DISCLOSURE

REDACTED PROTOCOL AMENDMENT 4

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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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)

INVESTIGATIONAL PRODUCT (IP):	**Sotatercept**
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PROTOCOL SUMMARY

Title of Study

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)

Indication

Low- and intermediate-1 (int-1) risk myelodysplastic syndromes (MDS) or non-proliferative CMML by International Prognostic Scoring System (IPSS, Appendix B) with anemia (hemoglobin [Hgb] ≤ 9.0 g/dL)

Objectives

The primary objective of this study 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 int-1 risk MDS or non-proliferative CMML.

The secondary objectives of this study are to evaluate the:

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

Study Design

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, Appendix B), 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 five subjects into each of the 0.1 mg/kg and 0.3 mg/kg treatment groups. Following treatment of five 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 one cycle of 21 days), all available safety and efficacy data will be assessed by a Steering Committee (Section 4.4). Based upon the occurrence of dose-limiting toxicity (DLT) (Section 4.1.1) 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 six subjects in the 0.5 mg/kg treatment group (with at least six subjects having completed at least three cycles of 21 days each), all available safety and efficacy data will be assessed by a Steering Committee from all dose levels. Based upon the occurrence of 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 six subjects in the 1.0 mg/kg treatment group (with at least six subjects having completed at least three cycles of 21 days each), all available safety and efficacy data will be assessed by a Steering Committee from all dose levels. Based upon the occurrence of 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. The 2.0 mg/kg sotatercept dose was reduced to 1.5 mg/kg for ongoing and newly enrolled subjects (Amendment 4).

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 six subjects have at least three cycles of treatment in the current dose level. Enrollment will continue beyond randomization in all dose levels (unless dose level[s] is closed due to safety reasons or lack of efficacy as recommended by the Steering Committee) until up to a total of 20 subjects in each dose level.

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 four subjects experiencing an event) experience a DLT of related (suspected) adverse event (AE) ≥ Grade 2 (other than Hgb or hypertension DLT as defined in Section 4.1.1), the Steering Committee may recommend the closure of the treatment group.

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

Moreover, if > 33% of the subjects (minimum two subjects experiencing an event) experience a hypertension DLT (Refer to Section 4.1.1) confirmed by the investigator by two readings obtained 5 minutes apart, the Steering Committee may recommend the closure of the treatment group. In order to harmonize DLT assessment for hypertension across the study, additional guidance must be followed as defined in Section 4.1.1).

Additionally, for any treatment group that accrues a minimum of 10 subjects or less if recommended 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), the Steering Committee may recommend the closure of the treatment group.

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 evaluable subjects will be enrolled in Part 2 (Expansion Cohort) and complete treatment at the dose level of sotatercept that demonstrates the greatest frequency of HI-E.

Steering Committee Recommendation

Based on the 02 Mar 2015 Steering Committee's review of safety, efficacy and pharmacokinetic data of subjects enrolled in the Part 1 dose levels, including the sotatercept 2.0 mg/kg cohort level:

Part 1 - The sotatercept 2.0 mg/kg cohort was closed. Ongoing and newly enrolled subjects are to be dose reduced to sotatercept 1.5 mg/kg.

Part 2 - Subjects enrolled into Part 2 (Expansion Cohort) will receive sotatercept at 1.0 mg/kg.

This update is reflected in Amendment 4.

Total Number of Subjects: Up to approximately 75-115 evaluable subjects

Study Population

This is a study of patients with low- and int-1 risk MDS or non-proliferative CMML, with anemia. Subjects will be aged ≥ 18 years and have documented diagnosis of MDS or non-proliferative CMML (white blood cell [WBC] count ≤ 13,000 /mm3,World Health Organization [WHO], Vardiman, 2009) that meets IPSS (Appendix B) criteria for low- or int-1 risk MDS or non-proliferative CMML. Anemia is defined as patients requiring at least 2 units of RBCs within 84 days of enrollment for Hgb ≤ 9.0 g/dL. Subjects will have had no response or loss of response to prior treatment with rHu EPO (≥ 40,000 U/wk x 8), or darbepoetin alpha (≥ 500 mcg Q3W x 4), or low chance of response to erythroid-stimulating factors reflected by endogenous serum EPO concentration > 500 mIU/mL.

Length of Study

The study is comprised of the following periods:

Screening – Assessments to be performed up to 28 days prior to enrollment (Day 1).

Treatment – Comprised of five complete cycles of 21 days each of treatment on a schedule of once Q3W. Subjects who have a sustained Hgb increase or a decreased transfusion burden by 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 three cycles (Cycles 6-8) for the purpose of meeting response criteria.

End of Treatment – Assessments to be conducted upon:

Completion (≥ 5 cycles) of participation in the Treatment Period of the study, **prior** to the first dose of sotatercept in the Extension Period.

Early (< 5 cycles) termination of participation in the Treatment Period of the study, **after** last dose of sotatercept.

Extension – After completing 5 cycles of treatment (or up to 8 cycles for potential late responders), subjects who qualify for the Extension Period (refer to Section 4.1.2) may enter the Extension Period and continue treatment, subject to Rules for Delay, Reduction, and Discontinuation of Treatment (Section 8.2.1), until disease progression (PD), treatment failure, or other reason, as appropriate, listed in Section 12, Discontinuations. Visits will be once Q3W to coincide with the schedule of treatment administration.

End of Extension – Assessments to be conducted upon completion of participation in the Extension Period of the study.

Follow-up – Following the End of Treatment (last dose of sotatercept administered) in the Treatment Period or the Extension Period, follow-up will include a 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 for MDS, whichever is first; assessment of PK at a single time point 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 subject's first administration of sotatercept.

The End of Trial is defined as either the date of the last visit of the last subject to complete the study, or the date of receipt of the last data point from the last subject that is required for primary, secondary analysis, as pre-specified in the protocol and/or the Statistical Analysis Plan, whichever is the later date.

The sponsor may decide to 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 that remain on study may be consented and continue to receive treatment with IP. It must be the opinion of the investigator that the remaining subject(s) continue to receive benefit from treatment with IP.

Study Treatments

In Part 1, subjects will be randomized to one of up to five treatment groups (contingent on number of treatment groups open at time of randomization) to be administered sotatercept 0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg, 1.0 mg/kg, or 2.0 mg/kg by SC injection once Q3W for a total of 5-8 complete cycles of 21 days each in the Treatment Period. Subjects may continue to receive treatment at the same dose and frequency in the Extension Period if protocol-defined criteria are met (refer to Section 4.1.2).

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 six subjects have at least three cycles of treatment in the current dose level. Based on the Steering Committee assessment of efficacy, safety and PK data in Part 1, the sotatercept 2.0 mg/kg cohort was closed with ongoing and newly enrolled subjects dose reduced to 1.5 mg/kg in Part 1; 15 additional evaluable subjects will be enrolled in Part 2 (Expansion Cohort)at the 1.0 mg/kg dose level of sotatercept (Amendment 4).

In both Part 1 and Part 2, after completing five cycles of treatment (or up to eight cycles for potential late responders), subjects who qualify for the Extension Period (refer to Section 4.1.2) may enter the Extension Period and continue treatment, subject to Rules for Delay, Reduction, and Discontinuation of Treatment (Section 8.2.1), until PD, treatment failure, or other reason, as appropriate, listed in Section 12, Discontinuations.

Overview of Procedures

Procedures to be conducted in this study include, but are not limited to, medical history, height, record of prior medications and treatments, MDS disease history (including diagnostic, karyotype, cytogenetics, and **historic mutational analysis** information [ie,SF3B1, and other MDS-related molecular mutations]), baseline assessments and prior MDS therapy (ie, prior ESAs, non-ESA therapy), transfusion log (for collection of all prior transfusions [ie, red blood cell, platelets, whole blood, etc]) from at least 12 weeks prior to enrollment, up through 3 months post last dose of sotatercept and associated pre-transfusion Hgb levels at closest time prior to RBC transfusions, if available, record of prior/current therapies/procedures, record of AEs, physical examination, vital signs, weight, blood pressure, electrocardiogram (ECG), Eastern Cooperative Oncology Group (ECOG) performance status, hematology, serum chemistry, , serum erythropoietin, urinalysis, pregnancy testing, PK, ADA, MDS response assessment, bone marrow aspirate, smear of peripheral blood, bone marrow biopsy, .

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1. INTRODUCTION

Myelodysplastic syndromes (MDS) are a spectrum of hematologic malignancies characterized pathologically by presence of morphologic dysplasia and clinically by bone marrow failure resulting in persistent and progressive cytopenias. There is considerable variation in both the clinical manifestation and severity of individual disorders within this group, ranging from the relatively mild and painless condition of refractory anemia (RA) to the much more severe refractory anemia with an excess of blasts (RAEB) that often progresses to acute leukemia (Heaney, 1999). The current treatment algorithm is based dominantly on risk stratification using the International Prognostic Scoring System (IPSS, Appendix B, Greenberg, 1997). In patients with low- or intermediate-1 (int-1) risk groups by IPSS the goal of treatment is alleviation of cytopenias (Komrokji, 2011).

More than 90% of patients diagnosed with MDS will have anemia during their course of disease; and 30%-50% of patients will be transfusion-dependent. Red blood cell (RBC) transfusion dependence is an independent adverse prognostic factor in MDS (Komrokji, 2011). Anemia in MDS results from ineffective erythropoiesis. Accelerated apoptosis is the hallmark of early disease, while up-regulation of survival signals and clonal evolution are features of higher risk disease. Impaired clonogenic growth of primitive erythroid progenitors and impaired erythropoietin receptor signaling are major causes of anemia. Inflammatory cytokines and immune suppression within the microenvironment amplify accelerated apoptosis and the inherent defective erythroid maturation. Options for treating anemia in low- or int-1 risk MDS are limited. Erythroid-stimulating agents (ESAs) offer response rates of 20%-40%. Lenalidomide, in non-deletion (5q) (non-del [5q]), lower risk MDS transfusion independence (TI), response rates are 26% with TI response duration less than a year (Raza, 2008). Azacitidine and decitabine yield hematological improvements in approximately 40% of patients; however, most patients' responses are typically of short duration. Although bone marrow transplantation (BMT) can cure low and int-1 risk MDS, given the advanced age and greater incidence of co-morbidities in patients with MDS the significant morbidity and mortality associated with BMT does not allow such treatment in the majority of patients. The vast majority of patients with low- or int-1 risk MDS will remain RBC transfusion-dependent and succumb from complications of the disease or iron overload rather than progression of the disease. There is an unmet need to develop novel agents for treating anemia in lower risk non-del (5q) MDS (Komrokji, 2011).

1.1. Sotatercept for Treatment of Anemia in Lower (Low- or Intermediate-1) Risk MDS

Treatment with sotatercept resulted in increased hematocrit (HCT), hemoglobin (Hgb), and absolute RBC number in both nonclinical and clinical studies. The rapid and sustained increases in Hgb and HCT were observed in two Phase 1 studies in healthy volunteers, a Phase 2a study in subjects with multiple myeloma (MM), and a Phase 2 study in subjects with breast cancer. The ability for sotatercept to increase rapidly and sustain Hgb in subjects with anemia supports the clinical development of sotatercept for the treatment of anemia associated with lower risk MDS.

In Phase 1 single-dose and multiple-dose studies of sotatercept in postmenopausal women (Studies A011-01 and A011-02, respectively), a Phase 2 study in subjects with osteolytic lesions

associated with MM that examined concurrent administration of sotatercept with melphalan, prednisolone, and thalidomide (MPT) anti-myeloma therapy (Study A011-04), and a Phase 2 study in subjects with breast cancer, increases in Hgb, RBC count, and HCT were observed following treatment with sotatercept, and these increases remained detectable throughout the course of study. The observed Hgb, RBC count, and HCT effects of sotatercept were dose-dependent and time-dependent. These Phase 1 and Phase 2 clinical data are consistent with the increased hematologic parameters observed in nonclinical studies. Results from the four completed clinical studies A011-01, A011-02, A011-04, and A011-08 are summarized in the Section 1.3, Summary of Clinical Experience.

Although the mechanism(s) underlying the stimulatory effect of sotatercept on erythropoiesis is not fully understood, the result of clinical experience in healthy subjects showed a rapid and sustainable increase in mature erythrocytes released into circulation, suggesting that this impacts late stages of erythropoeisis.

Activin Receptor Signaling

The activins (A-E) are a group of proteins that form dimers and heterodimers. All are part of the superfamily of transforming growth factor-β (TGF-β) proteins. The activin first described, activin A was initially identified as a gonadal differentiation factor involved in modulating secretion of follicle-stimulating hormone (FSH) from the pituitary (Ying, 1988). Subsequently, the pleiotropic nature of activin A has become more apparent (Woodruff, 1998). There is a growing body of data suggesting a role for activins in bone remodeling, specifically as a negative regulator of bone growth (Perrien, 2007). Before the two molecules were shown to be identical (Rivier, 1985), activin A was also described as erythroid differentiation factor (EDF), effecting the maturation and differentiation of RBCs (Murata, 1988). The mechanism(s) by which activin A influences erythropoiesis remains under investigation and, in fact, there are data from in vitro and in vivo studies that support erythropoiesis-stimulatory (Shiozaki, 1992; Shiozaki, 1989) and erythropoiesis-inhibitory effects (Nakao, 1991).

The high-affinity activin type II receptor (ActRIIA) binds a number of ligands in the TGF-β superfamily including activins A and B, myostatin, and other growth differentiation factors (GDFs), as well as a number of the bone morphogenetic protein (BMP) family members. The ligand-bound ActRIIA then recruits the low-affinity Type I receptor (ActRIA or ALK-4) and then the receptor heterocomplex, through its cytoplasmic protein kinase activity, activates the SMAD signaling cascade to eventually influence nuclear transcriptional factors (Chen, 2002; Mathews, 1994). The competitive binding of activin receptor ligands in the blood and tissues by the sotatercept soluble fusion protein can result in inhibition of the ActRIIA receptor .

1.2. Sotatercept

Sotatercept (ActRIIA-IgG1Fc) is a fusion protein consisting of the extracellular domain (ECD) of activin receptor IIA (ActRIIA) fused to the human IgG1 Fc domain, which includes the heavy chain hinge and constant domains CH2 and CH3. The ECD sequence of ActRIIA is completely conserved among numerous species including mouse, rat, cynomolgus monkey, and humans; thus mouse, rat, and cynomolgus monkeys have been considered relevant species for nonclinical evaluation of sotatercept.

1.3. Summary of Clinical Experience

1.3.1. A011-01: A Phase 1a Study in Healthy Postmenopausal Women (Single-Dose)

Sotatercept was first studied in a Phase 1a, single center, randomized, double-blind, placebo-controlled, single-dose, dose-escalation study in healthy, postmenopausal women (Ruckle, 2009). Sotatercept was diluted in normal saline was administered as an IV infusion (over approximately 1 hour) or as a SC injection on Day 1. Dose levels were 0.01, 0.03, 0.1, 0.3, 1.0, and 3.0 mg/kg IV and 0.03 and 0.1 mg/kg SC. A total of 48 subjects were enrolled; five active and one placebo subject at each of the IV and SC dose levels. All subjects were followed for 4 months following a single-dose administration.

The pharmacokinetic (PK) profile of sotatercept was linear. The overall mean exposure (AUC) was proportional to doses (0.01 to 3.0 mg/kg IV, and 0.03 and 0.1 mg/kg SC). Across IV doses ranging from 0.1 through 3.0 mg/kg, the mean CL ranged from 0.092 to 0.128 mL/h/kg, the volume of distribution ranged from 73.7 to 110 mL/kg, and the mean terminal half-life in serum ($t_{1/2,}$ z) ranged from 23.7 to 31.8 days, with no apparent dependence on dose. After SC administration of 0.03 and 0.1 mg/kg, sotatercept was completely absorbed, and the mean $t_{1/2,}$ z was approximately 30 days, with no apparent dependence on dose.

The most commonly occurring (ie, those occurring in more than 1 subject in any treatment group) treatment-emergent adverse events (AEs) were headache, infusion site reaction, injection site hemorrhage, and toothache. The majority of the injection site reactions and injection site hemorrhages were in the first IV cohort and were related to infiltration of the IV site. The majorities of treatment-emergent AEs were mild in severity and were judged to be unrelated to sotatercept. No death, serious AE (SAE), or AE leading to discontinuation was reported. Changes in RBCs, Hgb, reticulocytes, liver function tests, glucose, uric acid, amylase, and lipase occurred in some subjects. Mild, transient elevations in pancreatic enzymes, liver enzymes, or glucose were reported as AEs in five subjects.

There were no clinically significant changes from baseline in vital signs, physical examination, endocrine function, or electrocardiogram (ECG). Preservation of adrenal cortical function was monitored through evaluation of serum electrolytes (sodium and potassium) and through cortisol response to adrenocorticotropic hormone (ACTH) stimulation.

No clinically significant finding was observed at doses up to 3.0 mg/kg IV, and sotatercept was well tolerated in healthy, postmenopausal women in single doses up to 0.1 mg/kg SC and 3.0 mg/kg IV, the highest dose tested in this study.

1.3.2. A011-02: A Phase 1b Study in Healthy Postmenopausal Women (Multiple Doses)

Study A011-02 was a Phase 1b, single-center, randomized, double-blind, placebo-controlled, multi-dose, dose-escalation study to evaluate the safety, tolerability and pharmacodynamics of sotatercept in healthy postmenopausal women. Four cohorts of 10 subjects each were planned at the following doses: 0.1, 0.3, 1.0, and 2.0 mg/kg administered SC. Within each cohort, subjects were to be randomized to either active or placebo treatment in an 8:2 ratio. Subjects were to receive one SC injection of sotatercept or placebo every 28 days for a total of four doses. All subjects were to be followed for 12 weeks after the last dose.

The treatment phase of the study was terminated early after a treatment-related SAE was attributed to a dose-limiting pharmacodynamic effect. While on study, one subject in the 1.0 mg/kg cohort experienced an SAE of progressive and persistent hypertension that was attributed to a rapid and significant increase in both Hgb (up to 20 g/dL) and HCT (up to 57.3%). Due to symptoms of headache, nausea, eye pain, dizziness, and vomiting approximately 1 week following the second dose, the subject was hospitalized for monitoring and evaluation of Grade 2 hypertension. Head magnetic resonance imaging (MRI), fundoscopy, and ECG were performed and were reported as normal. The hypertension was monitored and initially managed with antihypertensive medication. The headache resolved following corrective treatment by phlebotomy. The SAE resolved on Day 3 after the detection of hypertension and the subject was discharged from the hospital the following day. The hypertension resolved by the end of the study without need of antihypertensive medication. For headaches, the subject received aspirin prophylactically until the end of the study and continued taking ibuprofen as needed. Further details can be found in the Investigator's Brochure. In addition, two subjects who were treated with sotatercept 1.0 mg/kg showed increases in Hgb but were asymptomatic at the time of the consultation and underwent prophylactic phlebotomies.

Based on the magnitude of the hematopoietic response, the Sponsor suspended dose escalation to the 2.0 mg/kg dose and further dosing in all cohorts as a result of this dose-limiting SAE of hypertension, attributed to a pharmacodynamic effect at the 1.0 mg/kg dose level. A total of 31 subjects were enrolled and treated. Doses of sotatercept administered included 0.1, 0.3, and 1.0 mg/kg (Cohorts 1, 2, and 3 respectively). All subjects randomized to active treatment in Cohort 1 received all four planned doses of sotatercept. Due to early discontinuation of IP, subjects randomized to active treatment in Cohort 2 received three doses of sotatercept, and subjects randomized to active treatment in Cohort 3 received two doses of sotatercept. Subjects randomized to placebo treatment received between one to four doses of study treatment.

Following administration of the first dose, dose- and time- dependent increases in Hgb, HCT, and RBCs were observed (see Table 1 below for changes in Hgb):

Table 1: Hemoglobin, Mean Change from Baseline (Study A011-02, a Phase 1b Study in Healthy Postmenopausal Women)

Evaluation Time Point	Mean Change from Baseline (g/dL)			
	Placebo (N=7)[a]	Sotatercept 0.1 mg/kg (N=8)	Sotatercept 0.3 mg/kg (N=8)	Sotatercept 1.0 mg/kg (N=8)
Baseline Mean, pre-Dose 1	13.20	13.11	13.30	12.71
Day 8	0.17	0.68	0.85	1.21
Day 15	-0.27	0.43	0.44	1.75
Day 29	0.27	0.61	1.21	2.68[b]
Day 36	0.56	0.64	1.89	2.96
Day 43	-0.02	0.89	1.21	2.85
Day 57	0.27	1.28	1.64[b]	2.09
Day 64	0.53	1.11	2.49	2.21
Day 71	-0.10	1.34	2.09	1.66
Day 85	0.38	1.18[b]	2.55	1.86
Day 92	0.00[c]	1.04	1.60[c]	3.80[c]
Day 99	-0.20	1.21	3.20[c]	1.28[c]
Day 113	-0.02	1.30	1.29	1.04
Day 141	0.30	0.95	0.34	2.30
Day 169	0.20[c]	0.06	-	2.00[c]

[a] The number of placebo subjects with data decreases over time as a result of the early termination of the study (ie, there were placebo subjects in each dosing cohort). There were seven placebo subjects with data at baseline, Days 8, 15, and 36; six subjects with data at Days 29, 43, 57, and 85; five subjects with data on Days 71 and 113; four subjects with data on Day 64; three subjects with data on Day 141; two subjects with data on Day 99; and one subject with data on Days 92 and 169.
[b] Number of doses administered per treatment group: 0.1 mg/kg, four doses; 0.3 mg/kg, three doses; 1.0 mg/kg, two doses. Data beyond this study day were considered follow-up results.
[c] n=1.
- Data not available.
Source: CSR A011-02 in-text Table 9.

Other than the SAE of Hgb increase, no life-threatening event was reported. The most notable AEs were those related to increases in hematologic laboratory measures in the 1.0 mg/kg dose group: HCT, Hgb, and RBC count. The AEs of increased Hgb and/or HCT were reported for seven of the eight subjects in this dose group. These events were reported as mild or moderate elevations; all were considered probably related to study drug treatment. Three of the subjects in the 1.0 mg/kg group with elevated Hgb underwent phlebotomies and all Hgb elevations resolved by the end of the follow-up period. No erythroid lineage AEs were reported in the 0.1 or 0.3

mg/kg treatment groups. Hemoglobin for all subjects with elevations returned to within normal limits by the end of the study.

Paresthesia and dizziness were reported more frequently in the sotatercept groups, though the events were < Grade 2 and generally not considered drug related. Other frequently reported events (eg, fatigue, upper respiratory infection) did not appear to increase with dose and were generally mild.

Adrenal cortical function was monitored through evaluation of serum electrolytes (sodium and potassium) and through cortisol response to ACTH stimulation. All ACTH stimulation test results were normal.

The PK profile of sotatercept was linear after SC administration. Both $AUC_{0\text{-}28d}$ and maximum concentration (C_{max}) were dose proportional from 0.1 to 1.0 mg/kg following the first SC administration. The $t_{1/2,}$ z of sotatercept following the last dose in all three dose groups was identical, with mean $t_{1/2,}$ z being approximately 23 days. Based on one-compartmental modeling, the mean apparent total clearance (CL/F) ranged from 3.05 to 3.90 mL/d/kg and the mean apparent volume of distribution (Vz/F) ranged from 97.47 to 103.03 mL/kg, with no apparent dependence on dose.

Bone mineral density was assessed by dual-energy X-ray absorptiometry (DXA). A dose-dependent increase in the BMD of the total hip from baseline to end of study was observed, with a significant and rapid increase of 2.4% in the 1.0 mg/kg dose group, compared to a 0.7% decrease in the placebo group. Bone mineral density results for lumbar spine showed slight increases of 0.4% to 1.0% from baseline to study end in all active treatment groups, compared with a 0.5% decrease in the placebo group.

1.3.3. A011-04: A Phase 2a Study in Patients with Osteolytic Lesions of Multiple Myeloma

Study A011-04 was a Phase 2a, multi-center, randomized, double-blind, placebo-controlled, multiple-dose, parallel group, dose-escalation study to evaluate the safety, tolerability, and efficacy of sotatercept in subjects with osteolytic lesions of MM.

In this study, subjects were randomized in a 4:1 ratio to one of three doses of sotatercept (0.1, 0.3, and 0.5 mg/kg) or placebo, administered every 28 days by SC injection, for up to four doses over a 3-month period. Sotatercept was evaluated in combination with the anti-myeloma therapy of melphalan (4 mg/m^2 on Days 1 to 7), prednisolone (40 mg/m^2 on Days 1 to 7), and thalidomide (100 mg per day) (MPT). The sites, Sponsor and Sponsor representatives were blinded to treatment assignment.

Thirty subjects were randomized and received at least one dose of study treatment: six subjects received placebo, 24 subjects received sotatercept (eight subjects per dosing cohort [0.1, 0.3, and 0.5 mg/kg sotatercept]). Twenty-six (86.7%) subjects completed the study. Two subjects discontinued study treatment due to AEs, including one subject in each of the 0.1 and 0.5 mg/kg dose groups. Two subjects discontinued study treatment due to non-AE reasons including one subject in the 0.1 mg/kg dose group who withdrew consent and was discontinued, and one subject in the 0.3 mg/kg dose group who was discontinued at the request of the investigator.

In this study, 50.0% of subjects were female and the mean (range) age was 60.9 (41 to 79) years.

The mean time since diagnosis of MM was 3.3 years, the majority of subjects had stage III MM disease at screening (83.3%) and had received prior chemotherapy (93.3%). A total of 43.3% of subjects were receiving bisphosphonates at screening, which continued during the study.

Fourteen out of 24 subjects (58%) who received sotatercept received three doses or more (four out of eight subjects in the 0.5 mg/kg dose cohort, five out of eight subjects in the 0.3 mg/kg dose cohort, and five out of eight subjects in the 0.1 mg/kg dose cohort).

Table 2 summarizes the most frequent AEs ≥ 5% in all treatment groups

Table 2: Adverse Events Reported in ≥ 5 % Percent of Subjects Overall (Study A011-04)

Preferred Term[a]	Placebo (N=6)		Sotatercept Treatment Group						All Sotatercept (N=24)	
			0.1 mg/kg (N=8)		0.3 mg/kg (N=8)		0.5 mg/kg (N=8)			
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Subjects with ≥ one AE		1 (16.7%)		5 (62.5%)		3 (37.5%)		7 (87.5%)		15 (62.5%)
Neutropenia		1 (16.7%)		2 (25.0%)		2 (25.0%)		3 (37.5%)		7 (29.2%)
Leukopenia		0 (0.0%)		1 (12.5%)		0 (0.0%)		1 (12.5%)		2 (8.3%)
Granulo-cytopenia		0 (0.0%)		1 (12.5%)		1 (12.5%)		1 (12.5%)		3 (12.5%)
Anemia		0 (0.0%)		1 (12.5%)		1 (12.5%)		1 (12.5%)		3 (12.5%)
RTI		0 (0.0%)		1 (12.5%)		0 (0.0%)		0 (0.0%)		1 (4.2%)
Thrombo-cytopenia		0 (0.0%)		0 (0.0%)		0 (0.0%)		1 (12.5%)		1 (4.2%)
Pyrexia		0 (0.0%)		0 (0.0%)		0 (0.0%)		0 (0.0%)		0 (0.0%)
BP increased		0 (0.0%)		1 (12.5%)*		0 (0.0%)		0 (0.0%)		1 (4.2%)
Bronchitis		0 (0.0%)		0 (0.0%)		0 (0.0%)		0 (0.0%)		0 (0.0%)
Compression fracture		0 (0.0%)		0 (0.0%)		0 (0.0%)		0 (0.0%)		0 (0.0%)
Pathological fracture		0 (0.0%)		0 (0.0%)		0 (0.0%)		1 (12.5%)		1 (4.2%)

BP = blood pressure; RTI = respiratory tract infection.

[a] Adverse events (AEs) were those that were treatment-emergent, defined as newly acquired or worsened during or after administration of first dose of study treatment. A subject with multiple occurrences of an AE counted only once under each preferred term.

* Indicates the adverse event was assessed by the investigator as related (possibly, probably, or definitely) to study drug (sotatercept or placebo).

Increases in Hgb were observed within 28 days after administration of the first dose of sotatercept/placebo and sustained for ≥ 28 days from baseline at any time as presented in Table 4.

Table 4: Number of Subjects with an Increase in Hgb from Baseline at Any Time and Sustained for ≥ 28 Days (Study A011-04)

Increase in Hemoglobin	Dose Sotatercept/Placebo				
	0.1 mg/kg (N=8)	0.3 mg/kg (N=8)	0.5 mg/kg (N=8)	Placebo (N=6)	Overall (N=30)
≥1.0 g/dL	5	3	7	4	19
≥1.5 g/dL	3	3	5	2	13
≥2.0 g/dL	2	3	2	0	7

Source: Table 14.3.2.7, Clinical Study Report A011-04.

Improvements in hip bone mineral density were observed in selected sotatercept dose groups. A mean percentage increase from baseline in hip BMD was observed in the 0.1 mg/kg and 0.3 mg/kg sotatercept dose groups at Days 85 and 169/early termination; whereas, the placebo group showed a mean percentage decrease at both time points.

As with serum bone biomarkers, the BMD results tended to be more variable in subjects who were on bisphosphonates. In subjects who were not taking bisphosphonates, a maximum mean

percent increase was observed for most BMD parameters (total, hip, and lumbar spine) in most sotatercept dose groups; whereas, there was a maximum mean percent decrease in the placebo group. Further, substantial improvements in BMD were observed in some subjects, and these improvements were more likely to occur in subjects who received the full course of sotatercept treatment. Review of individual data showed that 8/24 (33.3%) subjects who received sotatercept had a ≥ 5% increase from baseline in spine or femur BMD at one or more time points during the study period. Further, a ≥ 5% increase in BMD was observed in 4/6 subjects who received all four sotatercept doses versus 2/8 subjects who received three doses and 2/10 subjects who received one or two doses. One of 6 (16.7%) subjects who received placebo also showed a ≥ 5% increase in spine or femur BMD during the study period.

Taken together, these data, suggest a beneficial pharmacodynamic effect of sotatercept on erythropoiesis in a patient population with cancer CIA.

1.3.4. A011-08: A Phase 2 Study in Women with Metastatic Breast Cancer with Chemotherapy-induced Anemia

Study A011-08 was a Phase 2, double-blind, randomized, placebo-controlled study to evaluate the efficacy, safety, and tolerability of sotatercept for the treatment of CIA in women with metastatic breast cancer. Subjects were randomized to one of three sotatercept (0.1, 0.3, and 0.5 mg/kg) treatment groups or to a placebo treatment group. Planned enrollment included 30 subjects in each of the three sotatercept treatment groups and 15 subjects in the placebo treatment group (2:2:2:1 ratio). Study treatment was administered via SC injection every 28 days for up to 4 treatments (Days 1, 29, 57, and 85). Subjects were administered concurrent treatment with a myelosuppressive chemotherapy regimen for metastatic breast cancer per standard of care at the study site.

Due to changes in guidance for the treatment of CIA and a slower than expected rate of enrollment, the study was terminated after 30 subjects were enrolled. All 30 subjects had been administered at least one dose of treatment: five subjects in the placebo treatment group, eight subjects in the sotatercept 0.1 mg/kg treatment group, 10 subjects in the sotatercept 0.3 mg/kg treatment group, and seven subjects in the sotatercept 0.5 mg/kg treatment group. The majority of subjects (29/30 [96.7%]) were white; all of the subjects were female; with a median age of 51 years; and age ranged from 32 to 74 years. Demographic characteristics were similar across treatment groups.

Fourteen of 30 (46.7%) subjects completed study treatment. Fourteen subjects in the three sotatercept treatment groups combined and two subjects in the placebo treatment group prematurely discontinued study treatment. Of the 16 subjects who withdrew during the treatment period, eight subjects (50.0%) discontinued due to PD, four subjects (25.0%) withdrew consent, three subjects (18.8%) discontinued due to an AE, and one subject (6.3%) discontinued due to administration of an ESA.

Of the 25 subjects in the three sotatercept treatment groups combined, four (16.0%) were administered the planned four doses of study treatment. In the 0.1 mg/kg, 0.3 mg/kg, and 0.5 mg/kg treatment groups, respectively, 1/8 (12.5%), 3/10 (30.0%), and 0/7 (0.0%) subjects were administered all four doses of sotatercept. Fourteen of 25 (56.0%) subjects in the three sotatercept treatment groups combined skipped and/or had at least one dose modification during the treatment period. One of five (20.0%) subjects in the placebo treatment group was

administered all four doses, and 3/5 (60.0%) subjects had skipped a dose and/or had a single dose modified during the treatment period.

The primary efficacy endpoint was the rate of hematopoietic response, defined as the proportion of subjects who demonstrated a Hgb increase ≥ 1 g/dL from baseline for 28 consecutive days up to two months after the last dose of study treatment, in the absence of RBC transfusion or treatment with an ESA (Table 5).

Table 5: Primary Efficacy Analysis: Subjects with Hemoglobin Increase from Baseline of at Least 1 g/dL for 28 Consecutive Days – Per Protocol Set, Central Laboratory Results (Study A011-08)

		Sotatercept Treatment Group			
	Placebo (N=5)	**0.1 mg/kg (N=5)**	**0.3 mg/kg (N=9)**	**0.5 mg/kg (N=4)**	**All Sotatercept (N=18)**
Responder	1 (20.0%)	0 (0.0%)	3 (33.3%)	2 (50.0%)	5 (27.8%)
Nonresponder	4 (80.0%)	5 (100%)	6 (66.7%)	2 (50.0%)	13 (72.2%)

Five of the 18 (27.8%) subjects in the three sotatercept (0.1, 0.3, and 0.5 mg/kg) treatment groups combined demonstrated a response (ie, were responders). One of five (20.0%) subjects in the placebo group demonstrated a response. Response rates among subjects in the sotatercept 0.3 mg/kg (33%) and 0.5 mg/kg (50%) treatment groups were greater than those in the sotatercept 0.1 mg/kg (0%) and placebo (20%) treatment groups, and suggest a possible sotatercept dose-response relationship.

Assessments of safety in this study were consistent with the known profile of safety of sotatercept. Overall, 20 of 25 (80.0%) subjects in the three sotatercept treatment groups combined and all five (100%) subjects in the placebo treatment group reported ≥ 1 AE. Most AEs were assessed by the investigator as unrelated to study treatment. There were no hypertension or thromboembolic events reported as AEs in subjects administered sotatercept.

The results of this study suggest that sotatercept is safe and demonstrates hematopoietic activity when administered as repeated doses of 0.1, 0.3, or 0.5 mg/kg administered every 28 days for the treatment of CIA in subjects with metastatic breast cancer. These findings are consistent with a robust hematopoietic response following each repeated treatment of sotatercept at doses of 0.3 or

0.5 mg/kg, but also indicate that responses decline during the intervals between repeated treatments. These data suggest that a shorter dosing interval might result in a more sustained hematopoietic response and provide a rationale for a dosing interval of less than 28 days.

1.5. Rationale for Study

In normal hematopoiesis, TGF-β inhibits proliferation of hematopoietic stem cells (Sitnicka, 1996), and negatively regulates erythropoiesis (Zermati, 2000a; Zermati, 2000b). Because TGF-β signaling generally has a negative effect on cell growth, inactivation of this pathway may prevent suppression of primary hematopoietic stem cells and facilitate terminal erythroid maturation. Increased plasma concentrations of TGF-β, and upregulation and overactivation of SMAD2, have been reported in bone marrow progenitors in patients with MDS and provide evidence of activation of sustained TGF-β signaling in MDS (Zhou, 2011). Thus, activation of SMAD2 by TGF-β signaling may be an important event in ineffective hematopoiesis, and inhibition of SMAD2 could stimulate hematopoiesis from primary MDS progenitors. Evidence to support this concept is provided in the observation that in vivo administration of LY-2157299, an antagonist of TGF-β receptor I kinase, improved anemia in a transgenic mouse model overexpressing TGF-β and stimulated hematopoiesis in bone marrow from patients with MDS (Zhou, 2011).

Sotatercept has the potential to provide benefit in a variety of conditions in which ineffective erythropoiesis contributes significantly to anemia and overall disease morbidity, including MDS. The ability of sotatercept to rapidly increase and sustain Hgb concentrations in anemic patients supports the clinical development of sotatercept for the treatment of patients with anemia associated with MDS.

1.6. Summary

Based on the safety data from the two completed Phase 1 studies, single doses of sotatercept up to 3.0 mg/kg IV and multiple doses of sotatercept up to 0.3 mg/kg SC were generally well-

tolerated in healthy postmenopausal women.

Additionally, preliminary review of available safety data from ACE-011-MDS-001 in the 0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg, and 1.0 mg/kg dose levels shows a benign safety profile consistent with the known safety profile of sotatercept, with no new safety signals identified. Furthermore, analysis of clinical and PK/PD data from completed studies at single dose levels up to 3.0 mg/kg IV (A011-01) and multi-dose levels up to 1.0 mg/kg SC (A011-02) in regards to dose required for a sustained hemoglobin increase, support exploration of dose levels up to 2.0 mg/kg.

ACE-011-MDS-001 includes strict monitoring procedures to ensure that safety is appropriately and adequately monitored and would continue at dose levels up to 2.0 mg/kg. They include a Steering Committee that will closely monitor safety and efficacy data throughout study conduct, weekly hemoglobin and blood pressure monitoring required per protocol, specific dose reduction/modification/discontinuation guidelines and clearly-defined dose-limiting toxicity definitions to ensure safety is adequately assessed at all dose levels prior to each treatment administration.

As with all biologics, there is the potential for anti-drug antibodies that can be associated with increased drug clearance and hypersensitivity reaction. Celgene will monitor the data and communicate to Investigators any new findings. Investigators should monitor subjects for signs and symptoms of injection site and hypersensitivity reactions. Treat injection site and

hypersensitivity reactions according to your standard of care. Sotatercept should not be administered to any subject who develops hypersensitivity to sotatercept.

Please refer to the Investigator Brochure for additional detailed information on the pharmacology, toxicology, drug metabolism, clinical studies, and AE profile, of sotatercept.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of this study 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 int-1 risk MDS or non-proliferative CMML.

2.2. Secondary Objectives

The secondary objectives of this study are to evaluate the:

1. Safety of sotatercept
2. Rate of 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 (TPAML)
6. Time to progression to events of higher risk MDS (TTPHR) (ie, int-2 or high risk IPSS)
7. Progression-free survival (PFS)
8. Overall survival (OS)
9. Pharmacokinetics (PK) of sotatercept

3. STUDY ENDPOINTS

3.1. Primary Endpoint

The primary endpoint of this study is the rate of HI-E (Appendix C) starting before the completion of five 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 three 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.

3.2. Secondary Endpoints

The secondary endpoints of this study are:

1. Safety of sotatercept – based upon assessments listed in Section 10.7.
2. RBC transfusion independence in transfusion-dependent subjects (Appendix C).
3. Time to HI-E (Appendix C).
4. Duration of HI-E (Appendix C).
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 (Appendix C).
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 (eg, int-2 or high-risk IPSS, Appendix B).
7. Progression-free survival (PFS) – the time between randomization (Part 1) or start of therapy (Part 2) and PD (Appendix C) 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.

4. OVERALL DESIGN OF THE STUDY

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, by IPSS (Appendix B), with anemia (Hgb ≤ 9.0 g/dL).

The study is comprised of 2 parts:

Part 1

Subjects will be stratified by concentration of serum EPO (< 500 versus ≥ 500 mIU/mL), 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, SC, 0.1 mg/kg or 0.3 mg/kg Q3W.

Enrollment will continue without hiatus beyond randomization of five subjects into each of the 0.1 mg/kg and 0.3 mg/kg treatment groups. Following treatment of five 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 one cycle of 21 days), all available safety and efficacy data will be assessed by a Steering Committee (Section 4.4). Based upon the occurrence of dose-limiting toxicity (DLT) (Section 4.1.1) 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 six subjects in the 0.5 mg/kg treatment group (with at least six subjects having completed at least three cycles of 21 days each), all available safety and efficacy data will again be assessed by a Steering Committee from all dose levels. Based upon the occurrence of 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 six subjects in the 1.0 mg/kg treatment group (with at least six subjects having completed at least three cycles of 21 days each), all available safety and efficacy data will again be assessed by a Steering Committee from all dose levels. Based upon the occurrence of 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. The 2.0 mg/kg sotatercept dose was reduced to 1.5 mg/kg for ongoing and newly enrolled subjects (Amendment 4).

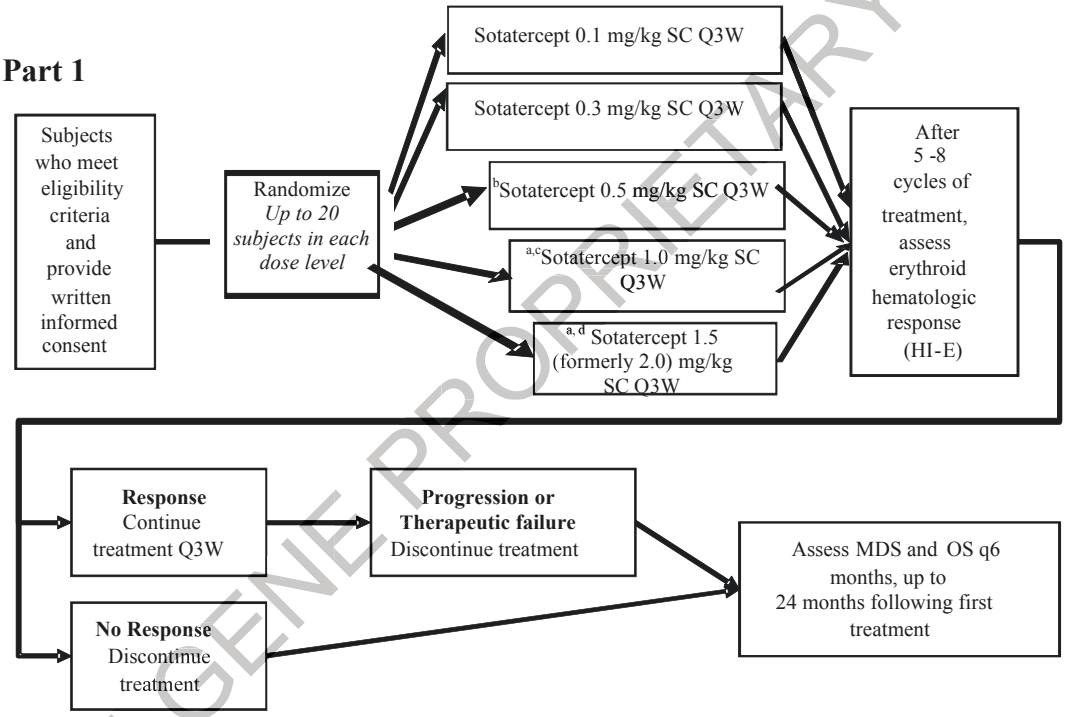
Intermediate cohorts (not to exceed 2.0 mg/kg) may be added at the time of dose escalation up to 1.0 mg/kg and up to 2.0 mg/kg (eg, 0.75 mg/kg or 1.5 mg/kg respectively) based on assessment by the Steering Committee of available safety and efficacy data when at least six subjects have at least three cycles of treatment in the current dose level. Enrollment will continue beyond randomization in all dose levels (unless dose level(s) is closed due to safety reasons or lack of efficacy as recommended by the Steering Committee) until up to a total of 20 subjects in each dose level. 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 four subjects experiencing an event) experience a DLT of related (suspected) AE ≥

Grade 2 (other than hypertension and hemoglobin DLT as defined in Section 4.1.1), the Steering Committee may recommend the closure of the treatment group.

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

Moreover, if > 33% of the subjects (minimum two subjects experiencing an event) experience a hypertension DLT (Refer to Section 4.1.1) confirmed by the investigator by two readings obtained 5 minutes apart, the Steering Committee may recommend the closure of the treatment group. In order to harmonize DLT assessment for hypertension across the study, additional guidance must be followed as defined in Section 4.1.1. Additionally, for any treatment group that accrues a minimum of 10 subjects or less if recommended 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 transfusion requirements if reduction seen is less than 4 units), the Steering Committee may recommend the closure of the treatment group.

Figure 4: 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 six subjects have at least three 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 five subjects in the 0.1 mg/kg SC and five subjects in the 0.3 mg/kg SC treatment groups with the last subject for each group having completed at least one 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 six subjects in the 0.5 mg/kg treatment group (or current dose level if intermediate cohort is added) with at least six subjects having completed at least three 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 six subjects in the 1.0 mg/kg treatment group (or current dose level if intermediate cohort is added) with at least six subjects having completed at least three cycles of 21 days each, and an assessment of all available safety and efficacy data for all subjects. Per Steering Committee assessment on 02 Mar 2015, the sotatercept 2.0 mg/kg dose was reduced to 1.5 mg/kg. Subjects already receiving sotatercept 2.0 mg/kg were dose reduced to 1.5 mg/kg (Amendment 4).

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 (Expansion Cohort)

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

Steering Committee Recommendation

Based on the 02 Mar 2015 Steering Committee's review of safety, efficacy and pharmacokinetic data of subjects enrolled in the Part 1 dose levels, including the sotatercept 2.0 mg/kg cohort level:

Part 1 - The sotatercept 2.0 mg/kg cohort was closed. Ongoing and newly enrolled subjects are to be dose reduced to sotatercept 1.5 mg/kg.

Part 2 - Subjects enrolled in Part 2 (Expansion Cohort) will receive sotatercept at 1.0 mg/kg.

This update is reflected in Amendment 4.

4.1.1. Dose-limiting Toxicity

The following are DLTs if treatment-related (suspected):

Dose-limiting Toxicity (DLT)	Definition
Hemoglobin	Hgb > 12 g/dL (not influenced by transfusions) sustained for ≥ 7 days, confirmed by two assessments ≥ 1 week apart.
Hypertension*	
Subjects within normal limits (WNL) and not receiving antihypertensive treatment at baseline	≥ Grade 2 (140 mmHg systolic BP [blood pressure] 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 increase ≥ 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 increase ≥ 140 or diastolic increase ≥ 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)

* Hypertension DLT should be confirmed by study investigator and should be the mean of two readings obtained approximately 5 minutes apart with the patient seated for approximately 10 minutes prior to the initial reading.

4.1.2. 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 (or closest time prior to dosing that is logistically feasible for the study site).

Treatment – Comprised of five 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 five 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 three 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 three cycles (Cycles 6-8).

End of Treatment – Assessments to be conducted upon:

- Completion (≥ 5 cycles) of participation in the Treatment Period of the study, **prior** to the first dose of sotatercept in the Extension Period.
- Early (< 5 cycles) termination of participation in the Treatment Period of the study, **after** last dose of sotatercept.

Extension – After completion of 5 cycles of treatment (or up to 8 cycles for potential late responders), subjects who meet at least one of the criteria listed below may enter the Extension Period, subject to Rules for Delay, Reduction, and Discontinuation of Treatment (Section 8.2.1), until PD, treatment failure, or other reason, as appropriate, listed in Section 12, Discontinuations.

HI-E (Non-transfusion-dependent [NTD] subjects) with an increase ≥ 1.5g/dL Hgb from baseline, sustained over a period of ≥ 8 consecutive weeks in the absence of RBC transfusions.

HI-E (Transfusion-dependent [TD] subjects) with a decrease ≥ 4 units of RBCs transfused over a period of 8 consecutive weeks, relative to the number of units of RBCs transfused in the 8 weeks immediately prior to Day 1.

NTD subjects exhibiting at least a 1.0 g/dL rise in Hgb compared to baseline at the investigator's discretion.

TD subjects exhibiting a 50% reduction in transfusion requirement compared to baseline at the investigator's discretion.

End of Extension – Assessments to be conducted upon completion of participation in the Extension Period of the study.

Follow-up – Following the end of treatment (last dose of sotatercept administered) in the Treatment Period or the Extension Period, follow-up will include a 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 time point 3 months after the last treatment, assessment of 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.

4.2. Rationale for the Design of the Study

This is an open-label, randomized, Phase 2, parallel, dose-ranging, multicenter study designed to assess the effect of sotatercept on hematopoietic endpoints in subjects with low- and intermediate-1 risk myelodysplastic syndromes or non-proliferative CMML, by IPSS (Appendix B). The randomized, parallel-group, design is typical of Phase 2 studies evaluating a range of doses for an investigational drug. Subjects will be randomized to treatment groups to limit scientific bias within the study. The duration of treatment of 15 weeks (5 cycles) has been shown to be adequate to assess safety and to demonstrate a pharmacodynamic effect of sotatercept on hematopoietic parameters in both healthy volunteers and patients.

Dose escalation in 100% increment from 0.5 mg/kg to 2.0 mg/kg Q3W is proposed to achieve adequate separation in the systemic sotatercept exposure between doses. This would facilitate the evaluation of the dose-response relationship for effectiveness and toxicity as well as to minimize the number of subjects exposed to likely sub-therapeutic doses. 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 six subjects have at least three cycles of treatment in the current dose level. Three cycles of data in six subjects in the current dose level will ensure that an adequate amount of safety and efficacy data is available prior to dose escalation or treatment group closure at dose levels where limited multi-dose clinical data is available from previous studies (eg, 1.0 mg/kg and 2.0 mg/kg).

Note: Based on the 02 Mar 2015 Steering Committee's review of safety, efficacy and pharmacokinetic data of subjects enrolled in the Part 1 dose levels, including the sotatercept 2.0 mg/kg cohort level:

Part 1 - The sotatercept 2.0 mg/kg cohort was closed. Ongoing and newly enrolled subjects are to be dose reduced to sotatercept 1.5 mg/kg.

Part 2 - Subjects enrolled in Part 2 (Expansion Cohort) will receive sotatercept at 1.0 mg/kg.

4.3. Duration of the Study

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).

Treatment – Comprised of five complete cycles of 21 days each 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 three cycles (Cycles 6-8) for the purpose of meeting response criteria.

Extension – After completing 5 cycles of treatment (or up to 8 cycles for potential late responders), subjects who qualify for the Extension Period (refer to Section 4.1.2), may enter the Extension Period and continue treatment, subject to Rules for Delay, Reduction, and Discontinuation of Treatment (Section 8.2.1), until PD, treatment failure, or other reason, as appropriate, listed in Section 12, Discontinuations.

Follow-up – Following the End of Treatment (last dose of sotatercept administered) in the Treatment Period or the Extension Period, follow-up will include a 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 pharmacokinetics at a single time point 3 months after the last treatment, assessment of 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.

The End of Trial is defined as either the date of the last visit of the last subject to complete the study, or the date of receipt of the last data point from the last subject that is required for primary, secondary analysis, as pre-specified in the protocol and/or the Statistical Analysis Plan, whichever is the later date.

The sponsor may decide to 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 who remain on study may be consented and continue to receive treatment with IP. It must be the opinion of the investigator that the remaining subject(s) continue to receive benefit from treatment with IP.

4.4. Steering Committee

A Steering Committee will be established by charter. The Steering Committee will be comprised of Study Investigators, an Independent Cardiologist, representatives of Celgene, and may include additional ad hoc members. The Steering Committee will advise and recommend to the sponsor:

- Inclusion of the 0.5 mg/kg treatment group in the randomization scheme, based upon the occurrence of DLT (Section 4.1.1) in ≤ 1/5 subjects in Cycle 1 in the 0.1 mg/kg and 0.3 mg/kg treatment groups and a review of all available safety and efficacy data following treatment of five subjects in each of those treatment groups (with the last subject for each group having completed at least one cycle of 21 days).

- Inclusion of the 1.0 mg/kg treatment group in the randomization scheme, based upon the occurrence of DLT (Section 4.1.1) in ≤ 1/6 subjects in Cycle 1 in the 0.5 mg/kg treatment group and a review of all available safety and efficacy data (with at least six subjects in the 0.5 mg/kg treatment group having completed at least three cycles of 21 days each).
- Inclusion of the 2.0 mg/kg treatment group in the randomization scheme, based upon the occurrence of DLT (Section 4.1.1) in ≤ 1/6 subjects in Cycle 1 in the 0.5 mg/kg treatment group and a review of all available safety and efficacy data (with at least six subjects in the 1.0 mg/kg treatment group having completed at least three cycles of 21 days each). The 2.0 mg/kg sotatercept dose was reduced to 1.5 mg/kg for ongoing and newly enrolled subjects per Amendment 4.
- Inclusion of additional intermediate dose levels (not to exceed 2.0 mg/kg) based on assessment of all available safety and efficacy data at time of dose escalation to up to 1.0 mg/kg and up to 2.0 mg/kg (eg, 0.75 mg/kg or 1.5 mg/kg respectively).
- Discontinuation of enrollment and/or treatment in treatment groups without signal of efficacy or with unacceptable risk to the safety of the subject. For any treatment group that accrues a minimum of 10 subjects or less if recommended 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 transfusion requirements if the reduction observed is less than 4 units).
- Closure of a study treatment group:
  - if ≥ 40% of the subjects (minimum four subjects experiencing an event) experience a DLT of related (suspected) adverse event ≥ Grade 2 (other than a hemoglobin or hypertension DLT as defined in Section 4.1.1).
  - if > 33% of the subjects (minimum two subjects experiencing an event) experience hemoglobin > 12 g/dL (not influenced by transfusions) sustained for ≥ 7 days, confirmed by two assessments ≥ 1 week apart.
  - if > 33% of the subjects (minimum two subjects experiencing an event) experience a hypertension DLT (refer to Section 4.1.1) confirmed by the investigator as two readings obtained approximately 5 minutes apart with the subject seated for approximately 10 minutes prior to initial reading, the Steering Committee may recommend the closure of the treatment group. In order to harmonize DLT assessment for hypertension across the study, additional guidance must be followed as defined in Section 4.1.1.
- Changes to the protocol or conduct of the study based upon emerging clinical or scientific data from this and/or other studies.
- Procedures to ensure the safety of subjects and integrity of study data.
- Procedures to meet the overall goals and objectives of the study.

Meetings of the Steering Committee will occur:

- Following treatment of at least five 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 one cycle of 21 days).
- Following treatment of at least six subjects in the 0.5 mg/kg treatment group (with at least six subjects having completed at least three cycles of 21 days each).
- Following treatment of at least six subjects in the 1.0 mg/kg treatment group (with at least six subjects having completed at least three cycles of 21 days each).
- Following treatment of at least six subjects in the 2.0 mg/kg treatment group (with at least six subjects having completed at least three cycles of 21 days each).
- Following treatment of at least six subjects in any additional interim treatment group (eg, 0.75 mg/kg or 1.5 mg/kg) if previously recommended to be opened by the Steering Committee (with at least six subjects having completed at least three cycles of 21 days each).
- Following treatment of each block of approximately five to six subjects in each ongoing treatment group (with all subjects in each block having completed at least three cycles of 21 days each).
- Ad hoc

Additional details of the function and schedule of meetings of the Steering Committee will be specified in the Charter of the Steering Committee.

5. TABLE OF EVENTS

Table 7: Schedule of Assessments

Period	Screening	Treatment															End of Treatment Period[r] or Early Termination	Extension[s]	End of Extension Period[t]	Follow -up
Cycle		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5 (up to 6-8 for potential late responders[s])			After Completion of Treatment Period		For extension subjects- upon discontin-uation of study treatment	
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]	●	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Transfusion log[b]	●	●	-	-	●	-	-	●	-	-	●	-	-	●	-	-	●	●	●	●[v]
Record current therapies (including concomitant medications)/procedures	●	●	-	-	●	-	-	●	-	-	●	-	-	●	-	-	●	●	●	●[v]
Record adverse events[c]	Record on an ongoing basis.																			
Physical exam, including weight + vitals[d]	●	●	-	-	●	-	-	●	-	-	●	-	-	●	-	-	●	●	●	-

Table 7: Schedule of Assessments (Continued)

Period	Screening	Treatment															End of Treatment Period[r] or Early Termination	Extension[s]	End of Extension Period[t]	Follow -up
Cycle		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5 (up to 6-8 for potential late responders[s])			After Completion of Treatment Period		For extension subjects- upon discontinuation of study treatment	
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]	●	●	-	-	●	-	-	●	-	-	●	-	-	●	-	-	●	●	●	●
Pharmacokinetics[j]	-	●	●	●	●	●	●	●	-	-	●	-	-	●	-	-	●	●	●	●

Table 7: Schedule of Assessments (Continued)

Period	Screening	Treatment															End of Treatment Period[r] or Early Termination	Extension[s]	End of Extension Period[t]	Follow -up
Cycle		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5 (up to 6-8 for potential late responders[s])			After Completion of Treatment Period		For extension subjects- upon discontinuation of study treatment	
Day[a]	-28 to 0	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15				
Antidrug antibody (ADA)[k]	-	●	-	-	●	-	-	●	-	-	●	-	-	●	-	-	●	●	●	●[k]
MDS response assessment[l]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	●	-	●	●[u]
Bone marrow aspirate, standard[m] (with iron staining);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 (Appendix B), and blast percentage, cytopenia and karyotype; cytogenetics and **historic molecular mutational analyses** -(ie, SF3B1, and other MDS related molecular mutations), at original diagnosis (including all historical data) 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 (ie, transfusions) since sample obtainment is acceptable. All transfusions (ie, RBC, platelets, whole blood, etc) are to be recorded at baseline from at least 12 weeks prior to enrollment; up through 3 months post last dose of sotatercept and associated pre-transufsion hemoglobin levels at closest time prior to RBC transfusions, if available. .

[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 five 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 (or closest time prior to dosing that is logistically feasible for the study site). 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 five 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 five 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 the schedule in Table 7. 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 time point 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 (must be provided for the assay of ADA.

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

[m] Bone marrow aspirate, standard (with iron staining) - for: local assessment of cytogenetics employing standard banding overall and FISH for del (5q) only; preparation of smears with Wright and Giemsa stain for local and central assessment of cell differential, morphology, and cellularity; standard assessment by flow cytometry. For central assessment, refer to central lab manual for staining requirements. 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, 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] For Extension Subjects – assessments should be completed **prior** to the first dose of sotatercept in the Extension Period. For Early Termination Subjects – assessments to be completed **after** last dose of sotatercept.

[s] After completing 5 cycles of treatment (or up to 8 cycles for late responders), subjects who qualify for the Extension Period (refer to Section 4.1.2) may continue therapy until PD or treatment failure in the Extension Phase following a Q3W visit schedule. 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 eight consecutive weeks (potential late responders) may continue treatment for up to an additional three cycles (Cycles 6-8) for the purpose of meeting response criteria.

[t] End of Extension Period – Assessments to be conducted upon completion of participation in the Extension Period (discontinuation of sotatercept).

[u] 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.

[v] 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.

6. PROCEDURES

Procedures conducted on the day of treatment should be conducted prior to administration of treatment. Deviation of ± 5 business days from the day of the scheduled assessment is permitted during the Treatment Period, Extension Period, and Follow-Up Period (for visits that require sample collection). Other Follow-up Period visits will have a ± 15 business day window. If the deviation is due to missed or delayed visit, the subject should return to the original schedule as soon as possible. If the deviation is due to delayed dose, the subject should adhere to a schedule revised to ensure complete cycles of treatment.

An unscheduled visit can occur at any time. Source documentation must be maintained for unscheduled visits. The date and data from the unscheduled visit must be recorded on the appropriate CRF.

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 Day 1.

Procedures are to be performed according to the schedule in the Table of Events, Table 7, Section 5.

1. Randomize subject to sotatercept in the interactive voice response system (IVRS) system - Subjects who meet all eligibility criteria (Sections 7.2 and 7.3) will be stratified and randomized utilizing a validated IVRS. A subject will be randomized to a Treatment Group once a unique multi-digit subject identification number has been assigned by IVRS. Subjects should be randomized prior to preparation) of the first treatment (ie, on the same day, if logistically possible). Randomization is not applicable in Part 2. However, the subject should still be registered in the IVRS system prior to preparation of the first study treatment (ie, on the same day, if logistically possible).
2. Administer sotatercept – See Sections and 8.2.
3. Medical history
4. Height – without shoes
5. Record prior meds (medications) - within the 8-week period prior to enrollment (Day 1)
6. Record prior treatments - within the 8-week period prior to enrollment (Day 1)
7. Myelodysplastic Syndrome or non-proliferative CMML disease history and baseline assessment and prior therapy - to include date of diagnosis, WHO subtype, IPSS (Appendix B), and blast percentage, cytopenia, karyotype and **historic molecular mutational analysis data** - (ie, SF3B1, and other MDS-related molecular mutations) 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 and transfusions. For baseline MDS disease assessment, if the results of a bone marrow biopsy and/or aspirate performed within 90 days prior to screening period are available, they can be used contingent that the subject did not receive additional treatment (including ESAs and steroids) since the sample obtainment). Supportive care (ie, transfusions) since sample obtainment is acceptable.

8. Transfusion log – include all transfusions from at least 12 weeks prior to enrollment (Day 1) up through 3 months post last dose of sotatercept and associated pre-transfusion Hgb levels at closest time prior to RBC transfusions, if available.
9. Record of current therapies (including concomitant medications)/procedures
10. Record of AEs – include AEs beginning from the time of provision of written informed consent to participate in this study to 42 days after the last treatment.
11. Physical examination – by body system
12. Vital signs – Pulse rate, weight (without shoes)
13. Blood pressure (systolic and diastolic, after approximately 10 minutes seated, mean of two measurements, approximately 5 minutes apart) should be assessed during screening and on a weekly basis during the first five cycles. In addition, blood pressure should be recorded (at home by the subject or caretaker) approximately 24 hours after initial study drug administration during Cycle 1. On study drug dosing days, blood pressure must be assessed within 8 hours of study drug administration (or closest time prior to dosing that is logistically feasible for the study site). Monitoring of blood pressure may be done at home on non-dosing days. For home monitoring, a plan with instructions and thresholds on 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 five cycles of treatment, monitoring frequency may decrease to once per cycle at the investigator's discretion.
14. ECG – 12-lead with rhythm strip - 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 findings in ECG readings after completing five cycles of treatment, ECGs will not be required until the end of Treatment Period unless deemed necessary by the investigator.
15. ECOG performance status (Appendix D)
16. Hematology
    - Hemoglobin (Hgb) - must be assessed prior to each treatment administration
    - Hematocrit (Hct)
    - RBC count
    - Absolute reticulocyte count
    - Platelet count
    - WBC count and differential
    - Absolute neutrophil count (ANC)
    - Mean corpuscular volume (MCV)
17. Serum chemistry
    - 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) Appendix H]

19. Serum erythropoietin

20. Urinalysis
    - Albumin (quantitative)
    - Bilirubin
    - Creatinine (quantitative)
    - Glucose
    - Hemoglobin
    - Total protein (quantitative)
    - Ketones
    - pH
    - Albumin / creatinine ratio
    - Protein / creatinine ratio

Note: Clinical laboratory evaluations (serum chemistry, hematology, absolute reticulocyte count, , serum erythropoietin, urinalysis) will be performed by a central laboratory.

Local laboratory assessments are allowed in cases when timely results are needed (eg, randomization, study treatment and chemotherapy 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.

21. Pregnancy testing – Pregnancy tests, with a minimum sensitivity of 25 mIU/ml, 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.
22. Pharmacokinetics – Blood samples will be collected for assessment of pharmacokinetics in all subjects as per the schedule in Table 7. 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 assessment of pharmacokinetics at the end of the Extension Period. During the Follow-up Period a blood sample will be collected for assessment of PK at a single time point 3 months after the last treatment. At each PK time point,

approximately 3 mL blood will be collected and serum prepared .

23. 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 PK. A blood sample will be collected for 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 PK, 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 PK (ie, during the Follow-up Period) a serum sample must be provided for the assay of ADA.
24. MDS response assessment – per the International Working Group (IWG) Response Criteria in Myelodysplasia (Cheson, 2006; Appendix C), to include best response at end of treatment
25. Bone marrow aspirate, standard:
    - For local assessment of cytogenetics and central review of cytogenetics reports. Methods should employ:
        - Standard banding methods overall, and
        - Fluorescence in-situ hybridization (FISH) for d5q only.
    - For preparation of smears with Wright and Giemsa stain for local and central assessment of cell differential, morphology, and cellularity. For central assessment, refer to central laboratory manual for staining requirements.
    - For standard assessment by flow cytometry.
        - During the screening period, if cytogenetic results from within 90 days prior to start of screening period are available, they can be used contingent that the subject did not receive additional treatment (including ESAs and steroids) since sample obtainment. Supportive care (ie, transfusions) since sample obtainment is acceptable.
26. 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. Refer to central lab manual for staining requirements.

7. STUDY POPULATION

7.1. Number of Subjects and Sites

It is anticipated that up to approximately 140 subjects will be randomized to achieve 75-115 evaluable subjects (Section 10.3): up to 20 subjects in each of the sotatercept 0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg, 1.0 mg/kg and 2.0 mg/kg treatment groups, and following the assessment of efficacy and safety parameters in Part 1, an additional 15 subjects will be enrolled in Part 2 and complete treatment at the dose level of sotatercept that demonstrates the greatest frequency of HI-E.

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 six subjects have at least three cycles of treatment in the current dose level (refer to Section 4.1.). Up to 20 subjects may also be enrolled at these interim treatment groups.

Note: Amendment 4: Based on the 02 Mar 2015 Steering Committee's review of safety, efficacy and pharmacokinetic data of subjects enrolled in the Part 1 dose levels, including the sotatercept 2.0 mg/kg cohort level:

Part 1 - The sotatercept 2.0 mg/kg cohort was closed. Ongoing and newly enrolled subjects are to be dose reduced to sotatercept 1.5 mg/kg.

Part 2 - Subjects enrolled into Part 2 (Expansion Cohort) will receive sotatercept at 1.0 mg/kg.

This is a multicenter study that will be conducted at up to approximately 25 sites in the United States and Europe.

7.2. Inclusion Criteria

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

1. Provide written informed consent prior to the conduct of any study-specific assessment or procedure.
2. Age ≥ 18 years at the time of signing the informed consent form.
3. Able to adhere to the study visit schedule and other requirements of the protocol.
4. Documented diagnosis of MDS or non-proliferative CMML (WBC ≤ 13,000 /mm^3, WHO, Vardiman, 2009) that meets IPSS (Appendix B) criteria for low- or int-1 risk disease.
5. Anemia defined as requiring transfusion ≥ 2 units of RBCs within 84 days of enrollment for Hgb ≤ 9.0 g/dL.
6. No response or loss of response to prior treatment with rHu EPO (≥ 40,000 U/wk x 8 or equivalent), or darbepoetin alpha (≥ 500 mcg Q3W x 4 or equivalent), or low chance of response to ESAs reflected by endogenous serum EPO concentration > 500 mU/mL.

7. Subjects must have had no response or loss of response to no greater than 2 prior lines of treatment for MDS or non-proliferative CMML (not including treatment with ESAs or lines discontinued due to intolerance). Prior treatment with multiple agents given in combination will be considered one line.
8. All previous therapy, including ESAs, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), must have been discontinued ≥ 28 days before enrollment
9. Eastern Cooperative Group (ECOG) performance status (Appendix D) ≤ 2.
10. Adequate renal function reflected by creatinine < 1.5 X ULN and creatinine clearance > 50 mL/min according to Cockcroft-Gault formula (Appendix H).
11. Total bilirubin ≤ 3.0 mg/dL, except if associated with primary shunt hyperbilirubinemia (idiopathic dyserythropoietic jaundice).
12. AST (SGOT) and ALT (SGPT) ≤ 3.0 x ULN.
13. Females of childbearing potential participating in the study are to use highly effective methods of birth control during study participation and for 112 days (approximately five times the mean terminal half-life of sotatercept [23 days] based on multiple-dose PK data) following the last dose of sotatercept. Females of childbearing potential must have a negative serum beta-human chorionic gonadotropin (β-HCG) or urine pregnancy test within three days of sotatercept dosing (Day 1). Subjects must be counseled concerning measures to be used to prevent pregnancy and potential toxicities prior to the first dose of sotatercept. A female of childbearing potential is a sexually mature woman who has not undergone a hysterectomy or bilateral oophorectomy or who has not been postmenopausal for at least 24 consecutive months (ie, who has had menses at some time in the preceding 24 months).
14. Males must agree to use a latex condom during any sexual contact with females of childbearing potential while participating in the study and for 7 months (210 days) following the last dose of sotatercept, even if he has undergone a successful vasectomy. Subjects must be counseled concerning measures to be used to prevent pregnancy and potential toxicities prior to the first dose of sotatercept.
15. Free of metastatic malignancy (other than MDS) for ≥ 2 years.

7.3. Exclusion Criteria

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

Patients with MDS with chromosome 5q deletion without documented treatment failure to lenalidomide (ie, loss of response or no response after 4 months of treatment, intolerable to treatment, or having other cytopenia precluding use of treatment).

1. Women who are pregnant or breast feeding (women who are lactating must agree not to breast feed) or planning to become pregnant or breast feed during the period of treatment and for 112 days following the last dose of sotatercept.

2. Males who do not agree to use a latex condom or non-latex condom NOT made of natural (animal) membrane during sexual contact with females of childbearing potential or a pregnant female while participating in the study and for at least 7 months (210 days) following the last dose of sotatercept, even if he has undergone successful vasectomy.
3. Major surgery within 30 days prior to Day 1
4. Incomplete recovery or incomplete healing of wounds from previous surgery.
5. Subjects with classification of 3 or higher heart failure as classified by the New York Heart Association (NYHA) (Appendix E).
6. History of deep vein thrombosis, pulmonary emboli, embolic stroke, or myocardial infarction occurring within the past 6 months. Local central line thrombosis is allowed.
7. Subjects requiring ongoing anticoagulant treatment (eg, Coumadin, warfarin, heparin) during the course of the study. Aspirin is allowed.
8. History of severe allergic or anaphylactic reaction or hypersensitivity to recombinant proteins or excipients in the investigational product (refer to the Investigator's Brochure for further information).
9. A condition, including laboratory abnormality, that, as determined by the investigator, places the subject at unacceptable risk if he/she was to participate in the study or that potentially confounds interpretation of data from the study.
10. Concurrent use of anticancer cytotoxic chemotherapeutic agent or treatment.
11. Known positive for human immunodeficiency virus (HIV) or infectious hepatitis type C or active infectious hepatitis type B.
12. Clinically significant anemia unrelated to myelodysplastic disease (eg, iron, B12 or folate deficiencies, autoimmune or hereditary hemolysis, active gastrointestinal bleeding, and chronic renal insufficiency).
13. Thrombocytopenia (platelet count $< 30{,}000/\mu L$).
14. Uncontrolled hypertension (systolic blood pressure [SBP] ≥ 140 or diastolic blood pressure [DBP] ≥ 90).
15. Treatment with another investigational drug or device within 28 days prior to Day 1, or if the half-life of the previous product is known, within 5 times the half-life prior to dosing, whichever is longer.
16. Prior exposure to sotatercept (ACE-011).
17. Any significant medical condition, laboratory abnormality, or psychiatric illness that, as determined by the investigator, would prevent the subject from participating in the study or providing written informed consent.
18. Any condition including the presence of laboratory abnormality that, as determined by the investigator, places the subject at unacceptable risk if he/she were to participate in the study.

19. Any condition that, as determined by the investigator, confounds the interpretation of data from the study.

8. DESCRIPTION OF STUDY TREATMENTS

8.2. Treatment Administration and Schedule

Sotatercept will be administered after reconstitution as an SC (subcutaneous) injection to subjects by the study staff at the clinical site and administration will be documented in the study source record. Subcutaneous injections will be given in the upper arm, abdomen, or thigh. Calculated doses requiring reconstituted volume greater than 2 mL should be divided equally into two syringes and injected into two separate sites. Rotate sites for each injection.

Subjects will be assigned to be administered treatment as per one of the following regimens:

- Sotatercept 0.1 mg/kg SC Q3W
- Sotatercept 0.3 mg/kg SC Q3W
- Sotatercept 0.5 mg/kg SC Q3W
- Sotatercept 1.0 mg/kg SC Q3W
- Sotatercept 1.5 mg/kg SC Q3W (Amendment 4)

- Sotatercept 2.0 mg/kg SC Q3W (cohort closed – Amendment 4)

Additional intermediate dose levels may be added (eg, 0.75 mg/kg SC Q3W or 1.5 mg/kg SC Q3W, not to exceed 2.0 mg/kg SC Q3W) if recommended by the upon review of safety and efficacy data (Refer to Section 4.1) at time of dose escalation to 1.0 mg/kg and 2.0 mg/kg respectively).

Note: Amendment 4: Based on the 02 Mar 2015 Steering Committee's review of safety, efficacy and pharmacokinetic data of subjects enrolled in the Part 1 dose levels, including the sotatercept 2.0 mg/kg cohort level:

Part 1 - The sotatercept 2.0 mg/kg cohort was closed. Ongoing and newly enrolled subjects are to be dose reduced to sotatercept 1.5 mg/kg.

Part 2 - Subjects enrolled into Part 2 (Expansion Cohort) will receive sotatercept at 1.0 mg/kg.

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 three cycles (Cycles 6-8) for the purpose of meeting response criteria. After completing the Treatment Period, subjects who qualify for the Extension Period (refer to Section 4.1.2) may continue treatment in the Extension Period until PD or therapeutic failure.

8.2.1. Rules for Delay, Reduction, and Discontinuation of Treatment

Subjects must have Hgb assessed and results available within 8 hours (or closest time prior to dosing that is logistically feasible for the study site) prior to each study drug administration.

For subjects who are transfusion independent (ie, transfusion burden of < 4 units of RBCs in the eight weeks prior to randomization or enrollment), baseline (ie, Cycle 1 only) pre-dose Hgb should be ≤ 9.0 g/dL prior to dosing administration.

Subjects must have blood pressure assessed within 8 hours (or closest time prior to dosing that is logistically feasible for the study site) prior to each study drug administration. 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 initial reading.

Table 8: Rules for Delay, Reduction, and Discontinuation of Treatment

Observation	Action
• Hypertension DLT as defined in Section 4.1.1.	• Discontinue treatment
• Treatment-related (suspected) toxicity ≥ Grade 3 (other than Hgb or Hypertension)	• Discontinue treatment
• Treatment-related (suspected) toxicity ≤ Grade 2 that delays treatment by more than 3 months	• Discontinue treatment
For Hemoglobin ≤ 11 g/dL (prior to dosing)	
• Hgb ≤ 2 g/dL increase (not influenced by transfusions) at Day 21 from last dose	• Continue current dose
• Hgb > 2 g/dL increase (not influenced by transfusions) at Day 21 from last dose	• Continue dosing - one level dose reduction (see Table 9).
For Hemoglobin > 11 g/dL and ≤ 12 g/dL (prior to dosing)	
• Hgb ≤ 2 g/dL increase (not influenced by transfusions) at Day 21 from last dose	• Dose delay until Hgb ≤ 11 g/dL and hypertension < SBP 140 mmHg and < DBP 90 mmHg • Dosing can commence ≥ 7 days after the originally planned ACE-011 dose that was delayed. Hgb must be < 11 g/dL. • Subsequent ACE-011 dosing will resume 21 days following this revised treatment dose date
• Hgb > 2 g/dL (not influenced by transfusions) increase at Day 21 from last dose	• Dose delay • Hold dose for one treatment visit • Re-evaluate Hgb & BP prior to resuming treatment • If Hgb < 11 g/dL and hypertension < SBP 140 mmHg and < DBP 90 mmHg at the next scheduled visit, resume dosing - one level dose reduction (See Table 9)

Table 8: Rules for Delay, Reduction, and Discontinuation of Treatment (Continued)

Observation	Action
For Hemoglobin > 12 g/dL and ≤ 14 g/dL	
• Hgb > 12 g/dL and ≤ 14 g/dL (not influenced by transfusions) sustained for ≥ 7 days, confirmed by two assessments ≥ 1 week apart	• Dose delay • Hold dose for one treatment visit • Re-evaluate Hgb & BP prior to resuming treatment • If Hgb < 11 g/dL and hypertension < SBP 140 mmHg and < DBP 90 mmHg at the next scheduled visit, resume dosing - two level dose reduction (see Table 9)
For Hemoglobin > 14 g/dL	
• Hgb >14 g/dL(not influenced by transfusions), sustained for ≥7 days, confirmed by two assessments ≥1 week apart	• Discontinue treatment (see Section 12)

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. When indicated, per dose modification rules (Table 8) the dose of sotatercept should be reduced as per the schedule in Table 9, Sotatercept dose reduction levels.

Table 9: Sotatercept Dose Reduction Levels

Sotatercept Treatment Group	0.1 mg/kg	0.3 mg/kg	0.5 mg/kg	1.0 mg/kg	1.5 mg/kg[b]	2.0 mg/kg[b]
Dose Reduction #1	0.075 mg/kg	0.1 mg/kg	0.3 mg/kg	[a] 0.75 mg/kg	1.0 mg/kg	[a] 1.5 mg/kg
Dose Reduction #2	Discontinue treatment	0.075 mg/kg	0.1 mg/kg	0.5 mg/kg	0.75 mg/kg	1.0 mg/kg
Dose Reduction #3		Discontinue treatment	0.075 mg/kg	0.3 mg/kg	0.5 mg/kg	0.75 mg/kg
Dose Reduction #4			Discontinue treatment	0.1 mg/kg	0.3 mg/kg	0.5 mg/kg
Dose Reduction #5 (if applicable)				0.075 mg/kg	0.1 mg/kg	0.3 mg/kg
Dose Reduction #6 (if applicable)				Discontinue treatment	0.075 mg/kg	0.1 mg/kg
Dose Reduction #7 (if applicable)					Discontinue treatment	0.075 mg/kg
Dose Reduction #8						Discontinue treatment

[a] Dose reduction #1 for 1.0 mg/kg and 2.0 mg/kg treatment groups may be to 0.5 mg/kg and 1.0 mg/kg respectively, at the investigator's discretion. Subsequent dose reductions should then continue to follow Table 9 (eg, dose reduction #2 for 1.0 mg/kg treatment group would be 0.3 mg/kg).

[b] Sotatercept dose level 2.0 mg/kg has been discontinued, ongoing and newly enrolled subjects dose reduced to sotatercept 1.5 mg/kg (Amendment 4).

A dose reduction will be maintained unless subsequent dose reductions are indicated. Doses may not be increased.

If applicable, for additional intermediate treatment groups opened per recommendation by the Steering Committee (eg, 0.75 mg/kg, 1.5 mg/kg, Refer to Section 4.1), dose level reduction should still follow Table 9 (eg, if starting dose level is 0.75 mg/kg, dose reduction #1 would be 0.5 gm/kg, dose reduction #2 would be 0.3 mg/kg, and so on). If intermediate treatment group dose level is not found on Table 9, dose should be decreased by 25% for each required dose reduction step.

8.3. Method of Treatment Assignment

8.3.1. Part 1

Subjects will be stratified by concentration of serum erythropoietin (< 500 versus ≥ 500 mIU/mL) and by number of transfusions within 56 days prior to study enrollment (< 4 RBC units versus ≥ 4 RBC units), and then assigned randomly to one of two treatment groups wherein they will be administered sotatercept, SC, 0.1 mg/kg or 0.3 mg/kg Q3W. An IVRS will be utilized to ensure an equal weight central randomization based on a permuted-block randomization method according to stratification factors defined in Section 4.1, Design of Study. Following treatment of five 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 one cycle of 21 days), all available safety and efficacy data will be assessed by a Steering Committee (Section 4.4). Based upon the occurrence of DLT (Section 4.1.1) 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 six subjects in the 0.5 mg/kg treatment group (with at least six subjects having completed at least three cycles of 21 days each), all available safety and efficacy data will be assessed by a Steering Committee from all dose levels. Based upon the occurrence of 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 six subjects in the 1.0 mg/kg treatment group (with at least six subjects having completed at least three cycles of 21 days each), all available safety and efficacy data will be assessed by a Steering Committee from all dose levels. Based upon the occurrence of 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. The 2.0 mg/kg sotatercept dose was reduced to 1.5 mg/kg for ongoing and newly enrolled subjects (Amendment 4).

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 six subjects have at least three cycles of treatment in the current dose level. Enrollment will continue beyond randomization in all dose levels (unless dose level[s] is closed due to safety reasons or lack of

efficacy as recommended by the Steering Committee) until up to a total of 20 subjects in each dose level.

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 four subjects experiencing an event) experience a DLT of related (suspected) adverse event ≥ Grade 2 (other than hemoglobin or hypertension DLT as defined in Section 4.1.1), the Steering Committee may recommend the closure of the treatment group.

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

Moreover, if > 33% of the subjects (minimum two subjects experiencing an event) experience a hypertension DLT (refer to Section 4.1.1), the Steering Committee may recommend the closure of the treatment group. In order to harmonize DLT assessment for hypertension across the study, additional guidance must be followed as defined in Section 4.1.1. Additionally, for any treatment group that accrues a minimum of 10 subjects or less if recommended 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 transfusion requirements if the reduction is less than 4 units), the Steering Committee may recommend the closure of the treatment group.

8.3.2. Part 2

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

Steering Committee Recommendation

Based on the 02 Mar 2015 Steering Committee's review of safety, efficacy and pharmacokinetic data of subjects enrolled in the Part 1 dose levels, including the sotatercept 2.0 mg/kg cohort level:

Part 1 - The sotatercept 2.0 mg/kg cohort was closed. Ongoing and newly enrolled subjects are to be dose reduced to sotatercept 1.5 mg/kg.

Part 2 - Subjects enrolled into Part 2 (Expansion Cohort) will receive sotatercept at 1.0 mg/kg.

8.4. Packaging and Labeling

The IP will be labeled per local regulatory requirements. Additional information may be included on the label as applicable per local regulations.

8.5. Investigational Product Accountability and Disposal

Accountability for sotatercept is the responsibility of the investigator. Investigational clinical supplies must be received by a designated person at the clinical site and kept in a secured location. The investigational site must maintain accurate records indicating dates and amounts of sotatercept received, to whom it was administered (subject-by-subject accounting), and accounts

of sotatercept accidentally or deliberately destroyed or returned. Unless otherwise notified, all vials of sotatercept, both used and unused, should be saved for drug accountability. The used vials may be discarded, per the institution's standard practice, after drug accountability has been completed. The investigator must return all unused vials of sotatercept to Celgene at the end of the study, or the sotatercept may be destroyed at the clinical site with the permission of Celgene. For either scenario, the outcome must be documented on the drug accountability log. Celgene will instruct the investigator on the return, disposal and/or destruction of IP.

8.6. Investigational Product Compliance

Accurate recording of all IP administration will be made. The investigator or designee is responsible for accounting for all IP that is administered during the course of the study.

8.7. Overdose

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

SC 10% over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency. Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form. See Section 11.1 for the reporting of adverse events associated with overdose.

9. CONCOMITANT MEDICATIONS AND PROCEDURES

9.1. Permitted Concomitant Medications and Procedures

9.1.1. Medications

During screening, and during the study, subjects should take only stable doses of medications for chronic conditions that are not specifically excluded by the protocol. Concomitant medications will be recorded throughout the course of the study at each visit.

9.1.2. RBC Transfusions

Concurrent treatment for anemia with blood transfusions is recommended when Hgb is < 8 g/dL or at the discretion of the investigator if Hgb is ≥ 8 g/dL and associated with symptom(s) of anemia (eg, hemodynamic or pulmonary compromise requiring treatment) or comorbidity justifying a threshold ≥ 8 g/dL Hgb.

9.2. Prohibited Concomitant Medications and Procedures

Concomitant growth factors (G-CSF or GM-CSF) are not allowed except in case of febrile neutropenia.

Iron supplementation within 7 days of Day 1 (besides an oral multivitamin with iron) will not be allowed. If a subject becomes iron deficient during study treatment (ferritin < 100 ng/mL [< 224.7 pmol/L] or transferrin saturation < 20%), treatment with iron supplementation is at the discretion of the investigator.

No ESA is allowed.

No concurrent treatment with another investigational agent is allowed.

Concomitant anticoagulant treatment (eg, Coumadin, warfarin, heparin) is not allowed during study treatment. Aspirin is allowed.

9.3. Required Concomitant Medications and Procedures

None.

10. STATISTICAL ANALYSES

10.1. Overview

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, with anemia, defined as requiring ≥ 2 units of RBCs within 84 days of study enrollment. The study is comprised of 2 parts. In Part 1, subjects will be assigned randomly to one of two treatment groups wherein they will be administered sotatercept, SC, 0.1 mg/kg or 0.3 mg/kg Q3W. Randomization will be stratified by concentration of serum EPO (< 500 versus ≥ 500 mIU/mL) and by number of transfusions within 56 days prior to study enrollment (< 4 RBC units versus ≥ 4 RBC units). Enrollment will continue without hiatus beyond randomization of five subjects into each of the 0.1 mg/kg and 0.3 mg/kg treatment groups. Following treatment of five 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 one cycle of 21 days), all available safety and efficacy data will be assessed by a Steering Committee (Section 4.4). Based upon the occurrences of DLTs in Cycle 1, as described in Section 4.1.1, the 0.5 mg/kg treatment group may be included into the randomization scheme. Initiation of randomization into the 1.0 mg/kg and 2.0 mg/kg treatment groups will have the same requirements as initiation of randomization into the 0.5 mg/kg treatment group with the exception of requiring at least six subjects completing at least three cycles of 21 days each and all available safety and efficacy data will be assessed by a Steering Committee. Meetings of the Steering Committee are planned periodically throughout the study to review available safety and efficacy data. Also, the Steering Committee may meet to review efficacy and safety due to occurrences of DLTs or for lack of efficacy as described in Section 4.1.1.

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 six subjects have at least three cycles of treatment in the current dose level. 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.

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

Note: Amendment 4: Based on the 02 Mar 2015 Steering Committee's review of safety, efficacy and pharmacokinetic data of subjects enrolled in the Part 1 dose levels, including the sotatercept 2.0 mg/kg cohort level:

Part 1 - The sotatercept 2.0 mg/kg cohort was closed. Ongoing and newly enrolled subjects are to be dose reduced to sotatercept 1.5 mg/kg.

Part 2 - Subjects enrolled in Part 2 (Expansion Cohort) will receive sotatercept at 1.0 mg/kg.

10.2. Definitions of Study Populations

Five study populations will be used for analyses.

- The Intent-to-Treat (ITT) Population – All subjects randomized
- Safety Population – All subjects who take at least one dose of study medication
- Efficacy Evaluable (EE) Population – All ITT 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
- Transfusion-dependent Efficacy Population (TDE) – 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.
- Transfusion-independent Efficacy Population (TIE) – 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.

10.3. Sample Size and Power Considerations

Subjects will be enrolled to provide up to 115 evaluable subjects in this study (Parts 1 and 2, combined). An evaluable subject is one who meets criteria for HI-E (Section 3.1), or one who completes five cycles of 21 days each of treatment without meeting criteria for HI-E, and without major 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 three cycles (Cycles 6-8) for the purpose of meeting response criteria.

Confidence intervals for response rates based on various sample sizes are presented in Table 10.

Table 10: 95% Confidence Intervals for Selected Sample Sizes and Response Rates

N	Responses	Response Rate	Lower 95% CI	Upper 95% CI
20	4	0.20	0.057	0.437
20	6	0.30	0.119	0.543
20	10	0.50	0.272	0.728
20	14	0.70	0.457	0.881
20	16	0.80	0.563	0.943
15	3	0.20	0.043	0.481
15	6	0.40	0.163	0.677
15	9	0.60	0.323	0.836
15	12	0.80	0.519	0.957
10	2	0.20	0.025	0.556

Table 10: 95% Confidence Intervals for Selected Sample Sizes and Response Rates (Continued)

N	Responses	Response Rate	Lower 95% CI	Upper 95% CI
10	5	0.50	0.187	0.813
10	8	0.80	0.444	0.975
5	1	0.20	0.005	0.716
5	2	0.40	0.053	0.853
5	4	0.80	0.284	0.995

10.4. Background and Demographic Characteristics

Subjects' baseline transfusion dependency and baseline concentration of serum EPO (< 500 versus ≥ 500 mIU/mL) will be summarized using frequency tabulations. Subjects' age, height, weight, and baseline characteristics will be summarized overall and by treatment group using descriptive statistics, while gender, race and other categorical variables will be summarized using frequency tabulations. Data on medical history will be summarized using frequency tabulations by system organ class and preferred term.

10.5. Subject Disposition

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

10.6. Analysis of Efficacy

The primary objective of this study is to determine a safe, tolerable, and effective dose of sotatercept that results in the greatest frequency of HI-E in patients with anemia and low- or int-1 risk MDS or non-proliferative CMML. The primary endpoint of this study is the rate of HI-E (Appendix C) starting before the completion of five cycles of treatment. Subjects who have sustained Hgb increase or decreased transfusion burden by 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 three cycles (Cycles 6-8) for the purpose of meeting response criteria.

- HI-E (TIE) is an increase ≥ 1.5g/dL Hgb from baseline, sustained over a period of ≥ 8 consecutive weeks in the absence of RBC transfusion;

or

- HI-E (TDE) is a decrease ≥ 4 units of RBCs transfused over a period of 8 consecutive weeks, relative to the number of units of RBCs transfused in the 8 weeks immediately prior to Day 1.

Erythroid hematological improvement (HI-E) response rates will be presented separately for TIE and TDE subjects. The HI-E response rate and other binary endpoints will be summarized using

a point estimate and 95% CI.

The secondary endpoints of efficacy of this study are:

1. Achievement of transfusion-independence in transfusion-dependent subjects (Appendix C).
2. Time to HI-E (Appendix C); the time between randomization (Part 1) and the start of therapy (Part 2) and the date the start of HI-E.
3. Duration of HI-E (Appendix C); the length of time between the first assessment and the last assessment the subject was in HI-E response for subjects who had an HI-E response. If the subject had an HI-E response that continued at the subject's last assessment, the duration will be censored at the last assessment.
4. Time to progression to AML (TPAML); the time between randomization (Part 1) and start of therapy (Part 2) and the date of progression to AML (Appendix C). If a subject dies prior to progression, the subject will be censored at the date of death. If a subject does not have a progression to AML, the subject will be censored at the last assessment.
5. Time to progression to events of higher risk MDS (TTPHR); the time between randomization (Part 1) and start of therapy (Part 2) and date of progression to events of higher risk MDS (eg, int-2 or high risk IPSS, Appendix B). If a subject dies due to reasons other than progression to events of higher risk MDS, the subject will be censored at the death date. If a subject does not have progression to events of higher risk MDS, then the subject will be censored at the last assessment.
6. Progression-free survival (PFS) - the time between randomization (Part 1) and start of therapy (Part 2) and PD (Appendix C) or death. Subjects who progress or die will be considered to have had an event, except if this event occurs after the start of subsequent therapy for MDS, in which case the subject is censored at the time of last assessment of MDS prior to or on the first day of the first subsequent therapy for MDS. The date of progression is taken as the earliest date of: date of PD as evaluation of response, death date, if death is caused by PD, treatment termination date if reason is PD, progression date as documented on treatment termination page, progression date as documented on the follow-up visit page. Subjects who do not progress or die (lost to follow-up or still being treated without documented PD or started subsequent antitumor therapy) will be censored at the date of the last assessment of MDS.
7. Overall survival (OS) - the time between randomization (Part 1) and start of therapy (Part 2) and death. A subject, who dies regardless of the cause of death, will be considered to have had an event. All subjects who are lost to the follow-up prior to the end of the study or who are withdrawn from the study will be censored at the time of last contact. Subjects who are still being treated will be censored at the last available date when the subject was known to be alive.
8. Concentration of sotatercept in serum (Section 10.9).

For duration and time-to-event data, the Kaplan-Meier method will be used to estimate the distribution function. For continuous data, descriptive statistics will be provided. Data listings

will be provided for all relevant data collected during the studies. Further details will be included in the Statistical Analysis Plan.

10.7. Analysis of Safety

All subjects who take at least one dose of study medication will be included in analyses of safety. Exposure to sotatercept will be summarized. Adverse events, DLTs, vital signs, clinical laboratory information, ECG interpretations, and concomitant medications will be tabulated and summarized overall and by treatment group. The incidence of AEs will be summarized by severity based on the NCI CTCAE version 4.0 (current active minor version). The incidence of deaths, SAEs, and AEs leading to dose modifications and discontinuations of study treatment will be summarized overall and by treatment group. Safety information obtained during treatment, post-treatment (42 days after the last dose), and during follow-up will be provided for these analyses. Laboratory results will be summarized by NCI CTCAE grade overall and by treatment group.

10.8. Interim Analysis

In Part 1, following treatment of five 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 one cycle of 21 days), all available safety and efficacy data will be assessed by a Steering Committee (Section 4.4). Enrollment will continue without hiatus beyond randomization of five subjects into each of the 0.1 mg/kg and 0.3 mg/kg treatment groups. Based upon the occurrences of DLTs in Cycle 1 as described in Section 4.1.1, the 0.5 mg/kg treatment group may be included into the randomization scheme. Initiation of randomization into the 1.0 mg/kg treatment group will have the same requirements as initiation of randomization into the 0.5 mg/kg treatment group with the exception of requiring at least six subjects enrolled in the 0.5 mg/kg treatment group completing at least three cycles of 21 days each. Initiation of randomization into the 2.0 mg/kg treatment group will have the same requirements as initiation of randomization into the 1.0 mg/kg treatment group. Meetings of the Steering Committee are planned periodically throughout the study to review available safety and efficacy data. Also, the Steering Committee may meet to review efficacy and safety due to occurrences of DLTs or for lack of efficacy as described in Section 4.1.1.

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 six subjects have at least three cycles of treatment in the current dose level. Upon completion of up to 20 evaluable subjects in each of the treatment groups (Part 1), 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.

Note: Amendment 4: Based on the 02 Mar 2015 Steering Committee's review of safety, efficacy and pharmacokinetic data of subjects enrolled in the Part 1 dose levels, including the sotatercept 2.0 mg/kg cohort level:

Part 1 - The sotatercept 2.0 mg/kg cohort was closed. Ongoing and newly enrolled subjects are to be dose reduced to sotatercept 1.5 mg/kg.

Part 2 - Subjects enrolled in Part 2 (Expansion Cohort) will receive sotatercept at 1.0 mg/kg.

10.9. Pharmacokinetics

Pharmacokinetic parameters for sotatercept, such as C_{max}, time to maximum serum concentration (T_{max}), and AUC, will be estimated. Dose proportionality may be assessed using exposure data after the first dose. Descriptive statistics will be provided for serum concentrations and PK parameters. The relationship between exposure to sotatercept and response (ie, safety, efficacy,) may be explored, if appropriate.

11. ADVERSE EVENTS

11.1. Monitoring, Recording and Reporting of Adverse Events

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

An overdose, accidental or intentional, whether or not it is associated with an AE, or abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. If an overdose is associated with an AE, the overdose and adverse event should be reported as separate terms.

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

All AEs will be recorded by the investigator from the time the subject signs informed consent to 42 days after the last dose of IP. AEs and SAEs will be recorded on the AE page of the CRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours of the investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

11.2. Evaluation of Adverse Events

A qualified investigator will evaluate all adverse events as to:

11.2.1. Seriousness

An SAE is any AE occurring at any dose that:

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

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

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

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (ie, planned prior to starting of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

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

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

11.2.2. Severity / Intensity

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

The severity of AEs will be graded based upon the subject's symptoms according to the current active minor version of NCI CTCAE Version 4.0; http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

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

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

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

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

11.2.3. Causality

The investigator must determine the relationship between the administration of IP and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

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

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

11.2.4. Duration

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

11.2.5. Action Taken

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

11.2.6. Outcome

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered, recovered with sequelae, not recovered (death due to another cause) or death (due to the SAE).

11.3. Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE.

11.4. Pregnancy

11.4.1. Females of Childbearing Potential

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on IP, or within 112 days of the subject's last dose of IP, are considered immediately reportable events. IP is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The female subject may be referred to an obstetrician-gynecologist (not necessarily one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation.

The investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, spontaneous or therapeutic abortion), the investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety by

facsimile, or other appropriate method, within 24 hours of the investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

11.4.2. Male Subjects

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

11.5. Reporting of Serious Adverse Events

Any AE that meets a criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the CRF. All SAEs must be reported to Celgene Drug Safety within 24 hours of the investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent up to and including 42 days following the last study treatment), and those made known to the investigator at anytime thereafter that are suspected of being related to IP. SAEs occurring prior to treatment will be captured.

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

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

11.5.1. Safety Queries

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

11.6. Expedited Reporting of Adverse Events

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

In the United States, all suspected unexpected serious adverse reactions will be reported in an expedited manner in accordance with 21 CFR 312.32.

For countries within the European Economic Area (EEA), Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, suspected unexpected serious adverse reactions (SUSARs) in accordance

with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical studies of investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

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

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

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

The investigator must keep on file a copy of pertinent safety information including correspondence with Celgene and the IRB/EC. (See Section 15.3 for record retention information.)

Celgene Drug Safety Contact Information:

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

12. DISCONTINUATIONS

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

- Hgb > 14 g/dL (not influenced by transfusions), sustained for ≥ 7 days, confirmed by two assessments ≥ 1 week apart.
- Hypertension DLT as defined in Section 4.1.1.
- Any other (ie, excluding Hgb and hypertension) treatment-related (suspected) toxicity ≥ Grade 3.
- Treatment-related (suspected) toxicity ≤ Grade 2 that delays treatment by more than 3 months.
- Adverse event that, in the judgment of the investigator, may cause severe or permanent harm or that rules out continuation of treatment.
- Lack of therapeutic effect, defined by lack of HI-E (Appendix C) after five cycles (or up to eight cycles for potential late responders) of treatment.
- Requirement for reduction of dose to < 0.075 mg/kg Q3W.
- Hypersensitivity reaction to sotatercept.
- Disease progression.
- Withdrawal of consent.
- Death.
- Lost to follow-up.
- Pattern of significant noncompliance.
- Completed study, per protocol (5 complete cycles of 21 days each). Subjects who have a sustained Hgb increase or a decreased transfusion burden by 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 three cycles (Cycles 6-8) for the purpose of meeting response criteria. Survival data and AML progression will continue to be collected for up to 24 months from first dose of study treatment.

The reason for treatment discontinuation should be recorded in the CRF and in the source documents.

13. EMERGENCY PROCEDURES

13.1. Emergency Contact

In emergency situations, the investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page). This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on call Celgene/Clinical Research Organization (CRO) Medical Monitor, who will then contact you promptly.

Note: The back-up 24 hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

13.2. Emergency Identification of Investigational Products

This is an open-label study. The identity of the investigational product is clearly indicated on the packaging and labeling.

14. REGULATORY CONSIDERATIONS

14.1. Good Clinical Practice

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

14.2. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for GCP and in the local regulations. Celgene staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions. The investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The investigator is responsible for keeping a record of all subjects who sign an informed consent document and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The investigator, or a designated member of the investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The investigator must ensure timely and accurate completion of CRFs and queries.

14.3. Subject Information and Informed Consent

The investigator must obtain informed consent of a legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original informed consent document signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the informed consent document must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the informed consent document. The revised informed consent document signed and dated by the study

subject and by the person informing the study subject must be maintained in the investigator's study files and a copy given to the study subject.

14.4. Confidentiality

Celgene affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Celgene requires the investigator to permit Celgene's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed informed consent document, it is the responsibility of the investigator to obtain such permission in writing from the appropriate individual.

14.5. Protocol Amendments

Any amendment to this protocol must be approved by the Celgene Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

14.6. Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, informed consent document, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

IP can only be supplied to an investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by Celgene or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to

determine whether formal approval must be sought and whether the informed consent document should also be revised.

The investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating investigator and the IRB/EC. This statement also applies to any communication between the investigator (or Coordinating investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by Celgene and the IRB/EC prior to use.

14.7. Ongoing Information for Institutional Review Board / Ethics Committee

If required by legislation or the IRB/EC, the investigator must submit to the IRB/EC:

- Information on serious or unexpected AEs as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

14.8. Closure of the Study

Celgene reserves the right to terminate this study at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities, etc.).

In addition, the investigator or Celgene has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

15. DATA HANDLING AND RECORDKEEPING

15.1. Data/Documents

The investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of CRFs or CD-ROM.

15.2. Data Management

Data will be collected via CRF and entered into the clinical database per Celgene SOPs. This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

15.3. Record Retention

Essential documents must be retained by the investigator for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. The investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed informed consent documents for all subjects
- Subject identification code list, screening log (if applicable), and enrollment log
- Record of all communications between the investigator and the IRB/EC
- Composition of the IRB/EC
- Record of all communications between the investigator, Celgene, and their authorized representative(s)
- List of Sub-investigators and other appropriately qualified persons to whom the investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures
- Copies of CRFs (if paper) and of documentation of corrections for all subjects
- IP accountability records
- Record of any body fluids or tissue samples retained

- All other source documents (subject records, hospital records, laboratory records, etc.)
- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial)

The investigator must notify Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The investigator must obtain approval in writing from Celgene prior to destruction of any records. If the investigator is unable to meet this obligation, the investigator must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator/Institution should take measures to prevent accidental or premature destruction of these documents.

16. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by Celgene or its authorized representative for compliance with applicable government regulations with respect to current GCP and standard operating procedures.

16.1. Study Monitoring and Source Data Verification

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. Before the study is initiated at a site visit or at an investigator meeting, all aspects of the study are reviewed with the investigator and the staff. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, CRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the investigator. Monitoring will include on-site visits with the investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. At each monitoring visit, the facilities, investigational product storage area, CRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative for accuracy, adherence to the protocol and GCP.

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

16.2. Audits and Inspections

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

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

17. PUBLICATIONS

The results of this study may be published in a medical publication, journal, or may be used for teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations. Selection of first authorship will be based on several considerations, including, but not limited to study participation, contribution to the protocol development, and analysis and input into the manuscript, related abstracts, and presentations in a study.

18. REFERENCES

Acceleron Report Number A011-01: A single-center, randomized, double-blind, placebo-controlled, single-dose, dose-escalation study to evaluate the safety, tolerability, pharmacokinetics, and effects on bone biomarkers of ACE-011 (ActRIIA-IgG1) administered to healthy, postmenopausal volunteers. Report included in Original IND submitted on 27 March 2009 (Serial No. 0000).

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19. APPENDICES

Appendix A: The World Health Organization (WHO) Classification of the Myeloid Neoplasms and Leukemia (Vardiman, 2009)

Category	Peripheral Blood	Bone Marrow
Refractory anemia (RA)	Anemia < 1% blasts < $1x10^9$ monocytes	Erythroid dysplasia < 10 % myeloid or megakaryocytic dysplasia < 5% blasts < 15% sideroblasts
Refractory anemia with ring sideroblasts (RARS)	Anemia < 1% blasts < $1x10^9$ monocytes	Erythroid dysplasia < 10 % myeloid or megakaryocytic dysplasia < 5% blasts > 15% sideroblasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Bi-or pancytopenia < 1% blasts < $1x10^9$ monocytes	Dysplasia in > 10% of the cells in 2 or more cell lines < 5% blasts < 15% sideroblasts
Refractory anemia with multilineage dysplasia and ring sideroblasts (RCMD-RS)	Bi-or pancytopenia < 1% blasts < $1x10^9$ monocytes	Dysplasia in > 10% of the cells in 2 or more cell lines < 5% blasts > 15% sideroblasts
Refractory anemia with excess blasts type I & II (RAEB-1 & RAEB II)	Cytopenia Type I: 1-5% blasts Type II: 5-19% blasts	Uni or multilineage dysplasia Type I 5-9% blasts Type II 10-19% blasts
5q- syndrome	Anemia Normal or elevated platelets < 5% blasts	Normal or increased megakaryocytes <5% blasts
MDS unclassified (MDS-U)	Cytopenia < 1% blasts	unilineage dysplasia of myeloid or megakaryocytic line < 5% blasts
MDS/MPN Myelodysplastic syndromes/myeloproliferative neoplasms -CMML* --MDS/MPN-U		

* For this study only non-proliferative CMML will be included.

Appendix B: International Prognostic Scoring System for MDS (Greenberg, 1997)

Prognostic Variable	Survival and AML Evolution Score Value				
	0	0.5	1.0	1.5	2.0
Marrow Blasts (%)	< 5	5 to 10	n/a	11 to 20	21 to 30
Karyotype	Good Normal or any 1 of: -Y del(5q) del(20q)	Intermediate Any other chromosome anomaly	Poor chromosome 7 anomalies; Complex: ≥ 3 chromosome anomalies	n/a	n/a
Cytopenias: Neutrophil count < 1800/µL Platelets < 100,000/µL Hb < 10 g/dL	0 or 1	2 or 3	n/a	n/a	n/a

The total IPSS score and IPSS risk category are calculated as the sum of three individual scores based on the marrow blast percentage, the karyotype, and the number of cytopenias.

Risk Category	Combined Score = Sum of Marrow blast + Karyotype + Cytopenia Score
Low	0
Intermediate-1	0.5 to 1.0
Intermediate-2	1.5 to 2.0
High	≥ 2.5

Appendix C: International Working Group (IWG) Response Criteria in Myelodysplasia (Cheson, 2006)

Altering Disease Natural History	
Complete remission (CR)	Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines Persistent dysplasia will be noted Peripheral blood: Hemoglobin ≥ 11 g/dL Platelets ≥ 100 x 10^9/L Neutrophils ≥ 1.0 x 10^9/L Blasts 0%
Partial remission (PR)	All CR criteria if abnormal before treatment, except: Bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5% Cellularity and morphology not relevant
Marrow CR	Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment Peripheral blood: if HI responses, they will be noted in addition to marrow CR
Stable disease (SD)	Failure to achieve at least PR, but no evidence of progression for > 8 weeks
Failure	Death during treatment Disease progression characterized by worsening of cytopenias, increase in % of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment
Disease Progression (PD)	For patients with: • Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts • 5%-10% blasts: ≥ 50% increase in blasts to > 10% blasts • 10%-20% blasts: ≥ 50% increase in blasts to > 20% blasts • 20%-30% blasts: ≥ 50% increase in blasts to > 30% blasts Any of the following: • At least 50% decrement from maximum remission/response levels in granulocytes or platelets • Reduction in Hgb concentration by ≥ 2 g/dL • Transfusion dependence

Appendix C: International Working Group (IWG) Response Criteria in Myelodysplasia (Cheson, 2006) (Continued)

Altering Disease Natural History	
Disease transformation	Transformation to AML (30% or more blasts)
Relapse after CR or PR	At least one of the following: • Return to pretreatment bone marrow blast % • Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets • 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

Hematological Improvement (HI)	
Erythroid response (HI-E) (Pretreatment < 11 g/dL)	Hgb increase by ≥ 1.5 g/dL Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 weeks compared with the pretreatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a Hgb of ≤ 9.0 g/dL pretreatment will count in the RBC transfusion evaluation
Platelet response (HI-P) (Pretreatment < 100 x 10^9/L)	Absolute increase of ≥ 30 x 10^9/L for patients starting with > 20 x 10^9/L Increase from < 20 x 10^9/L to > 20 x 10^9/L and by at least 100%
Neutrophil response (HI-N) (Pretreatment < 1.0 x 10^9/L)	At least 100% increase and an absolute increase of > 0.5 x 10^9/L
Progression/relapse after HI	At least one of the following: • At least 50% decrement from maximum response levels in granulocytes or platelets • Reduction in Hgb by ≥ 1.5 g/dL • Transfusion dependence

Appendix D: ECOG Performance Status Scale

The ECOG Performance Status Scale is used to score a subject's quality of life through evaluation, by a health professional, of daily activities and how those activities are affected by the disease of the subject.

Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Appendix E: New York Heart Association – Classification of Heart Failure

Classification of Heart Failure

Class	Symptoms
Class 1	No limitation of activities. No symptoms from ordinary activities
Class 2	Mild limitation of activity. Comfortable with rest or mild exertion
Class 3	Marked limitation of activity and be comfortable only at rest
Class 4	Complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest

Appendix F: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0

Currently active minor version of NCI CTCAE, Version 4.0:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

Appendix H: Cockcroft-Gault Estimation Of Creatinine Clearance (Crcl)

Cockcroft-Gault estimation of creatinine clearance (CRcl): CRcl (mL/min) = (140 – age) (weight [kg]) / 72 (serum creatinine [mg/dl]); for females, the formula is multiplied by 0.85 (Cockcroft, 1976; Luke, 1990).

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: Thursday, 06 August 2015, 08:55 AM Eastern Daylight Time
Meaning: Approved, no changes necessary.
==========

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- ***Subjects in the sotatercept 2.0 mg/kg dosing group were dose reduced to sotatercept 1.5 mg/kg.***
- ***Subsequent enrollment into this dosing group is at sotatercept 1.5 mg/kg.***
- ***Enrollment into Part 2 (expansion) to commence without delay at a sotatercept dose level of 1.0 mg/kg.***

Revised Sections: Summary of Protocol, Section 4.1, 4.2, 7.1, 8.2, 8.2.1, 8.3.2, 10.1 and 10.8

The ACE-011-MDS-001 Steering Committee met on 02 Mar 2015 to review available safety, efficacy and pharmacokinetic data up to and including the sotatercept 2.0 mg/kg dose level (five subjects at 2.0 mg/kg). The following recommendations were made:

- Closure of the 2.0 mg/kg cohort to further enrollment and sotatercept dose reduction to 1.5 mg/kg, at the next planned dose administration, for active patients and subsequent patients enrolled to this cohort.
- Begin enrollment into Part 2 (expansion) of the study immediately at 1.0 mg/kg sotatercept.

A letter was sent to the investigative sites on 04 Mar 2015 directing immediate implementation of the Steering Committee recommendations listed above.

The Steering Committee recommendations have been incorporated in Amendment 4.

- ***Language was added to include the availability of a roll-over protocol for subjects that remain on study following the analysis of all key endpoints and objectives of the study.***

Revised Sections: Summary of Protocol and Section 4.3

Subjects who are still deriving benefit from sotatercept therapy will have the opportunity to continue therapy when enrolled into the planned rollover protocol, per investigator discretion.

- ***A request for historic MDS molecular mutational analysis data, if available, has been added.***

Revised Sections: Summary of Protocol, Sections 5 (Table of Events) and 6.

Historic MDS molecular mutational analysis data is requested to assess any correlation of a specific mutation(s) and safety and efficacy parameters.

- ***Recently published preclinical data has been added.***

Revised Section: Sections 1.1 and 1.2.1

- ***Addition of references related to recently published preclinical data***.

Revised Section: References

The amendment also includes several other minor clarifications and corrections:

- Addition of the name of the Therapeutic Area Head.

Revised Section: Celgene Therapeutic Area Head Signature Page

- Clarifying language has been added to describe the completion of treatment in the Treatment Period versus the completion of treatment in the Extension Period to facilitate more accurate data capture and assessment implementation.

Revised Sections: Summary of Protocol, Sections 4.1.2, 4.3 and 5 (Table of Events)

- Clarification on when transfusions should be recorded and recording of pre-transfusion hemoglobin levels.

Revised Sections: Summary of Protocol, Section 5 (Table of Events), and 6

- Clarification of subject eligibility for the Extension Period of the study has been added.

Revised Section: Section 4.1.2

- Clarification of bone marrow aspirate slide staining has been added to facilitate correct preparation.

Revised Sections: Section 5 (Table of Events) and 6

- Other administrative changes (e.g., correction of typographical errors, editorial changes, etc.) were also incorporated.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized in this section.

The main objective of this amendment is to include additional dose levels beyond 0.5 mg/kg, as described below:

- Additional dose levels added beyond 0.5 mg/kg cohort (ie, 1.0 mg/kg SC Q3W and 2.0 mg/kg SQ Q3W), as 0.5 mg/kg may be sub-therapeutic in study population.
- Additional safety measure added to ensure adequate data are available and reviewed by the Steering Committee prior to all future dose escalation.
- Additional safety measure added to allow potential exploration of intermediate dose levels (eg, 0.75 mg/kg and 1.5 mg/kg) at time of dose escalation to 1.0 mg/kg and 2.0 mg/kg respectively upon Steering Committee review of safety and efficacy data.
- Additional dose reduction levels added to account for additional dose levels added beyond 0.5 mg/kg.
- New text added to provide guidance to sites when total volume of calculated dose exceeds what is typically administered in one SC injection.
-
- New text added related to timing of Steering Committee meetings to account for additional dose levels beyond 0.5 mg/kg.

The following changes are based on feedback from the Steering Committee, site investigators, or site staff after commencement of enrollment and additional experience obtained during conduct of the trial.

- Additional guidance related to pre-dose Hgb level prior to Cycle 1 Day 1 treatment administration for subjects who are deemed TIE per protocol.
- New text added related to Steering Committee guidance on closure of treatment group to further enrollment due to lack of efficacy to minimize number of patients enrolled at sub-therapeutic doses after their review of safety and efficacy data.
- New text added to account for varying operational logistics at study sites related to timing of availability of pre-dose Hgb result.
- Clarification on HI-E definition for subjects who are classified as TIE per protocol.
- Clarification added that hypertension DLT should be confirmed by study investigator/clinical site at the clinical site and not based solely on a measurement taken at home by the subject or caretaker.

- Clarification added related to protocol-required prior ESA treatment, accepting either alpha or beta (applicable in EU) rHu EPO and to account that subjects may receive optimal dose regimen at varying frequencies.

Additional inclusion criteria added to limit number of lines of prior MDS treatment (not including ESAs) to balance heavily pre-treated and non-heavily pre-treatment patient population.

New text added to account for varying operational logistics at study sites related to timing of availability of pre-dose Hgb result.

New text added to clarify that weekly blood pressure monitoring at home (if applicable to subject) may be measured by subject or caretaker.

New text added related to "End of Trial" and "Overdose" definition from updated Celgene protocol template.

Other changes (eg, update of protocol template sections, correction of typographical errors, editorial changes, changes to ensure consistency of text throughout document, modifications related to Celgene Style Guide, etc.) were also incorporated and are detailed in Section 2, Itemized Changes.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below.

The following changes are based on feedback received from the Steering Committee, study investigators, and site staff upon review of Amendment 1 of protocol ACE-011-MDS-001 in forums such as the Steering Committee Kick-Off Meeting, Investigator Meeting, Site Initiation Visits, or site ad hoc review of the protocol:

- Add clarification related to the hypertension dose-limiting toxicity (DLT) definition to ensure harmonization of DLT assessment for hypertension across all study sites due to unique attributes of the study population.
- Provide clear parameters for Extension Period eligibility to offer flexibility for those subjects who do not meet protocol-defined erythroid hematological improvement (HI-E) to enter the Extension Period, at the investigator's discretion, if clinical benefit is seen at the conclusion of the Treatment Period.
- Remove the Cycle 3 Day 1 mandatory MDS response assessment as it is deemed too soon after initiation of treatment of study drug.
- Continue to follow efficacy parameters (ie Hgb and transfusions) for up to 3 months after the last dose of study drug or start of next treatment to assess potential late response after study drug discontinuation as is sometimes observed with erythroid stimulating agents (ESAs).
- Modify the adverse event reporting period to 42 days after the last dose is administered (regardless of causality) to account for the likelihood that the subject will begin additional cytotoxic treatment after treatment discontinuation. Beyond 42 days, all SAEs deemed suspected related to study drug will still be reported.
- Include chromosome del5q MDS patients who have failed on lenolidomide, intolerable to lenalidomide, or have other cytopenia precluding use of lenalidomide, as these patients could potentially benefit from treatment with sotatercept.

The following changes are based on review of Amendment 1 of protocol ACE-011-MDS-001:

- Increase the frequency of blood pressure monitoring from once per cycle to weekly during the first 5 cycles of treatment, with the added flexibility of home monitoring.
- Addition of an Independent Cardiologist to the Steering Committee to focus on potential cardiovascular effects of the study drug.
- Increase the contraception use requirement for males after the last administration of study drug from 112 days to 7 months/210 days to account for the limited data on the study drug's effect on spermatogenesis.

The following changes are based on review of Amendment 1 of protocol ACE-011-MDS-001:

- Agreement on additional language related to clarification of the hypertension DLT definition.
- Exclusion of subjects at high risk for cardiovascular events, including those requiring chronic anticoagulant therapy during the course of the study and those with myocardial infarction within 6 months of study start.
- Addition of ECG assessments during the Treatment Period to further explore potential cardiovascular effects of the study drug.

Other administrative changes (eg, update of protocol template sections, correction of typographical errors, editorial changes) were also incorporated and are detailed in Section 2, Itemized Changes.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below.

The following changes are based on feedback received following review of the final protocol ACE-011-MDS-001:

1. Revision of protocol title and Inclusion Criteria to reflect the inclusion of CMML as a sub-classification of the MDS/MPN sub-group as outlined in protocol Appendix A 'The World Health Organization (WHO) Classification of the Myeloid Neoplasms and Leukemia'.
2. Revision of the dose-limiting toxicity (DLT) criteria, Rules for Delay, Reduction and Discontinuation of Treatment (Table 7) and Reasons for Discontinuation for:
    a. Hemoglobin > 12 g/dL, sustained for ≥ 7 days, confirmed by 2 assessments ≥1 week apart.
    b. Hypertension ≥ Grade 2 according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0 (current active minor version), blood pressure values must be confirmed by two readings obtained 5 minutes apart.
    c. Treatment-related (suspected) toxicity ≥ Grade 3.
3. Clarification of definition of favorable safety profile as a safe, tolerable and effective dose of sotatercept that results in the greatest frequency of erythroid hematological improvement in patients with anemia and low- or intermediate-1 risk myelodysplastic syndromes.
4. Addition of specific early stopping criteria for an excess number of DLTs or the absence of efficacy within a dose cohort.
5. Revision of inclusion criteria to:
    a. Only allow subjects requiring red blood cell transfusions to be eligible for the study.
    b. Add language that females of child bearing potential must agree to use effective contraception while participating in this study.
    c. Add pregnancy prevention language for males participating in this study.
6. Revision of exclusion criteria to exclude subjects with uncontrolled hypertension (systolic blood pressure (SBP) ≥ 140 mm Hg or diastolic blood pressure (DBP) ≥ 90).
    a. Controlled hypertension for this protocol is considered ≤ Grade 1 according to NCI CTCAE version 4.0 (current active minor version).
7. Revision of Rules for Delay, Reduction and Discontinuation of Treatment Section, including Table 7, to:
    a. Clarify discontinuation due to treatment-related (suspected) toxicity ≥ Grade 3.

   b. Clarify discontinuation due to treatment-related (suspected) toxicity ≤ Grade 2 that delays treatment by more than 3 months.
   c. Provide dose reduction guidance for subjects who experience a rapid rise in hemoglobin.

8. Revision of Causality Section to define that a temporal relationship is not necessary to make causality possible.
9. Clarification of the Treatment Plan for Part 1 and Part 2 of the study.
10. Clarification of reporting of all Suspected Unexpected Serious Adverse Reactions in accordance with 21 Code of Federal Regulations (CFR) 312.32.

Additional changes include:

11. Addition of serum erythropoietin assessment during screening period to determine stratification
12. Modification of Introduction to include information about variation of anemia associated with myelodysplastic syndromes and revise description of sotatercept.
13. Clarification of the scope of activity and meeting schedule of the steering committee.
14. Clarification of the start of enrollment into Part 2 of the study.
15. Clarification of the study start timeframe as the date of randomization in Part 1 and the date of start of therapy in Part 2 of the study.
16. Revision of the approximate number of study sites to participate in the study.
17. Clarify use of central laboratory for clinical laboratory assessments and when a local laboratory is allowed to be utilized.
18. Clarify version of NCI CTCAE to be utilized in the study.
19. Addition of a reference.

Other administrative changes (eg, protocol template section updates, correction of typographical errors, editorial changes, etc.) were also incorporated and are outlined in Section 2, Itemized Changes.