2. Secondary Objectives

The secondary objectives are as follows:

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

CCI [redacted]

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a Phase 3, double-blind, randomized, placebo-controlled, multicenter study to determine the efficacy and safety of luspatercept (ACE-536) versus placebo for the treatment of anemia due to IPSS-R very low, low, or intermediate risk MDS in subjects with ring sideroblasts who require RBC transfusions. The study will have approximately 210 subjects randomized worldwide (i.e., 78 sites and 11 countries; US, Germany, France, Spain, Italy, UK, Sweden, Turkey, Belgium, Canada, Netherlands).

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

The study design is described in detail in Figure 1.

4.1.1. Screening Period

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

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

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

4.1.2. Randomization

Randomization will occur by a central randomization procedure using integrated response technology (IRT). Eligible subjects will be randomized at a 2:1 ratio of Luspatercept (ACE-536) versus Placebo:

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

OR

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

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

Stratification will be based on the following factors:

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

4.1.3. Double-Blind Treatment Period

Primary Phase: Weeks 1-24

The first dose of investigational product (IP) should be administered no later than 3 days after randomization, and can be on the same day as randomization. Subjects will receive IP (either luspatercept or matching placebo) on Day 1 of each 21-day treatment cycle.

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

Subjects should receive IP through at least the first 24 calendar weeks after the date of first dose unless the subject experiences unacceptable toxicities, withdraws consent, or meets any other treatment discontinuation criteria (Section 6).

Week 25 Visit: MDS Disease Assessment

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

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

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

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

AND

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

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

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

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

Extension Phase of the Treatment Period: After Week 25 Visit

Subjects who meet criteria to remain on double-blind treatment after completion of the Week 25 Visit MDS Disease Assessment may continue dosing on Day 1 of each 21 day treatment cycle in the Extension Phase of the Treatment Period until the subject experiences unacceptable toxicities, disease progression per IWG criteria for altering natural history of MDS (Cheson, 2006; Appendix E), withdraws consent, or meets any other discontinuation criteria (Section 6).

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

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

Serial measurements of safety and efficacy will continue on scheduled study visits (Day 1 of every treatment cycle) in the Extension Phase of the Treatment Period.

Best supportive care may continue to be used in combination with study treatment when clinically indicated per investigator.

The same dose titration, delay and/or reduction, and treatment discontinuation criteria will still apply in the Extension Phase of the Treatment Period (Section 4.2).

All subjects who have received at least one dose of study treatment should undergo end of treatment (EOT) evaluations when IP is discontinued (Section 4.1.7).

4.1.4. Posttreatment Follow-up Period

Safety Follow-up

All subjects discontinued from protocol-prescribed therapy for any reason will be followed for a period of 42 days after the last dose of IP for AE reporting, as well as SAEs made known to the Investigator at any time thereafter that are suspected of being related to IP. Females of childbearing potential should avoid becoming pregnant for 12 weeks after the last dose of IP and males will be advised to use a male latex condom or nonlatex condom NOT made out of natural (animal) membrane (for example, polyurethane), during any sexual contact with FCBP prior to starting investigational product and continue for 12 weeks following the last dose of IP, even if he has undergone a successful vasectomy.

Long-Term Follow-up

Transfusion data collection will continue up until 16 weeks from the date of last dose of IP.

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

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

4.1.5. Study Duration for Subjects

After a Screening Period of up to 5 weeks, eligible subjects who are randomized to receive IP (either placebo or luspatercept) should continue double-blind treatment through at least the first 24 calendar weeks of the study unless the subject experiences unacceptable toxicities, disease progression per IWG response criteria for altering natural history of MDS (Cheson, 2006; Appendix E), withdraws consent, or meets any other discontinuation criteria (Section 6).

Subjects who meet protocol defined criteria as determined by the Week 25 Visit MDS Disease Assessment may continue double-blind treatment beyond the Week 25 Visit (i.e. in the Extension Phase of the Treatment Period) until the subject experiences unacceptable toxicities,

disease progression per IWG criteria for altering natural history of MDS (Cheson, 2006; Appendix E), withdraws consent, or meets any other discontinuation criteria (Section 6).

For all subjects who receive at least one dose of IP, continuation of monitoring for progression to AML and other malignancies/pre-malignancies will occur in the Posttreatment Follow-up Period, along with subsequent MDS therapies, and overall survival for at least 3 years from the date of last dose of IP unless the subject withdraws consent from the study, dies or is lost to follow-up. Subject who receive at least one dose will also be followed for AEs up through 42 days post last dose.

4.1.6. Unscheduled Visits

Should it become necessary to repeat an evaluation (e.g. laboratory tests or vital signs), the results of the repeat evaluation should be entered as an additional unscheduled visit in the electronic case report form (eCRF).

4.1.7. End of Treatment Visits

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

If a subject is discontinued during a regular scheduled visit, all EOT procedures should be completed at that visit. If a procedure had been performed within 7 days of the EOT visit, it does not need to be repeated unless clinically indicated per investigator discretion (with the exception of blood pressure assessment and sample collection for hematology, chemistry, and urinalysis). Bone marrow procedure should only be performed at EOT visit if > 90 days from prior bone marrow procedure. End of Treatment Visit procedures/assessments may occur at 42 Day Follow-up assessment if subject is discontinued within +/- 7 days of 42 Day Follow-up assessment.

4.1.8. End of Trial

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

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

4.1.9. Visit Window

Except for the Week 25 Visit, all study visits during the Treatment Period (both Primary and Extension Phases) must occur within ± 3 days of the scheduled day. A ±14 day window is allowed for the Week 25 Visit. Week 25 Visit and Extension Cycle 1 Visit procedures/assessments may be combined and not need to be repeated if previously performed within ±7 days of the scheduled visit.

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

A window of ± 14 days is allowed for Posttreatment Long-Term Follow- up assessments (i.e. OS, Progression to AML, other malignancies/pre-malignancies, subsequent MDS therapies).

4.2. Treatment Administration and Schedule

4.2.1. Dose Titration Increase

Starting as soon as Cycle 3 Day 1 and assessed by the investigator prior to every subsequent treatment cycle, subjects may have the dose level increased in a stepwise manner beyond the starting dose of 1.0 mg/kg to 1.33 mg/kg, and from 1.33 mg/kg to 1.75 mg/kg, but the maximum total dose should not exceed 168 mg, during both the Primary and Extension Phases of the Treatment Period if all of the following criteria are met:

- Subject has ≥ 1 RBC transfusion event (for pre-transfusion Hgb of ≤ 9.0 g/dL) during the 2 most recent prior treatment cycles (~6 weeks).
- The two most recent prior treatment cycles assessed must be at the same dose level.
- Subject must not have met protocol dose delay and/or reduction criteria in the two most recent treatment cycles (exception of dose delay required due to influence of RBC transfusions). Refer to Table 3, footnote b.

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

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

Starting dose with dose increases and reductions are presented below for reference (Table 2).

Table 2: Starting Dose Level with Dose Reductions and Dose Titration

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

4.2.2. Dose Delay and Dose Reduction

Dose delay and/or reduction or discontinuation may be required due to increased hemoglobin or adverse events in either treatment arm (luspatercept or placebo). Table 3 below provides guidelines for dose modifications and dose delay.

Celgene or its authorized representative should be notified of dose modification or interruption within 24 hours.

Table 3: Dose Modification: Dose Delay, Dose Reduction, and Discontinuation Guidelines

Event at the Day of Dosing (Assessed prior to each IP administration)	Action
Any suspected related AE ≥ Grade 3[a,d]	Dose delay[c] until resolved to ≤ Grade 1 or baseline, and then reduce dose by 25%
≥ 2 dose reductions suspected related AE [a]	Discontinue treatment
ΔHgb ≥ 2.0 g/dL compared to pre-dose Hgb of previous treatment cycle	Reduce dose by 25%[b] if ΔHgb not influenced by RBC transfusions
Predose Hgb ≥11.5 g/dL	Dose delay until Hgb ≤ 11.0 g/dL

≥ 50% increase in white blood cell count (WBC) compared to pre-dose WBC of previous treatment cycle and above upper limit of normal in the absence of an associated condition (e.g. infection or concomitant corticosteroid use)	Dose delay; re-check 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 (e.g. infection or concomitant corticosteroid use); continue dose delay and collect bone marrow/peripheral blood samples to assess MDS disease status. Treatment may be resumed if: Absence of disease progression per IWG response criteria for altering natural history of MDS (Cheson, 2006) AND WBC values return below upper limit of normal[e] Discontinue treatment[f] if: Disease progression per IWG response criteria for altering natural history of MDS (Cheson, 2006; Appendix E) OR WBC remain above upper limit of normal[e]

Table 4: Dose Modification: Dose Delay, Dose Reduction, and Discontinuation Guidelines (Continued)

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

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

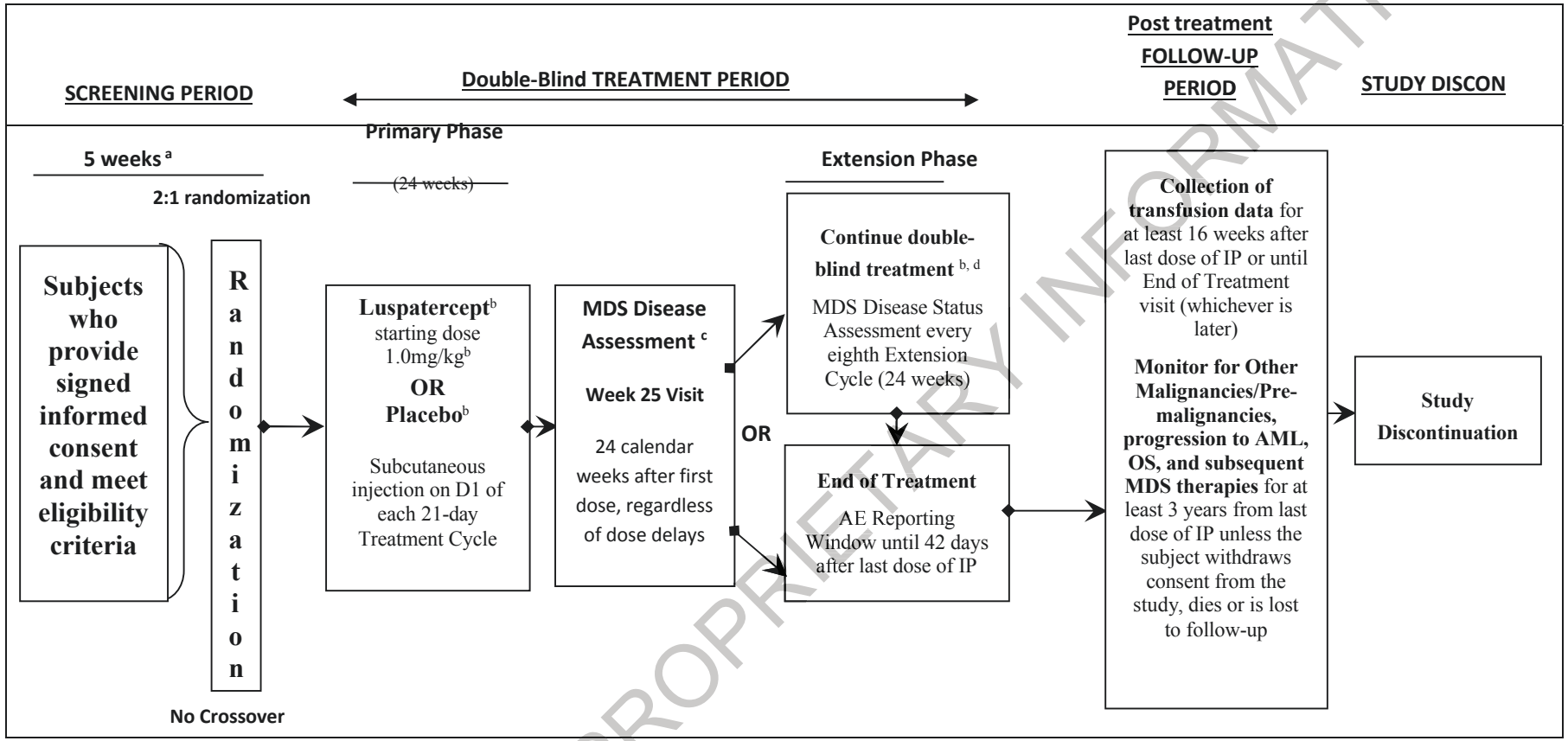
4.2.3. Overdose

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

Subcutaneous 10% over the protocol-specified dose

Hemoglobin and Hematocrit measurements from both central and local lab within 3 weeks past the date of overdose will be listed in a separate listing.

Figure 1: Overall Study Design



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

[b] Dose may be titrated up to a maximum of 1.75 mg/kg.

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

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

Table 5: Table of Events

	Screening	Treatment Period[1]									Posttreatment Follow-up • 42 Day Follow-up = Occurs 42 days after last dose of IP • 12 Week Follow-up = Occurs 12 Weeks after last dose of IP • Long Term Follow-up = Occurs every 3 months after 12 Week Follow-Up until at least 3 years post last dose of IP			
		Primary Phase *First 24 weeks of double-blind treatment* *Up to maximum of 8 Treatment Cycles* *(if no dose delays)*				Week 25[1,2] Visit *24 calendar weeks after first dose regardless of dose delays.*	Extension Phase *Continuation of double-blind treatment beyond Week 25 Visit*			EOT Visit[2]				
	Day -35 to -1	Every Cycle (ie,1,2,3 + up to max 8 cycles Day 1	Every Other Cycle Only) (ie, 1, 3, 5, 7) Day 1	Cycles 1 and 5 Only Day 8	Cycle 1 Only Day 15		Every Ext Cycle 1[2],2,3 + Day 1	Ext Cycle 4, 8, 12+ Day 1	Ext Cycle 8, 16, 24+ Day 1		42 Day Follow-up[2]	12, 24, 48 Week Follow-up	Long Term Follow-up	End of Study
STUDY ENTRY AND GENERAL ASSESSMENTS														
Informed Consent	X	--	--	--	--	--	--	--	--	--	--	--	--	--
Inclusion/Exclusion evaluations	X	--	--	--	--	--	--	--	--	--	--	--	--	--
Physical Examination	X	X				X	X			X				
Randomization[3]	X	--	--	--	--	--	--	--	--	--	--	--	--	--
Demographics	X	--	--	--	--	--	--	--	--	--	--	--	--	--
Medical History	X	--	--	--	--	--	--	--	--	--	--	--	--	--
Prior ESA Therapies	X	--	--	--	--	--	--	--	--	--	--	--	--	--
Prior RBC and Platelet Transfusions[4]	X	--	--	--	--	--	--	--	--	--	--	--	--	--
INVESTIGATIONAL PRODUCT (IP)														
IP Administration and Accountability[15]	--	X[3]	--	--	--	--	X	--	--	--	--	--	--	--

Table 4: Table of Events (Continued)

	Screening	Treatment Period[1]									Posttreatment Follow-up • 42 Day Follow-up = Occurs 42 days after last dose of IP • 12 Week Follow-up = Occurs 12 Weeks after last dose of IP • Long Term Follow-up = Occurs every 3 months after 12 Week Follow-Up until at least 3 years post last dose of IP			
		Primary Phase *First 24 weeks of double-blind treatment* *Up to maximum of 8 Treatment Cycles* *(if no dose delays)*				Week 25[1,2] Visit *24 calendar weeks after first dose regardless of dose delays.*	Extension Phase *Continuation of double-blind treatment beyond Week 25 Visit*			EOT Visit[2]				
	Day -35 to -1	Every Cycle (ie,1,2,3 + up to max 8 cycles Day 1	Every Other Cycle Only) (i.e. 1, 3, 5, 7) Day 1	Cycles 1 and 5 Only Day 8	Cycle 1 Only Day 15		Every Ext Cycle 1[2],2,3 + Day 1	Ext Cycle 4, 8, 12+ Day 1	Ext Cycle 8, 16, 24+ Day 1		42 Day Follow-up[2]	12, 24, 48 Week Follow-up	Long Term Follow-up	End of Study
SAFETY ASSESSMENTS														
ECOG Performance Status	X	X	--	--	--	X	X	--	--	X	--	--	--	--
Urinalysis[5]	X	C1D1 and D1 of every fourth cycle in Primary Phase (e.g. C1, C4, C8)				X	Ext C1D1, then D1 of every fourth Extension cycle until treatment discontinuation			X	--	--	--	--
Coombs' test[6]	X	--	--	--	--	--	--	--	--	--	--	--	--	--
Assessment of HIV/HepB/HepC status[6]	X	--	--	--	--	--	--	--	--	--	--	--	--	--
ECG (12-lead)	X	--	--	C5D8 only	--	--	--	--	--	X	--	--	--	--
Pregnancy Test and Counseling[7]	X	X	--	--	--	X	X	--	--	X	--	--	--	--
Adverse events	Continuous, after signing informed consent until 42 days after last IP administration											--	--	--
Prior and Concomitant medications/procedures	X	Continuous, until 42 days after last IP administration or until the EOT visit, whichever occurs later										--	--	--

Table 4: Table of Events (Continued)

	Screening	Treatment Period[1]									Posttreatment Follow-up • 42 Day Follow-up = Occurs 42 days after last dose of IP • 12 Week Follow-up = Occurs 12 Weeks after last dose of IP • Long Term Follow-up = Occurs every 3 months after 12 Week Follow-Up until at least 3 years post last dose of IP			
		Primary Phase *First 24 weeks of double-blind treatment* *Up to maximum of 8 Treatment Cycles (if no dose delays)*				Week 25[1,2] Visit *24 calendar* weeks *after first dose regardless of dose delays.*	Extension Phase *Continuation of double-blind treatment beyond Week 25 Visit*			EOT Visit[2]				
	Day -35 to -1	Every Cycle (ie,1,2,3 + up to max 8 cycles Day 1	Every Other Cycle Only) (ie, 1, 3, 5, 7) Day 1	Cycles 1 and 5 Only Day 8	Cycle 1 Only Day 15		Every Ext Cycle 1[2],2,3+ Day 1	Ext Cycle 4, 8, 12+ Day 1	Ext Cycle 8, 16, 24+ Day 1		42 Day Follow-up[2]	12, 24, 48 Week Follow-up	Long Term Follow-up	End of Study
Vital Signs (Height to be measured only at screening; Weight to be measured only at screening and prior to each IP administration)	X	X	--	X	X	X	X	--	--	X	--	--	--	--
Serum Chemistry[8]	X	X	--	--	--	X	X	--	--	X	--	--	--	--
EFFICACY ASSESSMENTS														
Hematology[9, 15]	X	X	--	X	X	X	X	--	--	X	--	--	--	--
Serum EPO	X[10]	--	X	--	--	X	--	--	--	X	--	--	--	--
Serum Ferritin	X[11]	X[11]	--	--	--	X	--	X	--	X	--	--	--	--
Transfusion Data Collection and Assessment	Assess and record on ongoing basis (prior to each dose of IP) until 16 weeks after last dose of IP or the End of Treatment Visit, whichever occurs later. Clinical site staff should confirm if any transfusions were received by the subject (including any at outside local institutions in between study visits) prior to each IP administration via use of patient diary or other local procedure in place at the investigational site.													--
MDS Disease Assessment[12]	--	--	--	--	--	X	--	--	X	X	--	--	--	--

Table 4: Table of Events (Continued)

	Screening	Treatment Period[1]								Posttreatment Follow-up • 42 Day Follow-up = Occurs 42 days after last dose of IP • 12 Week Follow-up = Occurs 12 Weeks after last dose of IP • Long Term Follow-up = Occurs every 3 months after 12 Week Follow-Up until at least 3 years post last dose of IP			
		Primary Phase *First 24 weeks of double-blind treatment* *Up to maximum of 8 Treatment Cycles* *(if no dose delays)*				Week 25[1,2] Visit *24 calendar* weeks *after first dose regardless of dose delays.*	Extension Phase *Continuation of double-blind treatment beyond Week 25 Visit*			EOT Visit[2]				
	Day -35 to -1	Every Cycle (ie,1,2,3 + up to max 8 cycles Day 1 | Every Other Cycle Only) (ie, 1, 3, 5, 7) Day 1	Cycles 1 and 5 Only Day 8	Cycle 1 Only Day 15		Every Ext Cycle 1[2],2,3 + Day 1	Ext Cycle 4, 8, 12+ Day 1	Ext Cycle 8, 16, 24+ Day 1		42 Day Follow-up[2]	12, 24, 48 Week Follow-up	Long Term Follow-up	End of Study
Bone Marrow Aspirate (BMA) and Peripheral Blood for cytomorphology and cytogenetic testing[13]	BM Biopsy and Aspirate Required	--	--	--	--	X	--	--	X	X	--	--	--	--
CCI [redacted]														

Table 4: Table of Events (Continued)

	Screening	Treatment Period[1]								EOT Visit[2]	Posttreatment Follow-up • 42 Day Follow-up = Occurs 42 days after last dose of IP • 12 Week Follow-up = Occurs 12 Weeks after last dose of IP • Long Term Follow-up = Occurs every 3 months after 12 Week Follow-Up until at least 3 years post last dose of IP			
		Primary Phase *First 24 weeks of double-blind treatment Up to maximum of 8 Treatment Cycles (if no dose delays)*				Week 25[1,2] Visit *24 calendar weeks after first dose regardless of dose delays.*	Extension Phase *Continuation of double-blind treatment beyond Week 25 Visit*							
	Day -35 to -1	Every Cycle (ie,1,2,3 + up to max 8 cycles Day 1	Every Other Cycle Only) (ie, 1, 3, 5, 7) Day 1	Cycles 1 and 5 Only Day 8	Cycle 1 Only Day 15		Every Ext Cycle 1[2],2,3 + Day 1	Ext Cycle 4, 8, 12+ Day 1	Ext Cycle 8, 16, 24+ Day 1		42 Day Follow-up[2]	12, 24, 48 Week Follow-up	Long Term Follow-up	End of Study
PK and ADA														
PK Sample Collection	--	C1,2,4, 6,8 Only	--	X	X	X	Extension C4D1 and D1 of every 4th Extension Cycle thereafter (e.g. Ext. C4, C8, etc.) for up to one year from the first dose in the Primary Treatment Phase.			X[18]	--	X[18]	--	--
ADA Sample Collection	--	C1,2,4, 6,8 Only	--	--	--	X	Extension C4D1 and D1 of every 4th Extension Cycle thereafter (eg, Ext. C4, C8, C12 C16+, etc.) for up to one year from the first dose in the Primary Treatment Phase.			X[18]	--	X[18]		
QUALITY OF LIFE														
EORTC QLQ-C30 CCI Questionnaire Completion	X	--	X[16]	--	--	X	Day 1 of Every Other Ext. Cycle (Ext. C1,C3, C5+, etc.)			X	--	--	--	--
CCI														

Table 4: Table of Events (Continued)

	Screening	Treatment Period[1]								EOT Visit[2]	Posttreatment Follow-up • 42 Day Follow-up = Occurs 42 days after last dose of IP • 12 Week Follow-up = Occurs 12 Weeks after last dose of IP • Long Term Follow-up = Occurs every 3 months after 12 Week Follow-Up until at least 3 years post last dose of IP			
		Primary Phase *First 24 weeks of double-blind treatment* *Up to maximum of 8 Treatment Cycles* *(if no dose delays)*				Week 25[1,2] Visit *24 calendar* weeks *after first dose regardless of dose delays.*	Extension Phase *Continuation of double-blind treatment beyond Week 25 Visit*							
	Day -35 to -1	Every Cycle (ie,1,2,3 + up to max 8 cycles Day 1	Every Other Cycle Only) (ie, 1, 3, 5, 7) Day 1	Cycles 1 and 5 Only Day 8	Cycle 1 Only Day 15		Every Ext Cycle 1[2],2,3 + Day 1	Ext Cycle 4, 8, 12+ Day 1	Ext Cycle 8, 16, 24+ Day 1		42 Day Follow-up[2]	12, 24, 48 Week Follow-up	Long Term Follow-up	End of Study
FOLLOW UP														
Monitoring for progression to AML and other malignancies/pre-malignancies [17] (Refer to Section 10.5 for details)	After signing ICF and until at least 3 years post last dose of IP or until death, lost to follow-up, withdrawal of consent for further data collection.													
Posttreatment MDS therapies[17]	--	--	--	--	--	--	--	--	--	--	--	X	X	X	X
Survival Follow-up[17]	--	--	--	--	--	--	--	--	--	--	--	X	X	X	X

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

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

[3] Randomization via IRT. The first dose of IP should be administered after, but within 3 days of randomization and can be on the same day as randomization. Refer to the IRT manual for additional information on randomization utilizing IRT. Documentation must be complete to confirm an average RBC transfusion requirement of at least 2 units of packed red blood cells (pRBCs) per 8 weeks during the 16 weeks immediately preceding randomization. Hemoglobin levels at the time of or within 7 days prior to administration of a RBC transfusion must have been ≤ 10.0 g/dL in order for the transfusion to be counted towards meeting eligibility criteria. Red blood cell transfusions administered when Hgb levels were > 10.0 g/dL and/or RBC transfusions administered for elective surgery will not qualify as a required transfusion for the purpose of meeting eligibility criteria. There must also not be any consecutive 56-day period that was RBC transfusion free during the 16 weeks immediately preceding randomization. [4] Subjects

must have at least 16 weeks documented transfusion history prior to randomization. This transfusion data includes hemoglobin measured prior to transfusion (pretransfusion Hgb). [5]Urinalysis assessed centrally and to include microscopic, quantitative analysis of urine. (e.g. microalbumin/albumin, protein, creatinine, microalbumin/creatinine ratio).

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

[7] Pregnancy test is required for all female subjects of childbearing potential. Serum beta human chorionic gonadotropin (β-hCG) will be performed at screening. A urine (or serum) pregnancy test will be repeated prior to the first administration of IP on C1D1, unless the screening pregnancy test was done within 72 hours of C1D1. During the Treatment Period, urine or serum pregnancy test is allowed. For males and FCBP, counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted prior to each IP administration or on a monthly basis (e.g. in the event of dose delays). [8] Serum chemistry (eg, sodium, potassium, chloride, bicarbonate [if available], calcium, magnesium, phosphorus, blood urea nitrogen [BUN], creatinine, creatinine clearance and/or estimated glomerular filtration rate, glucose, albumin, total protein, alkaline phosphatase, direct/indirect total bilirubin, AST/SGOT or ALT/SGPT, lactate dehydrogenase [LDH], uric acid) will be analyzed by the central laboratory.

[9] Hematology assessment (eg, red blood cell [RBC] count, complete blood count [CBC], white blood cell [WBC] with differential, hemoglobin, hematocrit, nucleated red blood cells [nRBC], absolute reticulocyte count, platelet count, mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], and red blood cell distribution width [RDW]) will be tested by the central laboratory. [10] EPO will be assessed centrally. During the Screening Period, the serum EPO level should be collected on the same day as a planned RBC transfusion, prior to the transfusion or 7 days after any RBC transfusion due to possible reduction of the serum level related to the hemoglobin level achieved after the last transfusion.

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

[12] During the Treatment Period, MDS Disease Assessment (which includes investigator assessment of clinical benefit and MDS disease status) should be completed by the investigator in conjunction with bone marrow/peripheral blood sample collection for cytomorphology and cytogenetics collected at the Week 25 Visit. Based on the outcome of the MDS Disease Assessment, subjects will either be discontinued from treatment with IP and enter the Posttreatment Follow-Up Period or continue double-blind treatment with IP in the Extension Phase of the Treatment Period. [13] During the Screening Period, bone marrow biopsy AND bone marrow aspirate are required. The screening BMB should be performed within 5 weeks prior to randomization. The screening BMA should be collected within the protocol screening window. After randomization, a bone marrow biopsy is collected only when adequate aspirate is not attainable. During the Extension Phase of the Treatment Period: Bone marrow and peripheral blood samples to be collected at Extension Cycle 8, Day 1 and Day 1 of every eighth Extension Cycle thereafter (ie, Extension Cycle 8, 16, 24+, etc. or approximately every 24 weeks in the event of dose delays). Bone marrow samples at End of Treatment Visit: Perform only if visit is > 90 days from prior bone marrow procedure. Refer to central laboratory manual for additional information related to sample collection

[redacted]

[15] On dosing days, local laboratory sample should be collected and Hgb levels assessed prior to each IP administration to ensure dose modification rules are followed as outlined in Section 4.2.2, Table 3. In these circumstances, a split sample should also be collected and sent to the central laboratory for analysis. Subjects must have blood pressure assessed prior to each IP administration.

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

[17] Long-Term Posttreatment Follow-up for Overall Survival (OS), Progression to AML, other malignancies/pre-malignancies, data collection for subsequent MDS therapies may be conducted by record review (including public records if allowed by local regulations) and/or telephone contact with the subject, family, or the subject's treating physician. The investigator must make every effort to obtain information regarding the subject's survival status before determining the subject is lost to follow-up.

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

4.3. Study Endpoints

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

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

Endpoint	Name	Description	Timeframe
CCI			

4.4. Blinding

The study is a double blind study where all subjects, study site staff and Celgene Corporation representatives with the exception of designated individuals (e.g. the pharmacist at the investigational site, the bioanalytical laboratory), will remain blinded to all treatment assignments until all subjects have completed the study, or at the time the study is unblinded (per DMC recommendation) and the database is locked.

4.5. Sample Size Determination

A total sample size of 210 (140 in experimental arm [luspatercept (ACE-536)], 70 in control arm [placebo]) will have 90% power to detect the difference between a response (RBC-TI ≥ 8 weeks Week 1 through Week 24) rate of 0.30 in the experimental arm (luspatercept [ACE-536]) and a response rate of 0.10 in the control arm (placebo). The sample size calculation is based on one-sided alpha of 0.025, test statistics on difference of proportions using pooled estimate of variance and 10% dropout rate.

5. GENERAL STATISTICAL CONSIDERATIONS

5.1. Reporting Conventions

Summary tables, listings, and any supportive SAS output will include a "footer" of explanatory notes that will indicate, at a minimum, the following:

- Program source (e.g., SAS program name, including the path, that generates the output) and
- Data extraction date (e.g., the database lock date, run date)

The purpose of the data extraction date is to link the output to a final database, either active or archived, that is write-protected for replication and future reference. An output date will also appear on each output page and will indicate the date the output was generated by the analysis program. Individual source listings will display all the relative values supporting corresponding tables and figures.

The day of the first dose of IP will be defined as Day 1. Baseline value will be defined as the last value measured on or before the date and time of the first dose of IP, unless otherwise specified; if multiple values are present for the same date, but time values taken on that date are not recorded on the eCRF , the average of these values will be used as the baseline, unless otherwise specified below. For subjects who were not treated, the baseline will be the assessment value taken on the visit of Cycle 1 Day 1 if available; otherwise, the value on or prior to randomization date will be used.

For efficacy analysis, the following definitions will be implemented for baseline Hgb, Epo, and platelete:

Since the Hgb value can be influenced by a RBC transfusion, the Hgb values used in efficacy analyses are required to satisfy the 14/3-day rule below:

- 14/3-day rule: Only Hgb values that are at least 14 days after a transfusion may be used unless there is another transfusion within 3 days after the Hgb assessment. If this occurs, the second Hgb value may be used (despite being < 14 days after the previous transfusion). The rationale is that the Hgb value < 14 days from the first transfusion was only somewhat influenced by that transfusion.

In efficacy analyses, after applying above 14/3-day rule, the baseline Hgb value is defined as the lowest Hgb value from the central, local laboratory, or pre-transfusion Hgb from transfusion records that is within 35 days on or prior to the first dose of IP if it is available.

Erythropoietin value can also be influenced by a RBC transfusion. Baseline EPO is defined as the highest EPO value within 35 days of the first dose of IP.

Baseline platelet is defined as the lowest platelet value within 35 days of the first dose of IP.

Summary statistics for continuous variables include sample size (n), mean, standard deviation (SD), median, minimum, the 25th (Q1) and 75th (Q3) percentiles, and maximum. All mean and median values will be formatted to one more decimal place than the measured value. SD values

will be formatted to two more decimal places than the measured value. Minimum and maximum values will be presented to the same number of decimal places as the measured value. Frequency summary for categorical variables includes number and percentage. All percentages will be rounded to one decimal place. Number and percentage values will be presented as xx (xx.x).

Summary statistics for ANCOVA include sample size (n), mean, standard error of the mean, least square mean, standard error of the least square mean, two-sided 95% confidence interval (CI) around least square mean, least square mean difference, standard error of the least square mean difference, two-sided 95% confidence interval (CI) around least square mean difference, and p-value.

All analysis and summary tables will have the population sample size for each treatment group in the column heading.

P-values will be rounded to 4 decimal places. P-values that round to 0.0000 will be presented as '<0.0001' and p-values that round to 1.000 will be presented as '>0.9999'.

All laboratory data will be reported using standard international (SI) units except for hemoglobin. Hemoglobin data will be reported using g/dL.

Subject data listings will be provided to support the tables. Graphs will be provided for the selected parameters.

All subjects will be summarized using dummy treatments in the tables, listings, and figures until study is unblinded. After study is unblinded, they will be summarized by actual treatments.

5.1.1. Dates Handling

Dates will be stored as numeric variables in the SAS analysis files and reported in DDMMMYYYY format (i.e., the Date9. datetime format in SAS). Dates in the clinical database are classified into the categories of procedure dates, log dates, milestone dates, outcome dates, and special dates.

- **Procedure Dates** are the dates on which given protocol-specified procedures are performed. They include the dates of laboratory testing, physical examinations, etc. They should be present whenever data for a protocol-specified procedure is present and should only be missing when a procedure is marked as "NOT DONE" in the database. Procedure dates will not be imputed.
- **Log Dates** are dates recorded in case report form (CRF) data logs. Specifically, they are the start and end dates for adverse events and concomitant medications/procedures. They should not be missing unless an event or medication is marked as *ongoing* in the database. Otherwise, incomplete log dates will be imputed according to the rules in Appendix A (e.g. for duration or cycle assignment etc). However, in listings, log dates will be shown as recorded without imputation.
- **Milestone Dates** are dates of protocol milestones such as randomization, IP start date, study termination, etc. They should not be missing if the milestone occurs for a subject. They will not be imputed.

- **Outcome Dates** are dates corresponding to study endpoints. In most cases they are derived either from a milestone, or a procedure date. They may be subject to endpoint-specific censoring rules if the outcome did not occur, but are not otherwise subject to imputation.
- **Special Dates** cannot be classified in any of the above categories and they include the date of birth. They may be subject to variable-specific censoring and imputation rules.

5.1.2. Calculation Using Dates

Calculations using dates (e.g., subject's age or relative day after the date of randomization) will adhere to the following conventions:

- Study days after the date of first dose of IP will be calculated as the difference between the date of interest and the date of first dose plus 1 day. The generalized calculation algorithm for relative day: Study Day = [(Target Date – Date of First Dose) + 1]. Note that Study Day 1 is the first dose date. Negative and zero study days are reflective of observations obtained during the baseline/screening period. Note: Partial dates for the first dose are not imputed in general. All effort should be tried to avoid incomplete first dose date.
- Age (expressed in days) is calculated: AGE = Informed Consent Date– Date of Birth + 1. In practice, age will be converted to years by dividing the difference by 365.25 days, then truncating to a whole number.
    - Prefer using calculated age from clinical database. When not available, may use calculated age from CRF or IVRS
    - Partial birth date: impute missing day as 15th of the month; impute missing month as July; set missing age for missing year
- Intervals that are presented in weeks will be transformed from days to weeks by using (without truncation) the following conversion formula:

  WEEKS = DAYS /7.
- Intervals that are presented in months will be transformed from days to months by using (without truncation) the following conversion formula:

  MONTHS = DAYS /30.4375.

5.1.3. Calculation of Cycles

The start date of each treatment cycle will be calculated based on IP exposure records for each subject. The start date of the first cycle (C_1) will be the date when the subject receives the first dose of IP.

Once the start dates, e.g., C_1, C_2, C_3… are calculated, the end date of each cycle is calculated as the day before the start date of the following cycle, i.e., $E_i = C_{i+1} - 1$. For the last cycle, the end date will be calculated as the start date plus 20 days, study discontinuation date, or the death date, whichever is earlier. The cycle number for each date of interest, e.g., AE or laboratory test,

will be calculated based on the cycle window set by their start and end dates. If a date is on or after C_i and before C_{i+1}, the corresponding cycle number will be i.

5.2. Analysis Populations

5.2.1. Intent-to-Treat Population

The intent-to-treat (ITT) population will include all subjects who were randomized, regardless of whether or not the subject received IP, or regardless of whether or not the subject met the eligibility criteria. All efficacy analyses will be conducted for the ITT population. Subjects will be analyzed based on randomized treatment group.

5.2.2. Safety Population

The Safety population will include all subjects who were randomized and received at least one dose of IP. The Safety population will be used for all safety analyses. Subjects will be analyzed according to the treatment they actually received.

5.2.3. Health-related QoL Evaluable Population

The HRQoL evaluable population is defined as all subjects in ITT population who completed the EORTC QLQ-C30 assessment at baseline (ie, Cycle 1 Day 1 Visit or Screening Visit if assessment at the Cycle 1 Day 1 Visit was not completed, captured or available) and at least 1 postbaseline assessment visit.

The completion of an HRQoL assessment for the EORTC QLQ-C30 at a given visit is defined as greater than or equal to half of the all items being answered (ie, ≥ 15 items of the 30 items within the EORTC QLQ-C30).

6. SUBJECT DISPOSITION

The number of all screened subjects, the number and percentage of subjects who were randomized and not randomized, the failed inclusion/exclusion criteria for subjects who were screened but not randomized will be included in the summary of screened subjects status. Percentage will be based on all screened subjects.

The number and percentage of analysis population allocation, the subjects who entered (randomized), completed, ongoing, discontinued, and primary reasons for discontinuation will be included in the disposition summary. Percentage will be based on all randomized subjects, i.e. ITT population.

Reasons for treatment discontinuation will be summarized with the following categories:

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

Reasons for study discontinuation will be summarized with the following categories:

- Screen failure
- Death
- Adverse event
- Withdrawal by subject
- Lost to follow up

- Study terminated by sponsor
- Protocol deviation
- Other

Frequency tabulation of subjects enrolled by site, country, and treatment group will be summarized for the ITT population.

A separate listing will be provided for screen failures.

7. PROTOCOL DEVIATIONS/VIOLATIONS

A protocol violation is defined as any departure from the approved protocol that: 1) impacts the safety, rights, and/or welfare of the subject; or 2) negatively impacts the quality or completeness of the data. A protocol deviation is an unplanned excursion from the approved protocol that does not result in harm to the study subjects or significantly affect the scientific validity of study data.

The protocol deviations/violations will be identified and assessed by clinical research physician or designee throughout all study periods.

Number and percentage of subjects with protocol violations will be summarized by protocol violation type and treatment group for the ITT population.

All protocol violations and deviations will be listed for the ITT population.

8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Summaries for the demographics and baseline clinical characteristics will be provided by treatment group for the ITT and Safety population.

8.1. Demographics

Summary statistics will be provided descriptively by treatment group for the following continuous variables:

- Age
- Weight (kg)
- Height (cm)
- Body mass index (BMI; kg/m^2)

Baseline BMI will be calculated as BMI (kg/m^2) = baseline weight (kg) / (height (m))^2. Age will be calculated as discussed in Section 5.1.2. Age recorded from the CRF will be used when date of birth is not available. Other variables will be used as recorded from the CRF.

A frequency summary (number and percentage) will be provided by treatment group for the following categorical variables:

- Age category (≤ 64, 65-74, and ≥75)
- Gender (male, female)
- Weight category (< 70, 70 to < 85, 85 to < 100, ≥ 100 kg)
- BMI category (<20, 20 to <25, 25 to <30, ≥30 kg/m^2)

8.2. Baseline Clinical Characteristics

A frequency summary (number and percentage) will be provided by treatment group for the following categorical baseline characteristics variables:

- ECOG performance status at baseline (Grade 0, 1, or 2, Missing)
- Time since original MDS diagnosis (≤ 2 , 2 to ≤ 5, > 5 years). Time since original MDS diagnosis is defined as the number of months from the date of original diagnosis to the date of informed consent.
- Average baseline RBC transfusion requirements (≥ 6 , < 6, < 4, ≥ 4 and < 6 units/8 weeks)

- Baseline transfusion burden (# of RBC transfusions/ last 8 weeks prior to first dose date; < 4, ≥ 4 and < 6, < 6, ≥ 6 units)
- Baseline transfusion burden (# of RBC transfusions/ 9- 16 weeks prior to first dose date; < 4, ≥ 4 and < 6, < 6, ≥ 6 units)
- Historic Serum Ferritin Results Available within 16 Weeks prior to first dose date
- Splicing factor 3B subunit 1(SF3B1) mutation (mutated vs non-mutated)
- Ring Sideroblasts status (>= 15-50% % vs > 50%)
- Serum EPO (<100, 100-<200, 200-500 and >500 U/L)
- Prior Erythropoiesis-Stimulating Agent
    - Yes vs. No
    - Longest Duration of Prior ESA treatment (< 6, 6 - 12, > 12 - 24, > 24 months)
    - Refractory to prior ESA vs. Intolerant to prior ESA
    - Time from end of prior ESA to start of study, defined as the number of months from the date of the end of prior ESA to the first dose date.
        - < 6 months
        - 6-12 months
        - > 12 – 24 months
        - > 24 months
- Renal status: Creatinine Clearance (CrCL) (40 - <60 vs. ≥60 mL/min)
- Iron Chelation Therapy usage status (Yes vs. No)
- Cardiovascular Comorbidities (*MACE events*)
- Comorbidity score similar to Charlson Comorbidity Index
- Platelets (<100, 100-400, > 400 (10^9/L))
- ANC (0.5 to < 1.0, ≥ 1.0 (10^9/L))
- Prior GCSF/GMCSF usage (Yes vs. No)

8.3. Baseline Hematology Characteristics

Baseline hematology characteristics consist of Hemoglobin, Platelet, and ANC at baseline. All baseline hematology characteristics will be summarized desc riptively.

8.4. MDS Diagnosis History

A frequency summary of MDS diagnoses at original (first) diagnosis will be presented by treatment group for the following categorical variables:

- Baseline MDS World Health Organization (WHO) Classification 2008 from Central Reading (e.g. MDS RARS, MDS RCMD, Other)
- IPSS-R risk at baseline (e.g. Very Low, Low, Intermediate, Missing)

8.5. Prior Transfusion History

A frequency summary of prior transfusion types (i.e., RBC, Platelets, Other) and reasons (i.e. Anemia, Thrombocytopenia, Internal bleeding, Surgery, Infection, Other) will be presented categorically by treatment group.

8.6. Medical History

Medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA; Version TBD). A frequency summary of medical history will be presented by treatment group, system organ class (SOC), and preferred term (PT), with SOCs sorted in alphabetical order and PTs within each SOC in descending order of frequency. Summary table by SOC only will also be provided in descending order of Luspatercept group.

8.7. Prior and Concomitant Medications

8.7.1. Prior Medication

Prior medications are defined as medications that were started before the date of first dose of IP (whether or not ended before the date of first dose of IP). Prior medications that continue into study treatment period will be also reported as concomitant medication.

Prior medications will be coded in the WHO drug dictionary (WHODD; TBD).

Prior medications will be summarized by Anatomical Therapeutic Chemical (ATC) 4 level and preferred term (PT), in alphabetical order for the ATC class, and within each ATC class, in alphabetical order for PTs.

8.7.2. Concomitant Medication

Concomitant medication is defined as medications that were taken from the date of first dose of IP until 42 days after the last dose of IP or End of Treatment (EOT) Visit, whichever occurs later. If a medication is started before the date of first dose of IP and continues on or after the date of first dose of IP, then it will be considered both a prior medication and a concomitant medication.

Concomitant medications will be coded in the WHO drug dictionary (TBD).

The ATC coding scheme of the WHO will be used to group medications into relevant categories. A frequency table by Anatomical Therapeutic Chemical (ATC) class (level 4) and preferred term

will be provided, in alphabetical order for the ATC class, and within each ATC class, in alphabetical order for PTs.

8.8. Concomitant Procedures and Surgeries

Concomitant procedures and surgeries are defined similarly to concomitant medications.

Concomitant procedures and surgeries will be coded according to the MedDRA (Version TBD) and summarized by SOC and PT, with SOCs sorted in alphabetical order and PTs within each SOC in descending order of frequency.

8.9. Coombs' Test

Coombs test results at screening will be provided in a data listing.

8.10. Pregnancy

Pregnancy test results will be provided in a data listing for all female subjects of childbearing potential.

9. STUDY TREATMENTS AND EXTENT OF EXPOSURE

Study treatment and extent of exposure summaries will be provided based on the Safety population.

9.1. Treatment Duration

The treatment duration (weeks) is defined as:

[(the treatment end date) – (the date of the first dose of IP) + 1]/7.

For subjects who discontinued treatment, the end date of the last cycle as defined in Section 5.1.3 will be used as the treatment end date. It is calculated as last IP date plus 20 days, study discontinuation date, or the death date, whichever is earlier. For subjects who are still on treatment at the time of data cutoff, the cutoff date will be used as the treatment end date.

Descriptive statistics will be summarized for treatment duration by treatment group and overall.

9.2. Number of Doses Received

Total number of doses received by subjects will be summarized both descriptively and categorically (1, 2, 3, 4, 5, 6, 7, 8, 9-16, 17-24, 25-36, >36) for the Safety population by treatment group.

Number of doses received at time of completion of Primary Treatment Phase (or discontinued earlier) will be summarized.

9.3. Average Length of Cycle between Doses

The average length of cycle between doses (days) is defined as [(the treatment end date) – (the date of the first dose of IP) + 1]/ the total number of doses received. The treatment end date is defined in Section 9.1.

The average length of cycle between doses (days) will be summarized descriptively by treatment group and overall.

9.4. Cumulative Dose

The cumulative dose (mg) for IP is defined as the sum of all actual dose given during the Treatment Period. Cumulative dose will be summarized descriptively by treatment group and overall.

9.5. Dose Modification

Descriptive statistics will be summarized by treatment group and overall for the following variables:

- Number of subjects who have at least one dose delay,
- Number of subjects with at least one dose reduction
- Reasons for the dose delay (any suspected related AE ≥ grade 3, pre-dose Hb≥11.5 g/dL, other, missing)
- Reasons for the dose reduction (increase in Hgb ≥2.0 g/dL, any suspected related AE ≥ grade 3, other, missing)
- Time to first dose delay (days)
- Time to first dose reduction (days)
- Time to first dose delay due to AE
- Time to first dose reduction due to AE
- Time of first dose delay due to Hgb increase
- Time to first dose reduction due to Hgb

The subjects with dose titration will be summarized by maximum dose level (e.g. 1.0 mg/kg, 1.33 mg/kg, 1.75 mg/kg).

10. PHARMACOKINETIC ANALYSIS

10.1.1. Pharmacokinetic Analysis

Blood samples for PK will be taken at the following visits during the study (see Table 4):

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

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

Luspatercept concentration data will be listed by subject, including arm, treatment period, visit, dose level, dosing date/time, actual sample collection date/time, and actual sample time (day) relative to the first dose.

10.1.2. Anti-Drug Antibodies Analysis

Blood samples will be collected for assessment of ADA against luspatercept in serum in all subjects at the following visits during the study (see Table 4). The maximum ADA monitoring

period will be 1 year from the first dose of the Primary Treatment Phase unless justified by safety reasons:

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

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

  Antidrug antibodies sampling per investigator's or sponsor's discretion is allowed and should be recorded as an unscheduled visit.

The ADA results will be listed by subject, including arm, treatment period, visit, dose level, dosing date/time, actual sample collection date, and actual sample time (day) relative to the first dose.

The number and percentage of the subjects for each ADA test will be presented by treatment group and ADA status. The number and percentage of the subjects and median (range) titer for binding ADA to luspatercept will be presented by treatment group, visit, and ADA status. The Box plot of ADA trend over time may be provided.

The ADA status of a subject during treatment is determined based on the longitudinal ADA results as following:

- Negative: All samples (baseline and post-baseline) are negative.
- Positive to treatment-emergent ADA:
  - At least one post-baseline sample is positive if the baseline sample is negative, or
  - At least one post-baseline sample is positive with a titer ≥ 4-fold of the baseline titer if the baseline sample is positive
- Positive to preexisting ADA:
  - Baseline sample is positive and all post-baseline samples are negative, or
  - Both baseline and post-baseline samples are positive, but all positive post-baseline sample have a titer < 4-fold of the baseline titer.

11. EFFICACY ANALYSIS

All efficacy analyses will be performed on the ITT population, except the analysis of EORTC QLQ-C30 scores that will be performed on the HRQoL evaluable population.

A sequential gate-keeping approach will be used to control the overall type I error rate in order to perform hypothesis testing on multiple endpoints. Two endpoints, the primary efficacy endpoint of RBC transfusion independence (RBC-TI) ≥ 8 weeks and the key secondary endpoint of RBC-TI ≥ 12 weeks (week 1-48 & week 1-24), will be tested sequentially in the pre-specified order. The primary efficacy endpoint will be tested first at the one-sided 0.025 significance level. In order to preserve the overall alpha level at 0.025 across the RBC transfusion independence endpoints, formal statistical inference for the RBC-TI ≥ 12 weeks analysis (first tested for week 1-48, then week 1-24) can only be made if superiority of luspatercept is demonstrated for the primary efficacy endpoint, RBC-TI ≥ 8 weeks, at the one-sided 0.025 significance level.

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

The secondary efficacy variables will be analyzed and reported at the time of the analysis of the primary and key secondary efficacy endpoint.

Subjects will continue to be followed for progression to AML, other malignancies/pre-malignancies, subsequent MDS therapies, and overall survival for at least 3 years from the date of IP last dose unless the subject withdraws consent from the study, dies or is lost to follow-up.

Other than the pre-specified sequential testing of RBC-TI (≥ 8 weeks, then ≥12 weeks), no additional alpha adjustments for multiplicity will be made.

11.1. Determination of Week 24 and Week 48 cutoff date

Week 24:

For subjects who are on treatment at the end of the Primary Phase of the Treatment, a cutoff of first dose of IP + 168 days is used to determine end of week 24.

For subjects who are off treatment, off study, or died prior to the end of week 24, the earliest of the following 4 dates if applicable will be used to determine transfusion independence:

- Last dose date + 20 days
- End of study date
- Death date
- Final analysis cutoff date

Week 48:

For subjects who are on treatment, a cutoff of first dose of IP + 336 days is used to determine end of week 48.

For subjects who are off treatment, off study, or died prior to the end of week 24, the earliest of the following 4 dates if applicable will be used to determine transfusion independence:

- Last dose date + 20 days
- End of study date
- Death date
- Final analysis cutoff date

11.2. Analysis of Primary Efficacy Endpoint

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

Subjects have to have have at least 56 days of transfusion independence prior to (and including) Week 24 cutoff date to quality as a responder. Subjects who failed to achieve at least 56 days prior to or on cutoff date will be counted as non responders.

For the primary efficacy endpoint, 56-day RBC transfusion independence, the response rate will be calculated using the number of responders divided by number of subjects (responders plus non-responders). Subjects discontinued from the Primary Phase of the Treatment Period without achieving at least 56 days consecutive of RBC transfusion independence will be counted as non-responders. The response rates of the subjects who were randomized to luspatercept and the placebo will be calculated. In the primary efficacy analysis, the statistical hypothesis is

$$H_0: P_1 = P_2$$

$$H_a: P_1 > P_2$$

where P_1 denotes the true response rate in the luspatercept group, and P_2 denotes the true response rate in the placebo group.

The number and percentage of subjects who achieve RBC transfusion independence and corresponding 97.5% upper bound confidence intervals (CI) will be tabulated and presented by treatment group. The Cochran–Mantel–Haenszel (CMH) test will be used to test the difference between the two response rates at a one-sided significance level of 0.025, stratifying for average baseline RBC transfusion requirement (≥ 6 units versus < 6 units of RBC per 8 weeks), and baseline IPSS-R score (Very low, or low vs. Intermediate).

The p-value from the stratified Cochran-Mantel-Haenszel (CMH) chi-square test will be the confirmatory p-value for the test of the null hypothesis that the proportion of subjects achieving RBC transfusion independence is equal between the two treatment groups. If the p-value is less

than 0.025, the null hypothesis will be rejected, indicating that the true response rate in the luspatercept group is more than the true response rate in the placebo group. Summaries will include the difference in proportions between the two treatment groups with corresponding two-sided 95% CI and the common odds ratio with corresponding two-sided 95% CI. Subject listings with supporting data will be provided.

11.3. Analyses of Secondary Efficacy Endpoints

To control the overall Type I error rate (alpha), the key secondary endpoints will only be tested if superiority of luspatercept is demonstrated for the primary efficacy endpoint. The primary and key secondary endpoints are the only endpoints that will employ a sequential testing approach.

For other secondary variables, summary of descriptive statistics will be presented to describe continuous secondary variables. Kaplan-Meier methods will be used to estimate curves for time to event secondary variables. Counts and percentage will be used to describe categorical secondary variables.

11.3.1. Key Secondary Efficacy Endpoint

The key secondary endpoint, proportion of subjects achieving RBC-TI with duration ≥ 12 weeks is the absence of any RBC transfusion during any consecutive 84 day period during the Treatment Period (Week 1-48), i.e., days 1 to 84, days 2 to 85, days 3 to 86, etc. Subjects discontinued from the Treatment Period without achieving at least 84 consecutive days of RBC transfusion independence will be counted as non-responders.

Same approach as described in Section 11.1 will be used to assess RBC-TI with duration ≥ 12 weeks. Subjects have to have have at least 84 days of transfusion independence prior to (and including) Week 48 cutoff date to quality as a responder. Subjects who failed to achieve at least 84 days prior to or on cutoff date will be counted as non responders.

The key secondary endpoint will be tested in the same manner as primary efficacy endpoint, at a one-sided 0.025 significance level using the Cochran-Mantel-Haenszel (CMH) test.

11.3.2. Mean Hemoglobin Increase ≥ 1.0 g/dL

Hemoglobin (Hgb) increase ≥ 1.0 g/dL is defined as proportion of subjects with ≥ 1.0 g/dL mean Hgb increase (after applying 14/3 day rule) from baseline that is sustained over any consecutive 56-day period in the absence of RBC transfusions during the Treatment Period (Week 1-24, Week 1-48), in the time frames described in Section 11.1. The number and percentage of subjects achieving Mean Hgb increase ≥ 1.0 g/dL together with 95% CI will be presented by treatment group. The Cochran–Mantel–Haenszel (CMH) test will be used to compare Luspatercept treatment group to placebo group.

11.3.3. Total RBC Units Transfused over 16 Weeks

Total RBC units transfused over 16 weeks is defined as the total number of RBC units transfused over a fixed period of 16 weeks (Week 9-24; Week 33-48) compared to the total number of RBC units transfused in the 16 weeks immediately on or prior to the first dose date.

Total RBC units transfused from Week 9-24 is defined as sum of all transfused RBC units from first IP date + 56 days to first IP date + 168 days. Only subjects who are on treatment till end of week 24 will be included in this analysis. Total RBC units transfused from Week 33-48 is defined as sum of all transfused RBC units from first IP date + 231 days to first IP date + 336 days. This will only be calculated for subjects who are still on treatment at the end of 48 weeks.

Mean change in total number of RBC units transfused over a fixed 16-week period (Week 9-24, Week 33-48) from the total number of RBC units transfused in the 16 weeks immediately on or prior to first IP date will be summarized using descriptive statistics by treatment group. Subgroup analysis might be done to assess transfusion reduction.

11.3.4. Proportion of Subjects Achieving RBC-TI with Duration ≥ 8 Weeks (Week 1 - 48)

Proportion of subjects achieving RBC-TI with duration ≥ 8 weeks is the absence of any RBC transfusion during any consecutive 56-day period during the Treatment Period (Week 1-48). The number and percentage of subjects who achieve RBC transfusion independence will be presented by treatment group.

Similar approach as described in Section 11.2 will be used.

11.3.5. Proportion of Subjects Achieving Modified Erythroid Response

Proportion of subjects achieving the modified erythroid response (mHI-E) is defined as the proportion of subjects meeting the modified HI-E criteria per the International Working Group (IWG) (Cheson, 2006; Appendix E) sustained over any consecutive 56-day period during the Treatment Period (Week 1–24, Week 1-48). Subjects meeting the modified HI-E criteria are derived as below:

For subjects with < 4 units/8 weeks at baseline, a responder must satisfy the following conditions:

i. there are no RBC transfusion within the response interval

ii. mean of Hemoglobin increase >= 1.5 g/dL from baseline

For subjects with >=4 units at baseline, a responder must satisfy the following conditions:

i. decrease of at least 4 units from baseline over any consecutive 56-day period

The number and percentage of subjects who achieve mHI-E together with 95% CI will be presented by treatment group. The Cochran–Mantel–Haenszel (CMH) test will be used to compare Luspatercept treatment group to placebo group.

11.3.6. Duration of RBC-TI

Duration of RBC-TI is defined as the longest duration of RBC-TI for subjects achieving RBC TI ≥ 8 weeks during the Treatment Period (Week 1 - 24, Week 1 – 48, during entire study treatment) . Subjects who maintain RBC-TI at the time of the analysis will be censored. Wee 24 and Week 48 cutoff dates as described in Section 11.1 will be used in the calculation.

Duration of RBC transfusion independence curve will be estimated using Kaplan-Meier (KM) methods and treatment groups will be compared using a stratified log-rank test. KM estimates for median duration of RBC-TI as well as two-sided 95% CIs will be summarized for each treatment group, adjusted for the stratification variables. Hazard ratio will be calculated using Cox model stratified for the 2 strata.

Plots of the KM survival curves will be presented for the two treatment groups, with adjustment for the stratification variables.

11.3.7. Time to RBC-TI

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

Time to RBC-TI (in days) will be summarized using descriptive statistics by treatment group.

11.3.8. Health-related QoL assessed by EORTC QLQ-C30

The European Organization for Research and Treatment of Cancer Quality-of-Life questionnaire (EORTC QLQ-C30) is a validated health-related quality of life (HRQoL) measure developped to subjectsmeasure the HRQoL of patients with cancer. It is commonly used in MDS research (Pinchon, 2009). It is composed of 30 items that address 15 domains, including one global health status, five functional domains (i.e., physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), and nine symptom domains (i.e., fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Domain 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.

To interpret the difference in change score from baseline between treatment groups and change score at the individual level, a ≥10-point change in any domain of the QLQ-C30 is commonly considered clinically-meaningful at an individual level (Osoba, 1998). Other cut-off values for clinically-meaningful change across different domains have also been reported (Cocks, 2012).

The primary EORTC QLQ-C30 domains of interest for the assessment are fatigue, dyspnea, global health status/QoL, physical functioning, and emotional functioning domains, as they are considered to be most clinically relevant to patients with MDS in the literature (Abel, 2014; Caocci, 2009; Williams, 2013) . A ≥10-point change in any domain of the QLQ-C30 is commonly considered clinically-meaningful at an individual level.12 Other cut-off values for clinically-meaningful change across different domains have also been reported.

The EORTC QLQ-C30 scores will be calculated according to scoring algorithms defined by the authors (Appendix 16.1.9).

To assess the extent of missing data at each assessment visit by treatment group, the PRO compliance rate for the EORTC QLQ-C30 will be estimated per treatment group on the ITT population. Subjects are considered compliant with completion of the EORTC QLQ-C30 assessment if at least half of the EORTC QLQ-C30 items are non-missing (i.e., ≥15 out of the 30 items) at a given assessment visit.

To assess the effect of luspatercept versus placebo on HRQoL, the following key analyses will be performed based on the HRQoL evaluable population. To align the HRQoL analysis with analysis of key efficacity endpoints, the analysis of scores at Week 25 will be considered as primary. CCI [redacted]

11.3.8.1. Main analysis

A cross-sectional analysis of changes from will be performed to compare the scores at Week 25, Week 48 and end of treatment between treatment groups using ANCOVA models adjusted for baseline domain scores and randomization stratification factors. The least squares (LS) means (95% confidence intervals [CI] and p-values) for changes from baseline at each postbaseline visit for all domains within each treatment group, and the difference in the LS means (95% CIs, p-value) between treatment groups at each postbaseline visit, with the primary interest at the Week 25 Visit, will be estimated.

To avoid bias when interpreting differences between groups in HRQoL score changes from baseline (screening) to end of treatment, the corresponding treatment duration will be described per treatment groups for patients analyzed.

CCI [redacted]

11.3.9. Proportion of Subjects Achieving Hematological Improvement-Neutrophils

This is defined as the proportion of subjects meeting the HI-N criteria per the IWG (Cheson, 2006; Appendix E) sustained over any consecutive 56-day period during the Treatment Period (Week 1–24, Week 1-48). The number and percentage of subjects in the ITT population who achieve HI-N together with 95% CI will be presented by treatment group. The Cochran–Mantel–Haenszel (CMH) test will be used to compare Luspatercept treatment group to placebo group.

11.3.10. Proportion of Subjects Achieving Hematological Improvement-Platelets

This is defined as the proportion of subjects meeting the HI-P criteria per the IWG (Cheson, 2006; Appendix E) sustained over any consecutive 56-day period during the Treatment Period (Week 1–24, Week 1-48). The number and percentage of subjects in the ITT population who

achieve HI-P together with 95% CI will be presented by treatment group. The Cochran–Mantel–Haenszel (CMH) test will be used to compare Luspatercept treatment group to placebo group.

11.3.11. Mean Change in Mean Daily Dose of Iron Chelation Therapy

The change in daily dose of ICT for each subject is calculated as the difference of post-baseline mean daily dose and baseline mean daily dose. There will be two comparisons between luspatercept group and placebo group; mean change from baseline for mean daily dose of Iron Chelation Therapy (ICT) averaged over Week 9 -24, and mean daily dose of ICT averaged over Week 33 - 48.

Shift table of ICT status (receiveing ICT vs. not receiving ICT) at baseline and post baseline will be provided.

11.3.12. Mean Serum Ferritin Decrease

The change is calculated as the difference of post-baseline mean serum ferritin (Week 9-24, Week 33-48) and baseline mean serum ferritin. There will be two comparisons between luspatercept group and placebo group; mean change from baseline for mean serum ferritin averaged over Week 9-24, and mean serum ferritin averaged over Week 33-48.

11.3.13. Time to Progression to Acute Myelogenous Leukemia

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

The number and percentage of subjects progressing to AML will be presented by treatment group during the Treatment Period (Week 1-48), and randomization through at least 3 years post last dose. Time to AML progression curves will be estimated using KM methods and treatment groups will be compared using a log-rank test. Kaplan-Meier estimates for median time to AML progression as well as the two-sided 95% CIs will be summarized for each treatment group, adjusted for the stratification variables. Plots of the KM survival curves will be presented for the two treatment groups, with adjustment for the stratification variables.

At the time of the final analysis, a Cox proportional hazards model will be used to estimate the corresponding hazard ratio and two-sided 95% CI.

Time to AML progression from initial MDS diagnosis is defined as the time between original diagnosis of MDS and first diagnosis of AML as per WHO classification of ≥ 20% blasts in peripheral blood or bone marrow. It will be summarized using descriptive statistics by treatment group.

11.3.14. Overall Survival

Overall survival (OS) is calculated as the time from randomization to death of any cause. OS will be censored at the last date that the subject was known to be alive for subjects who were alive at the time of analysis and for subjects who discontinued from the study or were lost to follow-up.

The analysis of OS will be performed for the Treatment Period and Posttreatment Follow-up Period. Overall survival curves will be estimated using Kaplan-Meier (KM) methods and will be compared using a stratified log-rank test, stratifying by average baseline RBC transfusion requirement (≥ 6 units versus < 6 units of RBC per 8 weeks), baseline IPSS-R (very low or low versus intermediate). The p-value from the stratified log-rank test will be the confirmatory p-value. The analysis of OS will be conducted at the time of the analysis of the primary and key secondary efficacy endpoint.

Kaplan-Meier estimates for median OS and associated two-sided 95% CIs will be summarized for each treatment group, adjusted for the stratification variables. Plots of the KM survival curves will be presented for the two treatment groups, with adjustment for the stratification variables.

At the time of the final OS analysis, a stratified Cox proportional hazards model will be used to estimate the corresponding hazard ratio and two-sided 95% CI for luspatercept relative to placebo.

11.4. Subgroup Analysis

In addition to analyses that include all ITT subject , additional exploratory subgroup analyses will be performed within the following subgroups for primary and key secondary efficacy endpoint, i.e., RBC-TI ≥ 8 weeks (Weeks 1-48) and ≥ 12 weeks (Weeks 1-24), and HI-E response:

- Age group (≤ 64, 65-74, and ≥75)
- Sex (Male, Female)
- Race (White, non-White)
- MDS WHO classification at baseline
- Time since initial diagnosis at baseline (≤ 2 , 2 to ≤ 5, > 5 years)
- ECOG performance status at baseline (0 or 1, 2)
- Average baseline RBC transfusion requirement < 4, ≥ 4 and < 6, ≥ 6 units)
- Baseline transfusion burden (# of RBC transfusions/ last 8 weeks; < 4, ≥ 4 and < 6, ≥ 6 units)

- Baseline IPSS-R risk (Very low or Low, Intermediate)
- Longest Duration of Prior ESA treatment (< 6, 6 - 12, > 12 - 24, > 24 months)
- Renal (CrCL > 40 - 60 vs. ≥ 60 mL/min)
- SF3B1 (mutated vs non-mutated)
- Baesline serum EPO (<100, 100-<200, 200-500 and >500 U/L)
- Baseline Platelets (<100, 100-400, > 400 (10^9/L))

Primary and key secondary efficacy endpoint will be analyzed separately within each subgroup using the appropriate analysis methods as described in Sections 11.1 and 11.2.1, but formal hypothesis testing will not be performed in the subgroup analyses.

If the total number of subjects within one subgroup is less than 5% of the total sample size, that subgroup will be excluded in subgroup analysis.

More subgroup analysis might be explored if applicable.

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12. SAFETY ANALYSIS

All summaries of safety data will be conducted using the Safety population.

12.1. Adverse Events

Adverse events (AEs) will be coded according to the Medical Dictionary for Regulatory Affairs (MedDRA) Version TBD. 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). Adverse events that are not defined in the CTCAE should be evaluated for severity/intensity according to the following scale:

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

Adverse events will be classified as Not Suspected or Suspected depending on the relationship between IP administration and AE/SAE occurrence.

Not suspected: a causal relationship of AE 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 AE. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP and AE.

Treatment-emergent adverse events include adverse events that started on or after the date of first dose and on or before 42 days after the date of last dose of study treatment.

The following summaries of AEs will include incidence tables by treatment group and overall:

- All TEAEs regardless of causaulity
- TEAEs with CTCAE toxicity >= grade 3
- TEAEs leading to death
- TEAEs leading to permanent study drug discontinuation
- All Suspected TEAEs
- Serious TEAE
- Suspected Serious TEAEs
- TEAEs with CTCAE toxicity grade 3 or 4
- TEAEs leading to dose interruption
- TEAE leading do dose reduction
- TEAEs by age group (≤ 64, 65 to 74, >=75)
- TEAEs by gender
- TEAE by Crcl (40-<60, >=60)
- TEAE by maximam Dose received (1.0 mg/kg, 1.33 mg/kg, 1.75 mg/kg)
- TEAE in ADA positive subjects

If a subject experiences multiple AEs under the same SOC and PT, then the subject will be counted only once for that SOC and PT.

All AEs will be summarized by maximum severity (mild, moderate, severe, life- threatening, death and, if needed, missing). If a subject reports multiple occurrences of a specific event, the subject will be counted only once by the maximum severity. If the severity is missing for one or more of the occurrences, the maximum severity of the remaining occurrences will be used. If the severity is missing for all of the occurrences, the subject will be counted only once in the "missing" category of severity.

The relationship of an AE to IP is recorded on the AE CRF page as "Not suspected" and "Suspected." Adverse events with missing relationship to IP will be assessed as drug-related.

Listings for the corresponding summary tables for TEAE, Serious TEAE, TEAEs leading to study drug discontinuation and TEAEs leading to death will be presented separately.

12.1.1. Adverse Events by Cycle and Maximum Dose Received

The following summaries of TEAEs will include incidence tables by treatment and cycle group, dose level or maximum dose received:

- All TEAEs
- Serious TEAEs

The following cycle group will be used:

- Cycles 1-4
- Cycles 5-8
- Ext Cycles 1-4
- Ext Cycles 5-8
- Ext Cycles >=9

The following maximum dose level group will be used:

- 1.0 mg/kg
- 1.33 mg/kg
- 1.75 mg/kg

When summarizing TEAEs by maximum dose level, all AEs regardless of severity will be counted.

The analysis of TEAE by cycle will be based on the onset date of AE to determine the cycle. AEs with a duration that overlaps multiple cycles will only be counted in the first overlapped cycle. If an AE occurred multiple times in different cycle groups, it will be counted separately. If an AE occurred multiple times within the same cycle group, it will be counted only once.

12.1.2. Adverse Events of Interest

Adverse event of interest including but no limited to premalignant disorders and malignancies (including progression to AML or high risk MDS) will be summarized separately.

12.1.3. Death

A frequency table of the cause of death will be provided by treatment, including the number and percentage of subjects with deaths due to disease under investigation alone, subjects with deaths recorded as both disease under investigation and any TEAEs with an outcome of death, and subjects with an TEAEs with an outcome of death (but not due to disease under investigation).

Death during on-treatment period and post-treatment period will be summarized separately. On-treatment death is defined as any death occurred on or after first dose of IP until 42 days after the last dose of IP.

A listing of deaths will also be provided including deaths for all screened subjects during pre-treatment, on-treatment, and post-treatment period.

12.2. Clinical Laboratory Evaluations

Clinical laboratory values will be graded according to NCI CTCAE version 4.3 for applicable tests. Change in hematology, blood chemistry, urinalysis laboratory results from baseline to each scheduled time point will be provided for the safety population. Shift tables for change in maximum NCI CTCAE grades of laboratory values will be provided by treatment and scheduled time point for those laboratory parameters that have CTCAE grades. Separate shift tables will be provided with respect to normal ranges for all numeric laboratory parameters.

Separate listings will be provided for laboratory values.

12.3. Vital Sign Measurements

Change from baseline will be summarized descriptively by scheduled time point and treatment groups for weight (kg), temperature (C), pulse rate (bpm), respiratory rate (bpm), systolic blood pressure, and diastolic blood pressure (mmHg).

Maximum post baseline increase in systolic blood pressure and diastolic blood pressure increase from baseline will also be summarized for the following categories:

- no increase,
- increased <20 mmHg,
- increased >= 20 mmHg
    - (Systolic Blood Pressure ≥ 160 mmHg
    - Diastolic Blood Pressure ≥ 100 mmHg

Maximum post baseline decrease of at least 10% in weight will be summarized using the number and percentage.

12.4. Electrocardiograms

Electrocardiogram (ECG) parameters include heart rate, PR interval, QRS duration, RR interval, and QT are collected on the CRF page. The corrected value for QT interval will be derived based on Fridericia's formula as below:

Fridericia's formula: $QTcF = QT/(RR)^{1/3}$, where RR is derived as:

Calculated RR (msec) = 60000 (msec)/heart rate (bpm)

Recorded parameters, QTcFs and change from baseline values will be summarized at each time point by treatment group.

In addition, at baseline and maximum QTcF from post-baseline visits, the proportion of subjects having absolute QTcF and intervals of the following categories will be presented:

- > 450 ms
- > 480 ms
- > 500 ms

At maximum QTcF from post-baseline visits, the proportion of subjects who have an increase from baseline in QTcF intervals of the following categories will be presented:

- >30 ms
- > 60 ms

The overall electrocardiogram (ECG) interpretation will be summarized by presenting the number and percentage of subjects with 'Normal' 'Abnormal, Not Clinically Significant' and 'Abnormal, Clinically Significant' by treatment group. Shift from baseline to worst during the treatment in the overall ECG interpretation will be displayed in cross–tabulations for each treatment.

12.5. ECOG Performance Status

ECOG performance will be summarized categorically with a shift from baseline to worst post-baseline by scheduled time point and maximum shift by treatment.

CCI [redacted]

CCI [redacted]

[redacted]

15. TIMING OF ANALYSES

15.1. Interim analysis

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

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

The sponsor will remain blinded throughout the study.

15.2. Final analysis

Final analysis will be performed when all 210 subjects have completed 48 weeks of treatment or discontinued before 48 weeks. There is no plan to claim luspatercept superiority based on interim analysis efficacy results, thus the type I error rate remains at 0.025 one-sided for the final analysis. Additional follow-up analysis for efficacy and safety will be performed when all subjects have been followed for at least 3 years from the last dose of IP.

16. REFERENCES

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17. APPENDICES

17.1. Appendix A: Date Imputation Guideline

17.1.1. Impute Missing Adverse Events/ Prior or Concomitant Medications and Procedures/Medical History, End Date of Prior ESA treatment, Date of Original MDS Diagnosis.

Incomplete Start Date:

Missing day and month

- If the year is the **same** as the year of the first dosing date, then the day and month of the first doing date will be assigned to the missing fields.
- If the year is **prior to** the year of first dosing date, then December 31 will be assigned to the missing fields.
- If the year is **after** the year of first dosing, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year are the **same** as the year and month of first dosing date, then the first doing date will be assigned to the missing day.
- If either the year of the partial date is **before** the year of the first dosing date or the years of the partial date and the first dosing date are the same but the month of partial date is **before** the month of the first dosing date, then the last day of the month will be assigned to the missing day.
- If either the year of the partial date is **after** the year of the first dosing date or the years of the partial date and the first dose date are the same but the month of partial date is **after** the month of the first dosing date, then the first day of the month will be assigned to the missing day.
- If the stop date is not missing, and the imputed start date is after the stop date, the start date will be imputed by the stop date.

Missing day, month, and year

- No imputation is needed. The corresponding AE will be included as TEAE.

Incomplete Stop Date: If the imputed stop date is before the start date, then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the **same** as the year of the last dosing date, then the day and month of the last dosing date will be assigned to the missing fields.

- If the year of the incomplete stop date is **prior to** the year of the last dosing date or prior to the year of the first dosing date, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date but is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing date.
- If the year of the incomplete stop date is **after** the year of the last dosing date, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year of the incomplete stop date are the **same** as the month and year of the last dosing date, then the day of the last dosing date will be assigned to the missing day.
- If either the year of the partial date is **not equal to** the year of the last dosing date or the years of the partial date and the last dosing date are the same but the month of partial date is **not equal to** the month of the last dosing date, then the last day of the month will be assigned to the missing day.

17.2. 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 MDSRS-SLD

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

17.3. Appendix C: French-American-British (FAB) Myelodysplastic Syndromes (MDS) Classification System

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

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

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

17.4. Appendix D: International Prognostic Scoring System Score - Revised

IPSS-R Cytogenetic Risk Groups*,**

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

IPSS-R Prognostic Score Values*

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

IPSS-R Prognostic Risk Categories/Scores*

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

IPSS-R: Prognostic Risk Category Clinical Outcomes*

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

*Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Solé F, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood 2012;120(12):2454-65.
***Medians, years.
^ Median time to 25% AML evolution.
Schanz J, Tüchler H, Solé F, Mallo M, Luño E, Cervera J, et al. New comprehensive cytogenetic scoring system for primary myelodysplastic syndromes (MDS) and oligoblastic acute myeloid leukemia after MDS derived from an international database merge. J Clin Oncol 2012;30(8):820-9.

17.5 Appendix E: International Working Group Response Criteria for Myelodysplastic Syndromes

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

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

[a] Dysplastic changes should consider the normal range of dysplastic changes (modification).
[b] Modification to IWG (2000) response criteria.
[c] Criteria not applicable for ACE-536-MDS-001 patient population.
[d] 20 – 30% blasts is considered AML according to WHO classification (Vardiman, 2009).
Notes: Deletions to IWG criteria are not shown. To convert hemoglobin from grams per deciliter to grams per liter, multiply grams per deciliter by 10.
Source: Cheson, BD, Greenberg PL, Bennett JM, Lowenberg B, Wijermans PW, Nimer SD, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood 2006;108 (2):419-25.

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

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

KEY: HI-E = hem… hematologic improvement neutrophil response; HI-P = hematologic impr… nternational Working Group; RBC = red blood cell.

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

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

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

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

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

UserName: PPD
Title: PPD
Date: Wednesday, 13 June 2018, 11:51 AM, Eastern Daylight Time
Meaning: Approved, no changes necessary.
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UserName: PPD
Title: PPD
Date: Wednesday, 13 June 2018, 02:31 PM, Eastern Daylight Time
Meaning: Approved, no changes necessary.
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