DISCLOSURE

REDACTED STATISTICAL ANALYSIS PLAN

ACE-011-MDS-001

AN OPEN-LABEL, RANDOMIZED, PHASE 2, PARALLEL, DOSE-RANGING, MULTICENTER STUDY OF SOTATERCEPT FOR THE TREATMENT OF PATIENTS WITH ANEMIA AND LOW- OR INTERMEDIATE-1 RISK MYELODYSPLASTIC SYNDROMES OR NON-PROLIFERATIVE CHRONIC MYELOMONOCYTIC LEUKEMIA (CMML)

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STATISTICAL ANALYSIS PLAN

AN OPEN-LABEL, RANDOMIZED, PHASE 2, PARALLEL, DOSE-RANGING, MULTICENTER STUDY OF SOTATERCEPT FOR THE TREATMENT OF PATIENTS WITH ANEMIA AND LOW- OR INTERMEDIATE-1 RISK MYELODYSPLASTIC SYNDROMES OR NON-PROLIFERATIVE CHRONIC MYELOMONOCYTIC LEUKEMIA (CMML)

Prepared by:

Celgene Corporation

86 Morris Avenue

Summit, NJ 07901

STUDY DRUG: Sotatercept (ACE-011)

PROTOCOL NUMBER: ACE-011-MDS-001

DATE FINAL: May 1, 2018

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SIGNATURE PAGE

Study Statistician

Signature _____

Printed Name _____ Date _____

Therapeutic Head of Statistics

Signature _____

Printed Name _____ Date _____

Clinical Research Physician

Signature _____

Printed Name _____ Date _____

Safety Physician

Signature _____

Printed Name _____ Date _____

1. LIST OF ABBREVIATIONS

Table 1: Abbreviations and Special Terms

Abbreviation or special term	Explanation
ADA	Antidrug Antibody
AE	Adverse Event
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
ATC	Anatomical Therapeutical Chemical
AUC	Area Under the Curve
CMML	Chronic Myelomonocytic Leukemia
CR	Complete Response
CRF	Case Report Form
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-Limiting Toxicity
EBMT	European Group for Blood and Marrow Transplantation
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EE	Efficacy Evaluable Population
EPO	Erythropoietin
ESA	Erythropoietin Stimulating Agent

Abbreviation or special term	Explanation
ADA	Antidrug Antibody
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AML	Acute Myeloid Leukemia
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ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EE	Efficacy Evaluable Population
EPO	Erythropoietin
ESA	Erythropoietin Stimulating Agent
Abbreviation or special term	**Explanation**

Hgb	Hemoglobin
HI-E	Erythroid Hematological Improvement
IWG	International Working Group
IPSS	International Prognostic Scoring System
IVRS/IWRS	Interactive Voice/Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
MR	Minimal Response
MDS	Myelodysplastic Syndromes
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NTDE	Non Transfusion-Dependent Efficacy Population
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PK	Pharmacokinetics
PFS	Progression-free Survival
PR	Partial Response
RBC	Red Blood Cell
SAP	Statistical Analysis Plan
Abbreviation or special term	**Explanation**
SAS®	Statistical Analysis System (software package)
SD	Stable Disease
TDE	Transfusion-Dependent Efficacy Population
TEAE	Treatment-emergent Adverse Event

WHO	World Health Organization

2. INTRODUCTION

This statistical analysis plan (SAP) describes the analyses and data presentations to be performed for Celgene's protocol ACE-011-MDS-001, "An open-label, randomized, Phase 2, parallel, dose-ranging, multicenter study of sotatercept for the treatment of patients with anemia and low- or intermediate-1 risk myelodysplastic syndromes or non-proliferative chronic myelomonocytic leukemia (CMML)." It contains definitions of analysis populations, derived variables and statistical methods for the analysis of efficacy and safety.

This SAP will be finalized and signed off prior to final clinical database lock and analysis. All statistical analyses detailed in this SAP will be conducted using *SAS® Version 9.2 or higher*.

3. OBJECTIVES

The primary objective is:

- To determine a safe, tolerable and effective dose of sotatercept that results in the greatest frequency of erythroid hematological improvement (HI-E) in patients with anemia and low- or intermediate-1 risk Myelodysplastic syndromes (MDS) or non-proliferative chronic myelomonocytic leukemia (CMML).

The secondary objectives are:

1. Safety of sotatercept
2. Rate of red blood cell (RBC) transfusion independence in transfusion-dependent subjects
3. Time to HI-E
4. Duration of HI-E
5. Time to progression to acute myeloid leukemia (AML)
6. Time to progression to events of higher risk MDS (ie, int-2 or high-risk IPSS)
7. Progression-free survival (PFS)
8. Overall survival (OS)
9. Pharmacokinetics (PK) of sotatercept

4. INVESTIGATIONAL PLAN

4.1. Design of Study

This is an open-label, randomized, Phase 2, parallel, dose-ranging, multicenter study of sotatercept for the treatment of patients with low- and int-1 risk MDS or non-proliferative CMML (IPSS), with anemia requiring a transfusion (subjects should have received at least 2 units of RBCs within 84 days prior to study enrollment).

The study is comprised of 2 parts:

Part 1

Subjects will be stratified by concentration of serum erythropoietin (EPO, < 500 versus ≥ 500 mIU/mL) and by number of transfusions within 56 days prior to study enrollment (< 4 units of RBCs versus ≥ 4 units of RBCs), and assigned randomly to one of two treatment groups, wherein they will be administered sotatercept subcutaneously (SC) 0.1 mg/kg or 0.3 mg/kg once every 3 weeks (Q3W).

Enrollment will continue without hiatus beyond randomization of 5 subjects into each of the 0.1 mg/kg and 0.3 mg/kg treatment groups. Following treatment of 5 subjects in each of the 0.1 mg/kg and 0.3 mg/kg treatment groups (with the last subject for each group having completed at least 1 cycle of 21 days), all available safety and efficacy data will be assessed by a Steering Committee. Based upon the occurrence of dose-limiting toxicity (DLT) in ≤ 1/5 subjects in Cycle 1 in the 0.1 mg/kg and 0.3 mg/kg treatment groups, the 0.5 mg/kg treatment group will begin inclusion in the randomization scheme.

Following treatment of at least 6 subjects in the 0.5 mg/kg treatment group (with at least 6 subjects having completed at least 3 cycles of 21 days each), all available safety and efficacy data from all dose levels will be assessed by a Steering Committee. Based upon the occurrence of dose-limiting toxicity (DLT) in ≤ 1/6 subjects in Cycle 1 in the 0.5 mg/kg treatment group and an acceptable safety profile from all dose levels, the 1.0 mg/kg treatment group will begin inclusion in the randomization scheme.

Following treatment of at least 6 subjects in the 1.0 mg/kg treatment group (with at least 6 subjects having completed at least 3 cycles of 21 days each), all available safety and efficacy data from all dose levels will be assessed by a Steering Committee. Based upon the occurrence of dose-limiting toxicity (DLT) in ≤ 1/6 subjects in Cycle 1 in the 1.0 mg/kg treatment group and an acceptable safety profile from all dose levels, the 2.0 mg/kg treatment group will begin inclusion in the randomization scheme.

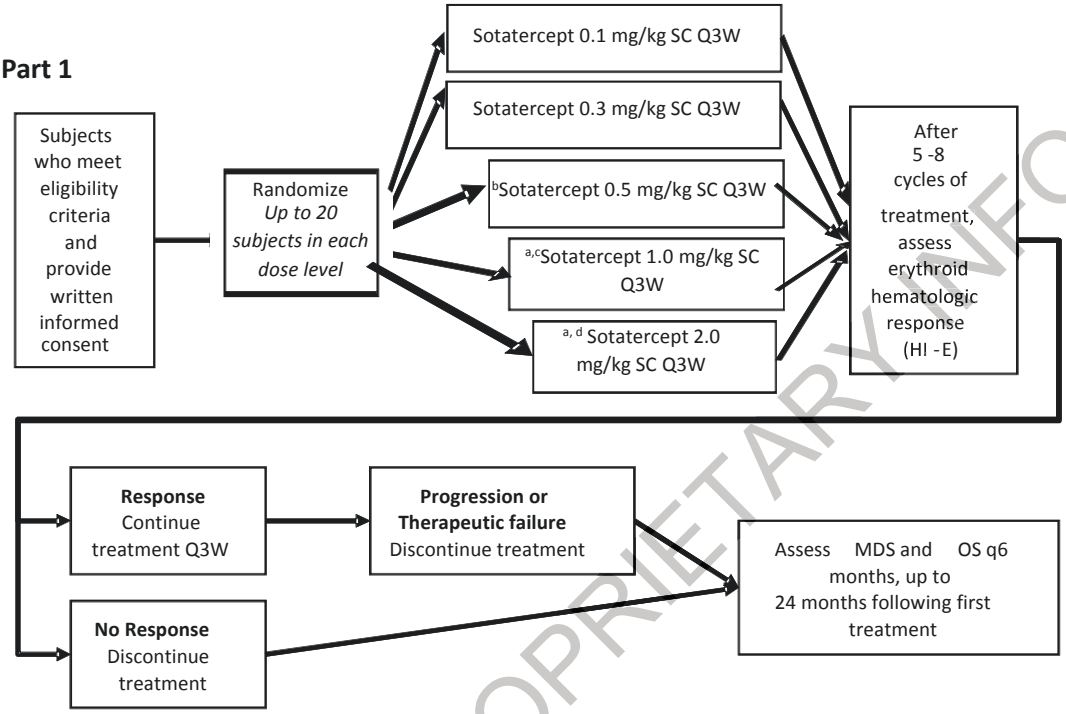
Meetings of the Steering Committee are planned periodically throughout the study to review all available safety and efficacy data. For any treatment group, if ≥ 40% of the subjects (minimum 4 subjects experiencing an event) experience a DLT of related (suspected) adverse event (AE) ≥ Grade 2 (other than Hgb or hypertension), the Steering Committee may recommend the closure of the treatment group.

In addition, if >= 33% of the subjects (minimum 2 subjects experiencing an event) experience Hgb > 12 g/dL (not influenced by transfusions) sustained for ≥ 7 days, confirmed by 2 assessments ≥ 1 week apart, the Steering Committee may recommend the closure of the treatment group.

Moreover, if ≥ 33% of the subjects (minimum 2 subjects experiencing an event) experience a hypertension DLT, the Steering Committee may recommend the closure of the treatment group.

Additionally, for any treatment group that accrues a minimum of 10 subjects or less if recommending by the Steering Committee (with the last subject having received at least one complete cycle of 21 days), in the absence of any sign of efficacy (defined as an increase of Hgb > 1 g/dL in the absence of transfusion or at least a 50% reduction in the transfusion requirements if the reduction observed is less than 4 units).

Figure 1: Design of Study



[a] Intermediate cohorts (not to exceed 2.0 mg/kg) may be added at the time of dose escalation up to 1.0 mg/kg and up to 2.0 mg/kg (eg 0.75 mg/kg or 1.5 mg/kg respectively) based on assessment by the Steering Committee of available safety and efficacy data when at least 6 subjects have at least 3 cycles of treatment in the current dose level.

[b] Randomization to the sotatercept 0.5 mg/kg SC Q3W treatment group may begin only after treatment of 5 subjects in the 0.1 mg/kg SC and 5 subjects in the 0.3 mg/kg SC treatment groups with the last subject for each group having completed at least 1 cycle of 21 days, and an assessment of all available safety and efficacy data for all subjects.

[c] Randomization to the sotatercept 1.0 mg/kg SC Q3W treatment group may begin only after treatment of at least 6 subjects in the 0.5 mg/kg treatment group (or current dose level if intermediate cohort is added) with at least 6 subjects having completed at least 3 cycles of 21 days each, and an assessment of all available safety and efficacy data for all subjects.

[d] Randomization to the sotatercept 2.0 mg/kg SC Q3W treatment group may begin only after treatment of at least 6 subjects in the 1.0 mg/kg treatment group (or current dose level if intermediate cohort is added) with at least 6 subjects having completed at least 3 cycles of 21 days each, and an assessment of all available safety and efficacy data for all subjects.

Upon completion of up to 20 evaluable subjects in each of the treatment groups, analyses will be conducted in order to evaluate the safety profile of sotatercept and identify the dose that results in the greatest frequency of HI-E.

Part 2

Following the assessment of efficacy and safety parameters in Part 1, 15 additional subjects will be enrolled in Part 2 at the dose level of sotatercept that demonstrates the greatest frequency of HI-E.

DLT

DLT's are described in Section 12.1.

Study Periods

Both Part 1 and Part 2 of the study are comprised of the following periods:

Screening – Assessments to be performed up to 28 days prior to enrollment (Day 1). If screening assessments, with the exception of Hgb and blood pressure, are conducted within 7 days of enrollment (Day 1), they are not required to be repeated at enrollment (Day 1). Hemoglobin and blood pressure must be assessed within 8 hours prior to study drug administration.

Treatment – Comprised of 5 complete cycles of 21 days each of treatment on a schedule of Q3W. Subjects requiring ≥ 4 units of RBC at baseline who fail to demonstrate, after completing 5 cycles of treatment, a decrease ≥ 4 units of RBC transfused over a period of 8 weeks, relative to the units of RBCs transfused in the 8 weeks immediately prior to enrollment (Day 1), will discontinue treatment. Subjects requiring < 4 units of RBC at baseline who have sustained Hgb increase by the end of Cycle 5 but for a period less than or equal to 8 consecutive weeks (potential late responders) may continue treatment for up to an additional 3 cycles (Cycles 6-8) for the purpose of meeting response criteria. Subjects requiring ≥ 4 units of RBC at baseline who have a sustained decrease in transfusion requirements by the end of Cycle 5 but for a period of less than or equal to 8 consecutive weeks (potential late responders) may also continue treatment for up to an additional 3 cycles (Cycles 6-8).

Extension – After completion of the Treatment Period, subjects who qualify may enter the Extension Period until PD, treatment failure, or other reason, as appropriate. Subjects who exhibit at least a 1.0 g/dL rise in Hgb or a 50% reduction in transfusion requirement compared to baseline if the reduction observed is less than 4 units at the end of the Treatment Period may also enter the Extension Period at the investigator's discretion. Visits will be Q3W to coincide with the schedule of treatment administration.

Follow-up – Following the End of Treatment in the Treatment Period or the Extension Period, Follow-up will include pregnancy test approximately 28 days after the last treatment, assessment of efficacy (ie, Hgb levels, transfusions) approximately 28 days after the last treatment and repeated once per month until 3 months after the last treatment or until the start of the next treatment, whichever is first, assessment of PK at a single timepoint 3 months after the last treatment, assessment of Antidrug Antibody (ADA) repeated every 3 months until 1 year after the last treatment, and assessment of progression to AML and OS every 6 months up to 2 years following the first administration of sotatercept.

5. STUDY ENDPOINTS

5.1. Primary Endpoint

The primary endpoint of this study is the rate of HI-E starting before the completion of 5 cycles of treatment. Subjects who have a sustained Hgb increase or a decreased transfusion burden by the end of Cycle 5 but for a period less than or equal to 8 consecutive weeks (potential late responders) may continue treatment for up to an additional 3 cycles (Cycles 6-8) for the purpose of meeting response criteria.

- HI-E [(for subjects that require a transfusion of < 4 units of RBCs) in the 8 weeks prior to randomization (Part 1) or start of therapy (Part 2)] is an increase ≥ 1.5 g/dL Hgb sustained over a period ≥8 weeks in the absence of RBC transfusion; or
- HI-E [(for subjects that require a transfusion of ≥ 4 units of RBCs) in the 8 weeks prior to randomization (Part 1) or start of therapy (Part 2)] is a decrease ≥ 4 units of RBCs transfused over a period of 8 weeks, relative to the number of units of RBCs transfused in the 8 weeks immediately prior to Day 1.

5.2. Secondary Endpoints

The secondary endpoints of this study are:

1. Safety of sotatercept.
2. RBC transfusion independence in transfusion-dependent subjects.
3. Time to HI-E.
4. Duration of HI-E.
5. Time to progression to AML; the time between randomization (Part 1) or start of therapy (Part 2) and the date of progression to AML.
6. Time to progression to events of higher risk MDS; the time between randomization (Part 1) or start of therapy (Part 2) and date of progression to events of higher risk MDS (e.g., int-2 or high-risk IPSS).
7. Progression-free survival (PFS) – the time between randomization (Part 1) or start of therapy (Part 2) and PD or death.
8. Overall survival (OS) – the time between randomization (Part 1) or start of therapy (Part 2) and death.
9. Concentration of sotatercept in serum.

[redacted]

5.4. Sample Size

Subjects will be enrolled to provide up to 115 evaluable subjects in this study (Parts 1 and 2, combined). An evaluable subject (for sample size determination only) is one who meets criteria for HI-E, or one who completes 5 cycles of 21 days each of treatment without meeting criteria for HI-E, and without deviation from protocol. Subjects who have a sustained Hgb increase or a decreased transfusion burden by the end of Cycle 5 but for a period less than or equal to 8 consecutive weeks (potential late responders) may continue treatment for up to an additional 3 cycles (Cycles 6-8) for the purpose of meeting response criteria.

6. GENERAL STATISTICAL CONSIDERATIONS

Subjects will be classified according to the sotatercept dose level assigned if the dose level was received at least once. If the assigned dose level was never received, then the subject will be assigned the initial dose level received.

Individual subject listings will be provided to support the corresponding tables.

6.1. 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 table and figure.

6.1.1. 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 procedure are performed. They include the dates of blood draws for laboratory testing, physical examinations, tumor scans, 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 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 15.1 (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, study drug 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 such as survival, progression, etc. In most cases they are derived either from a milestone (e.g., the survival date is derived from the death date), or a procedure date (e.g., the progression date is derived from the date of the tumor scan that was used to determine progression). 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 (see section 5.1.2 below).

Dates recorded in comment fields will not be imputed or reported in any specific format.

6.1.2. Calculation using dates

Calculations using dates (*e.g.*, subject's age or relative day after the first dose of study medication) will adhere to the following conventions:

- **Study days** after the start day of study drug will be calculated as the difference between the date of interest and the first date of dosing of study medication (e.g., sotatercept) plus 1 day. The generalized calculation algorithm for relative day: STUDY DAY = [(TARGET DATE – DSTART) + 1 where DSTART = the start day of study drug]. Note that Study Day 1 is the first day of treatment of study drug. For Study days before the start of study drug will be calculated as the difference between the date of interest and the first date of dosing of study medication. The generalized calculation algorithm for relative day: STUDY DAY = [(TARGET DATE – DSTART). Negative study days are reflective of observations obtained during the baseline/screening period. Note: Partial date for the first study drug is not imputed in general. All effort should be made to avoid incomplete study drug start date.
- Age (expressed in days) is calculated: AGE = DATE of RANDOMIZATION – DATE of BIRTH + 1. In practice, age will be transformed to years by dividing the difference by 365.25 days, then truncating.
    - Using calculated age from the clinical database is preferred. When not available, the calculated age from the case report forms (CRF) or interactive voice response system (IVRS) may be used
    - Partial birth date: impute missing day as 15th of the month; impute missing month as July; set age as missing if 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 /30.4167.

6.2. Data Included in Planned Analyses

6.2.1. Data Included in the Analysis for the Clinical Study Report (CSR)

The analysis for the CSR will be completed after all subjects have completed six cycles of sotatercept or have discontinued the study.

After the analysis for the CSR, any additional data collected will be included in a supplementary analysis. The CSR will be amended to include the additional analysis when it becomes available.

6.3. Analysis Populations

6.3.1. Intent-to-Treat Population

The Intent-to-Treat population is defined as all subjects who are enrolled in the study.

6.3.2. Safety Population

The Safety Population analysis set is defined as all subjects who receive at least one dose of study medication. Drug exposure and all safety analyses (including AEs, labs and deaths) will be based on the safety population.

6.3.3. Efficacy Evaluable (EE) Population

The Efficacy Evaluable Population analysis set is defined as all subjects who take at least one dose of study medication and have baseline and at least one post-baseline assessment of efficacy without major deviation from protocol.

6.3.4. Transfusion-Dependent Efficacy (TDE) Population

All subjects in the EE population who require a transfusion of $\geq$ 4 units of RBCs in the 8 weeks prior to randomization (Part 1) or start of therapy (Part 2) are transfusion dependent at randomization.

6.3.5. Non Transfusion-Dependent Efficacy (NTDE) Population

All subjects in the EE population who require a transfusion of < 4 units of RBCs in the 8 weeks prior to randomization (Part 1) or start of therapy (Part 2) are not transfusion-dependent at randomization.

6.3.6. Pharmacokinetic (PK) Population

All subjects who take at least one dose of study medication followed by collection of a sufficient amount of post-dose quantifiable pharmacokinetic (PK) samples will be included in the PK analysis set.

6.4. Definitions

6.4.1. Study Treatment Start Date

The start date of study treatment is defined as the first date when a dose of sotatercept was administered. The start date of subsequent cycles will be the dose dates of sotatercept, as this drug is given only once at the beginning of each cycle.

6.4.2. Study Treatment End Date

The treatment end date is the date the subject's treatment was discontinued as recorded on the treatment discontinuation page.

6.4.3. End Date of each Cycle

The end date of each cycle is one day prior to day 1 of the subsequent cycle. The end date of the last cycle is the study treatment end date. If for an analysis for a steering committee a subject is still on treatment, then the End Date of the Last Cycle is defined as the start date of last treatment cycle plus 21 days.

6.4.4. Calculation of Cycles

The cycle number for each date of interest, e.g., AE or lab, will be calculated based on the cycle window set by their start and end dates of each cycle. The number of the cycle is the number of doses of sotatercept that the subject has received. The total number of cycles is the number of sotatercept doses taken.

6.4.5. Baseline

The last available assessment, before the date of start of study treatment, is the baseline assessment. The average will be used if there are multiple records on the baseline day.

For transfusion dependent patients, baseline burden = transfusions received in 8 week window prior to first administration of investigational product. For transfusions on day -56, they should be included in baseline burden. For transfusions occurring on day of first drug administration, they should be counted as on study transfusion.

6.4.6. Treatment emergent assessment/event

Safety summaries for adverse events and deaths will be summarized based on treatment-emergent assessments/events. Treatment-emergent assessment/event is defined as any assessment/event reported as starting or worsening on or after the start date of study treatment and up to 42 days (inclusive) after the last date of study administration.

7. STUDY DISPOSITION

7.1. Subject Disposition

The subject disposition will be summarized using frequency and percentages for the end of treatment, end of extended treatment, and status of follow-up. The subject disposition will include the number of subjects enrolled and treated, and the number of subjects in each analysis populations. The subject disposition will also include a tabulation of the reasons for discontinuing treatment. The summary of subject disposition will be by assigned dosing level of sotatercept:

Reasons for **ending study treatment** will be collected on the CRF and will be summarized for all enrolled subjects with the following categories:

- Completed (per protocol)
- Disease Relapse
- Adverse events
- Withdrew consent
- Physician decision (Become eligible for allogeneic bone marrow or stem cell transplantation during treatment period)
- Death
- Lost to follow-up
- Protocol violation, specify
- Lack of Therapeutic Effect
- Other, specify

Status of **Follow-up phase** will be collected on the CRF and will be summarized for all treated subjects with the following categories.

- Alive
- Withdrew Consent from the survival follow-up
- Lost to Follow-up
- Dead

7.2. Protocol Violations / Deviations

Protocol violations / deviations will be summarized and listed by assigned dose level for the FAS population.

A protocol violation / deviation is defined as any departure from the approved protocol that:

- Impacts the safety, rights, and/or welfare of the subject;
- Negatively impacts the quality or completeness of the data; or
- Makes the informed consent document/form inaccurate.

Protocol violation / deviation will be monitored and reported throughout the study. Data of protocol violation / deviation will be finalized prior to database lock by clinical team with EXCEL sheet

8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Summaries for the demographics and baseline characteristics will be analyzed by assigned dose level for the safety population. For clinical characteristics, the baseline values are the last value collected on or before the start of study therapy. When there are retested values, the retest values will be used for the analysis. Continuous variables will be presented with descriptive statistics (N, Mean (SD), Median, Minimum and Maximum). Categorical variables will be presented with counts and percentages.

8.1. Demographics

Subject age, height, and weight will be presented as continuous variables. Gender, Race, and Race/Ethnicity will be presented as categorical variables.

8.2. Baseline Disease Characteristics

Baseline disease characteristics are:

- Previous therapies for MDS: yes, no;
- Number of previous therapies for MDS: 0, 1, 2, 3, 4, 5, >5;
- Time from MDS diagnosis (years): as a continuous variable;
- Time from MDS diagnosis (<=2 years vs. >2 years from diagnosis).
- RBC transfusion burden (56 days prior to randomization/dosing): as a continuous variable
- RBC transfusion burden categories (units during 56 days prior to randomization/dosing): (<4, ≥ 4);
- WHO Subtype classification: Refractory Cytopenia with 2 Unlineage Dysplasia (RCUD), Refractory Anemia with Ringed Sideroblasts (RARS), Refractory Cytopenia with Multilineage Dysplasia (RCMD), Refractory Anemia with Excess Blasts - 1 (RAEB-1), Refractory Anemia with Excess Blasts - 2 (RAEB-2), Myelodysplastic Syndrome - Unclassified (MDS-U), CMML non proliferative (CMML), MDS Associated with Isolated del (5q);
- RCUD Subtype (For subjects with WHO Subtype RCUD): Refractory Anemia, Refractory Neutropenia, Refractory Thrombocytopenia;
- Marrow blasts measured from a BMA smear (%): as a continuous variable;
- Karyotype IPSS: good, intermediate, poor;
- Number of Cytopenias;
- ECOG performance status: 0, 1 or 2 ;

8.3. Baseline Laboratories

Baseline value is defined as the last non-missing measurement on/before the first dose of the study drug, unless otherwise specified. Baseline Laboratories are:

- Hemoglobin (mg/dl): as a continuous variable;

- Serum erythropoietin level : as a continuous variable;
- Serum erythropoietin level : >500 mU/mL,250 -500, < 250 mU/mL;

Category variables will be summarized using a frequency distribution by treatment group and overall. Continuous variables will be summarized using descriptive statistics in the same way as continuous demographic variables in Section 8.1. All baseline characteristics will be provided in subject listings.

8.4. Medical History

Medical history data will be summarized using frequency tabulations by system organ class and preferred term by dose level for the safety population.

8.5. Prior MDS Therapy

Prior ESA and Non ESA medications with ATC code will be summarized and listed by assigned dose level for the safety population. The Anatomical Therapeutical Chemical (ATC) coding scheme of the World Health Organization (WHO) will be used to group medications into relevant categories for these tabulations.

8.6. Prior and Concomitant Medications

Prior medications are defined as non-study medications that were started before the start of the study treatment (regardless of whether they are stopped before the start of the study treatment or they continue to be used on or after the start of therapy). Prior medications that are ongoing at the start date of study treatment will be also reported as concomitant medications.

Concomitant mediations are defined as non-study medications that are started on or after the start of the study treatment, or started before the start of the study treatment and ended or were ongoing during the study treatment.

All prior and concomitant medications (summarized separately) will be summarized in frequency tabulations by assigned dose level. The Anatomical Therapeutical Chemical (ATC) coding scheme of the World Health Organization (WHO) will be used to group medications into relevant categories for these tabulations.

9. STUDY TREATMENTS AND EXTENT OF EXPOSURE

9.1. Treatment Duration

The treatment duration of sotatercept will be calculated in weeks and is defined as:

[(Study Treatment End Date) – (Study Treatment Start Date) + 1]/7

For interim analyses, the treatment duration of sotatercept for subjects still on treatment will be calculated in weeks and is defined as:

[(End Date of the last cycle) – (Study Treatment Start Date) + 1]/7

The number of cycles received will also be summarized for the safety population by assigned dose level. See sections 6.4.1, 6.4.2 and 6.4.3 for definitions of Study Treatment Start Date, Study Treatment End Date, and End Date of last cycle, respectively.

9.2. Dose Modification

Dose reductions/interruptions will be summarized by assigned dose level. Summaries include subjects who had at least one dose reduction/interruption.

10. EFFICACY ANALYSIS

All efficacy analyses will be carried out in the EE population unless otherwise specified. All analyses will be presented by assigned dose level of sotatercept.

10.1. RBC-Transfusion Analysis

The RBC-Transfusion analysis will be performed for subjects that require a transfusion of ≥ 4 units of RBCs in the eight weeks prior to randomization (Part 1) or start of therapy (Part 2), i.e. the TDE population.

Baseline RBC transfusion burden is the number of units of RBCs transfused in the 8 weeks immediately prior to the start of dosing (Study days -55 to 1). All RBC-transfusion records after the first dose of study drug will be used to assess the response.

Responder for Reduction in RBC-Transfusion Rate

The HI-E response is defined as a ≥ 4 unit decrease of RBCs transfused over a period of 8 weeks, relative to the number of units of RBCs transfused in the 8 weeks immediately prior and including Day 1 during any consecutive 56 days during the treatment period starting on Studyday 2, i.e. Study days 2 to 57, Study days 3 to 58, . . . etc.

The series of 56 day intervals which will be evaluated will begin with the interval that starts on Study day 2 and will end with the interval in which Study day 56 occurs on the last day of study therapy. If any of these intervals has a decrease ≥ 4 units of RBCs relative to the baseline RBC-transfusion burden, the subject is a responder. Subjects who do not achieve the response will be counted as non-responders. Subjects who discontinue from the study early without achieving the clinical response will be counted as non-responders regardless of how long the subject participates in the study.

Responder for RBC-Transfusion Independence

The response for RBC-Transfusion independence will be done similarly except a response occurs if no RBC-transfusions occur in a 56 day interval instead of a decrease of ≥ 4 units of RBCs relative to the baseline RBC-transfusion burden.

Time to HI-E Response

The Time to HI-E Response for subjects who respond is the time between the randomization date (subjects in Part 1) or the start date of therapy (subjects in Part 2) to the start date of the first 56 day interval that the subject was evaluated to be in response. For subjects who do not respond, the time to HI-E response is censored at the treatment discontinuation date.

Duration of HI-E Response

The Duration of HI-E Response is the end date of the first response period minus the start date of the first response period plus 1. The end date of the first response period is determined by extending the first 56 day interval until a decrease of ≥ 4 units (adjusted to 56 days) of RBCs relative to the baseline RBC-transfusion burden is no longer true and then using the previous date. The end date should be one day prior to a transfusion. If the first response does not end or the end date of the first response is beyond the end of treatment date, the end of treatment date is used.

10.2. Hemoglobin Analysis

The hemoglobin (Hgb) analysis will be performed for subjects that require a transfusion of < 4 units of RBCs) in the eight weeks prior to randomization (Part 1) or start of therapy (Part 2), i.e. the NTDE population.

Only Hgb measurements from the local laboratory page (and not the RBC-Transfusion page) will be used. Also, Hgb measurements taken within 2 weeks (inclusive) after an RBC-transfusion will not be used. Hgb measurements taken after the last dose of study treatment will not be used.

Baseline Hgb measurement is the last measurement taken prior to study drug excluding measurements taken within 2 weeks after an RBC-transfusion.

Responder for increase in Hemoglobin

HI-E is an Hgb increase ≥ 1.5 g/dL relative to baseline, sustained (i.e. consecutive Hgb measurements) over a period ≥ 56 days in the absence of RBC transfusion. The ≥ 56 day period must start after the start of treatment, i.e. the date of the first on-treatment Hgb measurement, and cannot extend beyond the end of study treatment date.

Time to HI-E Response

Time to HI-E Response for subjects who respond is the time between the randomization date (subjects in Part 1) or start date of therapy (subjects in Part 2) to the first Hgb measurement of the first HI-E response. For subjects who do not respond, the time to HI-E response is censored at treatment discontinuation date.

Duration of HI-E Response

Duration of HI-E Response for subjects who respond is the last date of the consecutive Hgb measurements of the first ≥ 56 day interval minus the first date of the consecutive Hgb measurements of the ≥ 56 day interval plus 1.

10.3. Time to Progression to AML and Time to Progression of higher risk MDS

The number and percent of subjects who progress to AML within the treatment phase and within the entire study will be tabulated, respectively, by assigned dose level. The time to AML progression will be assessed using the time between the randomization date (subjects in Part 1) or start date of therapy (subjects in Part 2) to the date of AML was diagnosed. The subjects who have AML will be considered to have the events. Subjects who died without AML will be censored at the date of death. Subjects who are lost to follow-up will be censored at the last known date when subjects did not have AML. Subjects who do not progress to AML by the last follow-up contact will be censored at the date of the last follow-up contact.

Time to progression to AML will be listed and Kaplan-Meier graphs by assigned dose level will be provided if sufficient events occur.

Time to progression of higher risk MDS will be done similarly to time to progression to AML except the assessment of progression of higher risk MDS will be used.

10.4. Progression Free Survival (PFS)

The number and percent of subjects with disease progression within the treatment phase and during the entire study will each be tabulated by assigned dose level. The time to disease progression will be assessed using the time between the randomization date (subjects in Part 1) or the start date of therapy (subjects in Part 2) and the date of disease progression (AML or high risk MDS). Subjects who have disease progression will be considered to have events. Subjects who died without AML will also be considered to have events with the event date as the date of death. Subjects who do not have disease progression and who are lost to follow-up will be censored at the last known disease progression assessment date. Subjects in the follow-up stage without disease progression at the last follow-up contact will be censored at the date of the last follow-up contact date.

Time to PFS will be listed and Kaplan-Meier graphs by assigned dose level will be provided if sufficient events occur.

10.5. Overall Survival

Overall survival will be assessed using the time between start of treatment and the death/censored date. Subjects who died (regardless of the cause of death) will be considered to have an event. Subjects who are alive at the end of the study, and subjects who are lost to follow-up, will be censored at the last date when subjects are known to be alive.

Time to overall survival will be listed and Kaplan-Meier graphs by treatment will be provided if sufficient events occur.

11. PHARMACOKINETIC ANALYSIS

11.1. Pharmacokinetic Analysis

11.1.1. Data Handling

Predose concentrations that are below the limit of quantitation (BLQ) or missing will be assigned a numerical value of zero for PK analysis. Postdose concentrations that are BLQ and occur before the first quantifiable concentration will also be treated as zero for PK analysis. Postdose concentrations that are BLQ but occur after the first quantifiable concentration on each day will be treated as missing for PK analysis.

Concentrations assigned a value of missing will be omitted from the calculation of descriptive statistics. A concentration value of zero will be excluded from the computation of geometric mean (geometric CV%).

In tables and listings for the derived PK data, there should be 4 decimal places for numerical values below 1, 3 decimal places for numeric values below 10 but above 1, and 2 decimal places for numeric values above 10. However, the listings of raw data should not have more decimal places than the actual data.

11.1.2. Pharmacokinetic Parameters

Pharmacokinetic parameters of sotatercept will be derived using a one-compartment model with first order absorption and elimination. All sotatercept serum concentration values obtained from Cycle 1 Day 1 to the end of study will be included in this analysis. Actual sampling and dosing times will be used in this analysis.

The model will be parameterized in terms of the absorption rate constant (k01), apparent clearance (CL/F), and apparent volume of distribution (V/F). Other parameters will be derived from the established model. The main compartmental pharmacokinetic parameters to be estimated are outlined as following:

k01	Absorption rate constant
CL/F	Apparent clearance from the central compartment
V/F	Apparent volume of distribution of the central compartment
T_{max}	Time to maximum serum concentration, calculated as ln(k01/k10)/(k01-k10), where k10 = (CL/F)/(V/F)
C_{max}	Maximum serum concentration for the starting dose, predicted at Tmax
AUC	Area under the serum concentration-time from time zero to infinity (or at the steady-date) for the starting dose, calculated as (Starting Dose)/(CL/F).
$t_{1/2}$	Elimination half-life, calculated as (ln2)/k10

Additional pharmacokinetic parameters may be determined when appropriate.

All sotatercept serum concentrations will be listed by dose group, subject, and scheduled time (visit and study day). The sotatercept serum concentrations will be summarized by dose group

and scheduled time, including N (number of observations), arithmetic mean, arithmetic standard deviation (SD), arithmetic coefficient of variation (CV%), geometric mean, geometric CV%, minimum, median, and maximum. Mean (SD) serum concentration-time profiles will be presented on linear scales by dose group for the first 4 weeks. Individual concentration plots will be provided by presenting the observed concentration data along with the one-compartment model-predicted concentration-time profile on the linear scale using actual sampling times and multiple dose data.

Pharmacokinetic parameters will be listed by dose group and subject, and they will be summarized descriptively by dose group (N, mean, SD, minimum, median, maximum, CV%, geometric mean, and geometric CV%). Dose proportionality may be assessed using the exposure data (e.g., C_{max}, AUC).

11.2. PK Analysis

ACE-011 plasma concentrations will be summarized by scheduled visits and treatment , and PK parameters will be summarized by treatment using descriptive statistics (N, mean, SD, coefficient of variation [CV%], geometric mean, geometric CV%, median, Min, and Max). Mean (±SD) and individual plot of plasma concentrations will be presented in both linear scale and semi-logarithmic scales.

Dose-proportionality may be evaluated using AUC and Cmax data from Cycle 1.

12. SAFETY ANALYSIS

Safety analyses will be conducted using the safety population and analyses will be presented by assigned dose level of sotatercept.

12.1. Dose-limiting Toxicity

Definition of Dose-Limiting Toxicity (DLT)

Dose-limiting Toxicity (DLT)	Definition
Hemoglobin	Hgb > 12 g/dL (not influenced by transfusions) sustained for ≥ 7 days, confirmed by 2 assessments ≥ 1 week apart.
Hypertension*	
Subjects within normal limits (WNL) and not receiving antihypertensive treatment at baseline	≥ Grade 2 (140 mmHg systolic or 90 mmHg diastolic) according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.0 (current active minor version) (Appendix F)
Prehypertensive subjects (systolic BP 120 - 139 mmHg or diastolic 80-89 mmHg) and not receiving antihypertensive treatment at baseline	Systolic ≥ 140 or diastolic ≥ 90 mmHg **AND:** Introduction of anti-hypertensive treatment **OR** An increase of > 20 mmHg (systolic or diastolic) from baseline
For patients with blood pressure controlled on antihypertensive treatment at baseline	Systolic BP ≥ 140 or diastolic ≥ 90 mmHg **AND:** More intensive antihypertensive treatment than previously used at baseline **OR** Additional antihypertensive treatment than previously used at baseline.
Any other treatment-related (suspected) toxicity	≥ Grade 2 per NCI-CTCAE Version 4.0 (current active minor version)

* Blood pressure values should be confirmed by mean of two readings obtained approximately 5 minutes apart with the patient seated for approximately 10 minutes prior to the initial reading.

A summary table of DLT will be presented by assigned dose level using the Safety Population.

12.2. Adverse Events

Adverse events (AEs) will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 18.0. The intensity of AEs will be graded according to the NCI-CTCAE Version 4.0. AEs, SAEs, and death will be summarized using the Safety Population.

Treatment-emergent adverse events (TEAEs) are defined as any AE occurring or worsening on or after the first treatment of the study medication and within 42 days after the last dose. TEAEs, AEs leading to study medication discontinuation, AEs leading to dose reduction/interruption, AEs related to study medication, and serious AEs will be summarized by system organ class and preferred term for each assigned dose level. A summary of AEs with NCI-CTCAE Grade 3 or higher, as well as the most frequent preferred terms, will be provided. If a subject experiences the same preferred term multiple times then the event will be counted only once and by greatest severity. All deaths and reasons for death will be summarized.

Listings for the corresponding summary tables will be presented.

12.3. Clinical Laboratory Evaluations

Clinical laboratory values will be graded according to NCI-CTC Version 4.0 for applicable tests. Shift from baseline to the worst grade observed during the treatment for selected laboratory results will be provided.

Separate listings will be provided for laboratory values.

12.4. Vital Sign Measurements

For vital signs, shift from baseline to worst during the treatment in below, within, and above the normal ranges will be displayed in cross–tabulations. Summary statistics (N, Mean, Standard Deviation, Median, Minimum, and Maximum) of observed and change from baseline values will be presented.

12.5. Electrocardiogram

The overall ECG interpretation will be summarized by presenting the number and percentage of subjects with ‘Normal’, ‘Abnormal, not clinically significant’ and ‘Abnormal, clinically significant’. Shift from baseline to worst during the treatment in the overall ECG interpretation will be displayed in cross–tabulations.

13. REFERENCES

Not Applicable

14. APPENDICES

14.1. Date Imputation Guideline

14.1.1. Impute Missing AE/ Prior or Concomitant Medications Start Dates

If the stop date is non-missing and the imputed start date is after the stop date, the start date will be imputed by the stop date.

Missing day and month

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

Missing day only

- If the month and year are **same** as the year and month of first day on study medication, then the start date of study medication will be assigned to the missing day.
- If the month and year are **before** the year and month of first day on study medication, then the last day of the month will be assigned to the missing day.
- If the month and year are **after** the year and month of first day on study medication, then the first day of the month will be assigned to the missing day.

Missing day, month, and year

- Included as TEAE

14.1.2. Impute Missing AE/ Prior or Concomitant Medications Stop Dates

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 dose date of study medication, then the day and month of the last dose date will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dose date, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is **after** the year of the last dose date of study medication, 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 dose date of study medication, then the day of the last dose date will be assigned to the missing day.
- If the month and year of the incomplete stop date are **before** the month and year of the last dose date of the study medication, then the last day of the month will be assigned to the missing day.
- If the month and year of the incomplete stop date are **after** the month and year of the last dose date of study medication, then the first day of the month will be assigned to the missing day.

14.2. Schedule of Assessments

Schedule of Assessments

Period	Screening	Treatment															End of Treatment Period or Early Termination	Extension[r]	End of Extension Period	Follow -up
Cycle		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5 (6-8 for potential late responders[r])			After Completion of Treatment Period			
Day[a]	-28 to 0	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15				
Randomize subject to sotatercept in IVRS system		•																		
Administer sotatercept		•			•			•			•			•				•		
Medical history, Height	•																			
Record prior meds and treatments	•																			
MDS disease history and baseline assessment and prior therapy[b]	•																			
RBC transfusion log	•	•			•			•			•			•			•	•	•	• t
Record current therapies (including concomitant medications)/procedures	•	•			•			•			•			•			•	•	•	• t
Record adverse events[c]	Record on an ongoing basis.																			
Physical exam[d]	•	•			•			•			•			•			•	•	•	
Vital signs, weight[d]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	

Schedule of Assessments (Continued)

Period	Screening	Treatment															End of Treatment Period or Early Termination	Extension[r]	End of Extension Period	Follow -up
Cycle		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5 (6-8 for potential late responders[r])			After Completion of Treatment Period			
Day[a]	-28 to 0	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15				
Blood Pressure[d]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
ECG[d]	•							•						•			•			
ECOG performance status[d]	•	•			•			•			•			•			•	•	•	
Hematology[e] assessed prior to each treatment Include CBC with diff and retic count	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•[e]
Serum chemistry[f]	•	•	•	•	•			•			•			•			•	•	•	
Urinalysis[h]	•	•			•			•			•			•			•	•	•	
Serum Erythropoietin	•	•	•	•	•			•			•			•			•			
Pregnancy testing[i]	•	•			•			•			•			•			•	•	•	•[i]
Pharmacokinetics[j]		•	•	•	•	•	•	•			•			•			•	•	•	•[j]
Antidrug antibody (ADA)[k]		•			•			•			•			•			•	•	•	•[k]

Schedule of Assessments (Continued)

Period	Screening	Treatment															End of Treatment Period or Early Termination	Extension[r]	End of Extension Period	Follow -up
Cycle		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5, (6-8 for potential late responders[r])			After Completion of Treatment Period			
Day[a]	-28 to 0	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15				
MDS response assessment[l]																	•		•	•[s]
Bone marrow aspirate, standard[m] Peripheral blood smear[n]	•																•		•	

[a] Variations of ±5 business days of the scheduled visit are permitted. An unscheduled visit can occur at any time during the study. Source documents for unscheduled visits must be maintained. The date of the visit and data generated must be recorded on the appropriate CRF. In the Follow-Up Period (for those visits not requiring sample collection only), a variation of ±15 business days of the schedule visit are permitted.

[b] MDS disease history and baseline assessment and prior therapy - to include date of diagnosis, WHO subtype, IPSS, and blast percent, cytopenia and karyotype at original diagnosis and at study baseline (assessed during the screening period prior to Day 1 dosing); and record of prior therapy for MDS including history of administration of erythropoiesis stimulating agents. For baseline MDS disease assessment, if bone marrow biopsy and/or aspirate results within 90 days prior to screening period are available, they may be used contingent that subject had no additional treatment (including ESAs and steroids) since sample obtainment. Supportive care (i.e. transfusions) since sample obtainment is acceptable.

[c] Record on an ongoing basis from the time of provision of written informed consent to participate in this study to 42 days after the last treatment. Beyond 42 after the last treatment, any SAE related to treatment should be reported.

[d] If physical examination, vital signs (except blood pressure), weight, or ECOG performance status were done within 7 days of Day 1, they do not need to be repeated at Study Day 1. Blood pressure should be monitored during screening, prior to each study drug administration, and on a weekly basis during the first 5 cycles. In addition, blood pressure should be assessed approximately 24 hours after the initial study drug administration during Cycle 1. On study drug dosing days, blood pressure must be assessed within 8 hours prior to study drug administration. Monitoring of blood pressure may be performed at home on nondosing days. For home monitoring, a plan with instructions and thresholds regarding when to contact the investigator in the event significant increases are observed should be established with the subject. In the absence of clinically significant changes

in blood pressure after 5 cycles of treatment, monitoring frequency may decrease to once per cycle at the investigator's discretion. ECG should be performed during screening, Cycle 3 Day 1, Cycle 5 Day 1, and at the End of Treatment Period. In the absence of clinically significant changes in ECG readings after completion of 5 cycles of treatment, ECGs will no longer be required until the End of Treatment Period unless deemed necessary by the investigator.

[e] Hematology, including CBC with differential and reticulocyte count are done at baseline and weekly during the treatment period. In the Follow-Up Period, Hematology values (ie, Hgb levels) will be collected approximately 28 days after the last treatment and repeated once per month until 3 months after the last treatment or until the start of the next treatment, whichever occurs first, to assess potential late response to sotatercept after discontinuation.

[f] Serum chemistry includes sodium, potassium, chloride, CO2 (bicarbonate), calcium, magnesium, phosphorus, BUN, creatinine, glucose, amylase, lipase, albumin, total protein, alkaline phosphatase, bilirubin (total and direct), AST/SGOT, ALT/SGPT, LDH, creatinine clearance (per Cockcroft-Gault formula).

[h] Urinalysis includes albumin (quantitative), bilirubin, creatinine (quantitative), glucose, Hgb, total protein (quantitative), ketones, pH, albumin/creatinine ratio, protein/creatinine ratio, .

[i] Pregnancy tests for females of childbearing potential. A female of childbearing potential is a sexually mature female who: 1) has not undergone hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months). Urine or serum pregnancy tests must occur within 3 days prior to sotatercept for Cycle 1. Urine or serum pregnancy tests must occur immediately prior to each treatment; approximately every 28 days during delays in treatment; at discontinuation of treatment; and approximately 28 days after the last treatment.

Note: Local laboratory assessments are allowed in cases when timely results are needed (eg, randomization, study treatment dosing decisions, hematology assessments between clinic visits). Whenever possible a "split" sample should also be forwarded to the central laboratory for analysis. Local laboratory data should be collected in the eCRF.

[j] Pharmacokinetics - Blood samples will be collected for assessment of pharmacokinetics in all subjects as per schedule. On days of treatment administration the sample must be collected prior to administration of sotatercept. During the Extension Period the sample must be collected prior to every other administration of sotatercept on days of treatment administration as per the schedule for assessment of ADA. A blood sample will be collected for the assessment of pharmacokinetics at the end of the Extension period. During the Follow-up Period a blood sample will be collected for assessment of pharmacokinetics at a single timepoint 3 months after the last treatment. At each pharmacokinetics time point, approximately 3 mL blood will be collected and serum prepared.

[k] Antidrug antibody (ADA) - Blood samples will be collected for assessment of ADA in all subjects. During the Treatment Period the sample must be collected prior to each administration of sotatercept on days of treatment administration. During the Extension Period the sample must be collected prior to every other administration of sotatercept on days of treatment administration as per the schedule of assessment of pharmacokinetics. A blood sample will be collected for the assessment of ADA at the end of the Extension period. At the end of the treatment, assessment of ADA will be repeated every 3 months until 1 year after the last treatment. If a serum sample is provided for assessment of pharmacokinetics, the assay for ADA will be performed on that serum sample and an additional sample need not be provided. If a serum sample is not provided for assessment of pharmacokinetics (ie, during the Follow-up Period) a serum sample ; prepare serum must be provided for the assay of ADA.

[l] MDS response assessment - per International Working Group (IWG) Response Criteria in Myelodysplasia, to include best response at end of treatment.

[m] Bone marrow aspirate, standard - for: local assessment of cytogenetics employing standard banding overall and FISH for d5q only; preparation of smear with Wright and Giemsa stain for local and central assessment of cell differential, morphology, and cellularity; standard assessment by flow cytometry. During screening, if cytogenetic results from within 90 days of Screening Period are available, they may be used contingent subject did not receive treatment (including ESAs and steroids) since sample obtainment. Supportive care (ie, ESAs and transfusions) since sample obtainment is acceptable.

[n] Peripheral blood smear - <0.1 ml of peripheral blood for preparation of smear with Wright and Giemsa stain for local and central assessment of cell morphology.

[r] After completing the Treatment Period, subjects who qualify for the Extension Period may continue therapy until PD or treatment failure in the Extension Phase. Subjects who have a sustained Hgb increase or a decreased transfusion burden by the end of Cycle 5 but for a period less than or equal to 8 consecutive weeks (potential late responders) may continue treatment for up to an additional 3 cycles (Cycles 6-8) for the purpose of meeting response criteria.

[s] MDS Response Assessment during Follow-up Period to include only progression to AML and OS assessed every 6 months up to 2 years following the first administration of sotatercept.

t Assessment of efficacy (ie, Hgb levels, transfusions) to continue approximately 28 days after the last treatment and repeated once per month until 3 months after the last treatment or until the start of the next treatment, whichever occurs first, to assess potential late response to sotatercept after discontinuation.

Celgene Signing Page

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

UserName:
Title:
Date: Friday, 04 May 2018, 05:28 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
==========

UserName:
Title:
Date: Monday, 07 May 2018, 01:24 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
==========