Phase I/II, Open-Label Study to Determine Safety and Efficacy of Sotatercept (ACE-011) in Adults with Red Blood Cell Transfusion-Dependent Diamond Blackfan Anemia

PROTOCOL NUMBER:	ACE-011-DBA-PI-0001
DATE PROTOCOL FINAL:	30JUN2018
STUDY DRUG:	Sotatercept (ACE-011)
INDICATION:	Adults with Diamond Blackfan anemia and red blood cell transfusion dependence
STUDY PHASE:	Phase I/II

BACKGROUND AND RATIONALE:

Diamond Blackfan Anemia

Diamond Blackfan anemia is a rare inherited pure red cell aplasia. Over the past ten years mutations have been described in genes encoding both the small and large ribosome associated proteins (Draptchinskaia, 1999; Gazda, 2006; Cmejla, 2007; Farrar, 2008; Gazda, 2008; Doherty, 2010; Landowski, 2013; Mirabello, 2014; Farrar, 2015). There is wide variability in clinical and biologic features, familial history, and therapeutic responses. Currently standard therapy includes corticosteroids, red blood cell (RBC) transfusions or hematopoietic stem cell transplantation (SCT) (Vlachos, 2001a). Approximately 80% of patients have an initial response to corticosteroids. Of these patients, approximately half will fail to achieve a taper to a tolerable steroid dose and will need to discontinue steroid therapy. These patients and the 20% who do not respond initially to steroid therapy must be maintained on a chronic red cell transfusion/iron chelation program. Chronic transfusion/chelation therapy has considerable treatment-related morbidity, most notably iron overload related organ failure.

Hematopoietic stem cell transplant has proved to be effective therapy for a select group of patients. Allogeneic stem cell transplantation with a histocompatible donor has been performed successfully in a number of patients. The Diamond Blackfan Anemia Registry of North America (DBAR) experience has been published (Vlachos, 2001b; Lipton, 2006). However, because of remissions (sustained physiologically acceptable erythropoiesis for $\geq$ 6 months without any medication or transfusion) in up to 20% of DBA patients, stem cell transplantation, regardless

of donor type, is not consistently offered to corticosteroid-dependent or transfusion-dependent DBA patients. For many patients, the lack of a suitable donor does not allow stem cell transplantation as a therapeutic option, as human leukocyte antigen (HLA) matched unrelated donor transplants have been associated with mortality and morbidity.

Historically the lack of truly effective and safe therapy has prompted the investigation of a number of other agents, including high-dose corticosteroids, immunosuppressive therapy (cyclosporine A and antithymocyte globulin), intravenous immunoglobulin, high-dose erythropoietin, interleukin-3, metoclopramide and others; however, these modalities have achieved, at best, anecdotal success (Vlachos, 2008).

Pathophysiology

Although somewhat controversial, there are data that suggest an intrinsic impairment of erythroid differentiation at the level of the erythroid burst-forming unit (BFU-E). The consequence is a decrease in differentiated erythroid colony forming cells (CFU-E) and in mature RBCs. The defect appears to be at the junction between erythropoietin (EPO)-independent and EPO-dependent BFU-E (Ohene-Abuakwa, 2005; Da Costa, 2010). Other data suggest the defect occurs later in many patients at the CFU-E/erythroblast level (Lipton, 1986; Narla, 2011). However, most persons with DBA have increased levels of erythropoietin and there is no improvement in anemia with pharmacologic doses of erythropoietin.

Many persons with DBA have mutations in genes encoding structural proteins of the small ribosomal subunit (Gustavsson, 1997; Willig, 1999) including *RPS19, RPS7, RPS10, RPS17, RPS24, RPS26, and RPS 29* or large subunit *RPL5, RPL11, RPL15, RPL31, and RPL35A*. Some mutations of unknown significance are reported in other *RP* genes (Doherty, 2010). However, 25-30% of persons with DBA have no detectable *RP* mutation. This suggests other mechanisms. Some phenotype/genotype correlations are known relating to congenital abnormalities (Gazda, 2008; Quarello, 2010).

Diagnosis

DBA diagnosis relies on several clinical and biological features. Classic criteria are: (1) macrocytic, normochromic, anemia; (2) reticulocytopenia; (3) bone marrow erythroid hypoplasia; (4) early onset of anemia (90% present before age one year) (Alter, 1976).

Congenital anomalies can affect the face, arms or hands, urogenital tract, and heart. Short stature and subsequent growth impairment are common. Most affected persons have increased erythrocyte adenosine deaminase (Glader, 1983) and hemoglobin (Hb) F. These findings are non-specific but provide supporting evidence for diagnosing non-classical DBA. The criteria for both classical and non-classical diagnoses have been updated (Vlachos, 2008).

Therapy

The two main therapeutic options are corticosteroids and RBC transfusions. About 80% of DBA patients initially respond to corticosteroids. Persons failing to respond are typically dependent on RBC transfusions throughout life. Other therapies such as interleukin-3 (Bastion, 1994), high dose corticosteroids, cyclosporine, anti-thymocyte globulin, immunoglobulin (reviewed in Vlachos, 2008) and metoclopramide (Abkowitz, 2002; Leblanc, 2007), are either of unproved benefit and/or seem to benefit relatively few patients. Pharmacological doses of erythropoietin are ineffective. Hematopoietic stem cell transplantation is the sole cure for the hematologic manifestation of DBA-related anemia but is usually only considered in corticosteroid-resistant persons because of substantial morbidity and mortality. Typically only transplants from HLA-identical sibling are considered; however, recent results show marked improvement in HSCT from unrelated HLA-molecularly matched donors. The best age at which to perform a transplant appears to be under 10 years of age (Vlachos, 2008).

Activin Biology

Sotatercept (ActRIIA-IgG1) is a humanized fusion-protein consisting of the extracellular domain of activin-receptor type IIA (ActRIIA) and the human IgG1 Fc domain. RAP-011 is the murine homologue of Sotatercept. Sotatercept and RAP-011 bind with high affinity to activin-A, blocking signaling through the endogenous ActRIIA-receptor. Activin-A is an erythroid-differentiation-factor (EDF) affecting late stages of RBC maturation (Murata, 1988). Substantial increases in hematocrit, hemoglobin and RBC numbers were observed in mice, rats and cynomolgus monkeys receiving RAP-011 or Sotatercept. Similar changes occur in rodent models of chemotherapy-induced anemia and chronic kidney failure. The mechanism(s) underlying these observations are not fully understood. Some immediate effects of Sotatercept

appear related to changes in plasma volume. However, long-term effects, independent of plasma volume, are substantial and are erythropoietin-independent.

Non-Clinical Safety Studies

Repeat-dose toxicology studies of Sotatercept of up to 3 and 6 months duration were done in rats and monkeys. In addition, a 3-month repeat-dose study in mice was done using RAP-011. Sotatercept-related effects were identified in the following organs/tissues: hematologic (rat and monkey), reproductive (rat only), adrenals (rat only), pancreas (rat only), and kidney (rat and monkey). In mice administered RAP-011, test article related effects were identified in the following organs/tissues: bone marrow, brain, kidney, heart and lungs.

Hematological (increased RBC parameters) and reproductive (epididymal granulomas, testicular degeneration, decreased sperm counts and motility, and changes in ovarian/uterine weights) findings are expected pharmacodynamic effects of ActRIIA signal inhibition. These likely occur via modulation of erythropoiesis and follicle-stimulating hormone (FSH) secretion, respectively. Only rats had adrenocortical (i.e., adrenal gland congestion or necrosis) and pancreatic (i.e., acini atrophy) findings. Neither finding was associated with clinical signs of adrenocortical (anorexia, weakness, gastrointestinal or serum electrolyte disturbances) or pancreatic (abnormal stool, weight loss) insufficiency. Kidney findings include glomerulonephritis and/or tubulo-interstitial nephritis or tubular degeneration/necrosis in rats, monkeys and mice. The glomerulonephritis was presumed to be from anti-Sotatercept antibody deposition. In the chronic monkey study with Sotatercept and in the mouse studies using RAP-011, kidney tubular changes were seen which did not correlate with glomerular lesions. Tubular lesions without glomerular findings are not typical of anti-drug antibody deposition in the kidney and may represent a direct effect of Sotatercept. Because tubular changes were observed at all dose levels, a second chronic monkey study using lower doses is in progress. Mineralization of the choroid plexus, myocardial degeneration and alveolar histiocytosis were seen in mice receiving RAP-011 intra-peritoneally (IP) at doses ≥10 mg/kg. NOAELs (No Observed Adverse Effect Level) from the 3-month toxicology studies of Sotatercept were noted at 3 and 30 mg/kg in rats and monkeys. Plasma exposures (AUC) at these doses are estimated to be 8- and 207-fold higher in rats and monkeys than the anticipated exposure in humans at the proposed dose of 0.1 mg/kg.

Animal Model Data

Mice treated with RAP-011 (murine ortholog of ACE-011) respond with a rapid increase in hematocrit, Hb, and RBC count (Carrancio, 2014). These effects are accompanied by an equally rapid stimulation of late-stage erythroid precursors in the bone marrow. RAP-011 also induces a significant increase in erythroid burst-forming units and erythropoietin, which could contribute to additional, sustained effects on RBC production. RAP-011 also was noted to have an effect in zebrafish models of ribosome insufficiency on RPS19 and RPS11. Treatment with RAP-011 restored Hb levels in these zebrafish. The beneficial effect of RAP-011 was also found to be synergistic with corticosteroid treatment (Ear, 2013).

Clinical Data

A011-01: A Phase-1a Study in Healthy, Post-Menopausal Women

One dose of Sotatercept was given by intravenous (IV)-infusion or a subcutaneous (SC)-injection (Ruckle, 2009). Intravenous dose levels were 0.01, 0.03, 0.1, 0.3, 1.0, and 3.0 mg/kg. Subcutaneous dose levels were 0.03 and 0.1 mg/kg. Forty-eight subjects were studied: 5 active subjects and 1 placebo subject at each IV and SC dose level. All subjects were followed for 4 months.

Pharmacokinetics (PK) of IV Sotatercept were linear; mean exposure (AUC) was proportional to dose. Mean clearance (CL) of IV doses was 0.092-0.128 mL/hr/kg, volume of distribution, 73.7-110 mL/kg, and mean $t_{1/2}$,z was 23.7-31.8 days (independent of dose). SC Sotatercept was completely absorbed. Mean $t_{1/2}$, z was about 30 days (independent of dose).

Treatment-emergent adverse events (AEs) occurring in >1 subject in any cohort were headache, infusion site reaction, injection site hemorrhage, and toothache. Most injection site reactions and hemorrhages were in the first IV cohort and were related to infiltration. Most treatment-emergent AEs were mild and judged unrelated to Sotatercept. No deaths, serious AEs (SAEs) or AEs leading to study discontinuation were reported.

A011-02: A Phase 1b Study in Healthy Post-Menopausal Women

Four cohorts of 10 subjects each were planned at 0.1, 0.3, 1, and 2 mg/kg given SC every 28 d for 4 doses. Subjects were randomized to Sotatercept or placebo at a 4:1 ratio within each cohort. Subjects were followed for 4 months after the last dose.

The treatment phase of the study was terminated early after a dose-limiting pharmaco-dynamic effect was seen.

Thirty-one subjects received Sotatercept doses of 0.1, 0.3, and 1 mg/kg (cohorts-1, 2, and 3)(Sherman, 2013). All subjects randomized to active treatment in cohort-1 received the 4 planned doses of Sotatercept. Subjects randomized to active treatment in cohort-2 received 3 doses of Sotatercept. Subjects randomized to active treatment in cohort-3 received 2 doses of Sotatercept because of early discontinuation of the investigational product after a dose-limiting pharmacodynamic effect was observed. Subjects randomized to placebo treatment received 1-4 doses of study treatment. Multiple doses of Sotatercept given subcutaneously produced a rapid and dose-dependent increase in hemoglobin evident by Day 8 in the 3 cohorts compared with placebo. Mean increases in hemoglobin were 0.68, 0.85, and 1.21 g/dL in the 0.1, 0.3, and 1 mg/kg dose cohorts compared with 0.17 g/dL for placebo. Increases were generally sustained for about 2 months following the last dose. One subject experienced a maximum increase of 6.4 g/dL on Day 36 after the second dose of 1 mg/kg of Sotatercept. Similar trends were observed in RBCs and hematocrit. However, mean and/or median reticulocytes did not fluctuate significantly in Sotatercept treatment arms versus placebo subjects.

A subject in the 1 mg/kg cohort had progressive hypertension coincident with a rapid rise in hemoglobin and hematocrit. Symptoms included headache, nausea, eye pain, dizziness and vomiting. Hypertension was managed with anti-hypertensive drugs and phlebotomy. The SAE was considered probably related to Sotatercept and resolved (see Investigator Brochure). The Sponsor (Acceleron Pharma, Inc) therefore suspended escalation to the 2.0 mg/kg dose level and further dosing in all cohorts.

An SAE of right knee re-injury was reported in a 50-year-old female with a prior motor vehicle accident in the 0.3 mg/kg cohort. The re-injury resulted in a total right knee replacement. The SAE resolved and was considered by the Investigator unrelated to Sotatercept.

The most common AEs were those related to increases in hematological laboratory parameters in the 1 mg/kg cohort, including increased hemoglobin and/or hematocrit in 7 of 8 subjects.

These events were mild or moderate and judged probably related to Sotatercept. Three subjects in the 1 mg/kg cohort had phlebotomies. All hemoglobin and hematocrit increases resolved. No erythroid-lineage AEs were reported in the 0.1 or 0.3 mg/kg cohorts. Hemoglobin levels in all subjects returned to normal by study end.

Mean AUC_{28d} and mean C_{max} were proportional to dose at 0.1-1 mg/kg following the 1st SC dose. The terminal half-life ($t_{1/2}$,z) of Sotatercept following the last dose in all three cohorts were identical, with mean of 23 days. Based on the one-compartmental modeling, the mean CL/F ranged from 3.05 to 3.90 mL/d/kg, the mean Vz/F ranged from 97.47 to 103.03 mL/kg and was dose-independent.

Bone mineral density (BMD) was assessed by dual-energy X-ray absorption spectroscopy (DXA). A dose-dependent increase in hip BMD was seen with a significant and rapid increase of 2.4% in the 1 mg/kg cohort compared to a 0.7% decrease in the placebo cohort. BMD results for lumbar spine showed slight increases of 0.4% to 1% from baseline to study end in all cohorts compared with a 0.5% decrease in the placebo cohorts.

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

Study A011-04 is a phase 2a, multi-center, randomized, multiple-dose study to evaluate the safety and efficacy of Sotatercept in subjects with osteolytic lesions of multiple myeloma (MM)(Abdulkadyrov, 2014). Subjects were randomized 4:1 to one of three dose levels of Sotatercept (0.1, 0.3 and 0.5 mg/kg) or placebo given every 28 days by SC injection for up to 4 doses over a 3-month period. Sotatercept was evaluated in combination with anti-myeloma therapy with melphalan (4 mg/m^2 on days 1-7), prednisolone (40 mg/m^2 on days 1-7) and thalidomide (100 mg per day continuously) (MPT). Each cycle was repeated every 4 weeks for up to 6 cycles. The sites, Sponsor and Sponsor representatives were blinded to treatment assignment.

Thirty subjects were randomized and received at least one dose of study medication: 6 subjects received placebo, 8 subjects received 0.1 mg/kg Sotatercept, 8 subjects received 0.3 mg/kg Sotatercept, and 8 subjects received 0.5 mg/kg Sotatercept. Twenty six (87%) subjects completed the study. One subject in the 0.1 mg/kg dose group and one subject in the 0.5 mg/kg dose group discontinued due to AEs. One subject in the 0.1 mg/kg dose group withdrew

consent and was discontinued, and one subject in the 0.3 mg/kg dose group was discontinued at the request of the investigator.

In this study, 50% of subjects were female and the mean (range) age was 60.9 (41 to 79) years. Mean time since diagnosis of MM was 3.3 years; the majority of subjects had stage III disease at screening (83%) and were heavily pretreated having received up to 7 prior chemotherapy regimens (93%). Forty-three percent of subjects were receiving bisphosphonates at screening and were continued on-study.

Fourteen subjects received ≥ 3 doses of Sotatercept (4 out of 8 subjects in the 0.5 mg/kg dose level, 5 out of 8 subjects in the 0.3 mg/kg dose level and 5 out of 8 subjects in the 0.1 mg/kg dose level). Twenty-two (92%) subjects receiving Sotatercept and 4 (68%) subjects receiving placebo reported at least one AE. Grade 3-4 AEs, regardless of attribution, were reported in 58% of subjects receiving Sotatercept and 17% of patients receiving placebo; no dose-related effect was apparent. Most subjects had AEs that were assessed as related to MPT: 21 (88%) subjects receiving Sotatercept and 4 (68%) subjects receiving placebo. No AEs were assessed by the Investigator as related to the study medication alone (Sotatercept or placebo). Two subjects had AEs assessed as possibly or probably related to study drug and possibly or probably related to MPT, one subject in the 0.1 mg/kg Sotatercept dose group (increased blood pressure; sudden death) and one subject in the 0.5 mg/kg Sotatercept dose group (hypertension). Four subjects had SAEs, 1 (13%) subject in the 0.1 mg/kg Sotatercept group and 3 (38%) subjects in the 0.5 mg/kg Sotatercept group. Three subjects had SAEs that were assessed as treatment-related. Of the 3 treatment-related SAEs, 2 SAEs were assessed as possibly related to MPT and unrelated to Sotatercept, and 1 SAE (sudden death) was assessed as probably related to MPT and possibly related to Sotatercept. One subject in the 0.5 mg/kg Sotatercept dose group discontinued study drug due to episodes of atrial fibrillation assessed as possibly related to MPT and unrelated to Sotatercept.

Increased Hb levels were observed in all Sotatercept dose groups, with a trend towards a dose-response relationship.

Please refer to the Investigator's Brochure for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of Sotatercept.

Protocol ACE-011-MDS-001: An Open-Label, Phase 2, Dose-Finding Study of Sotatercept (ACE-011) in Patients With Low- or Intermediate (Int)-1-Risk Myelodysplastic Syndromes (MDS) or Non-Proliferative Chronic Myelomonocytic Leukemia (CMML) and Anemia Requiring Transfusion

Study ACE-011-MDS-001 is a phase 2, open-label, dose-finding, multiple-dose study to determine a safe, tolerable, and effective dose of Sotatercept in patients with anemia and International Prognostic Scoring System (IPSS)-defined Low- or Intermediate (Int)-1-risk MDS or non-proliferative chronic myelomonocytic leukemia (CMML). Interim data are available and were presented at the 56th Annual Meeting of the American Society of Hematology (ASH) in December 2014 (Komrokji, 2014). Patients received subcutaneous Sotatercept at dose levels 0.1, 0.3, 0.5, or 1 mg/kg once every 3 weeks. The primary efficacy endpoint was rate of erythroid hematologic improvement as defined by modified International Working Group (IWG) 2006 criteria. The secondary endpoints included rate of achievement of RBC transfusion independence (TI) $\geq$ 56 days and safety.

A total of 54 MDS patients were enrolled as of the time of this interim report. Forty-six of 54 patients (85%) had a red blood cell (RBC) transfusion burden of $\geq$4 units/56 days (high transfusion burden; HTB) while 8 of 54 patients (15%) had a RBC transfusion burden of < 4 units/56 days (low transfusion burden; LTB). In this study, 30% of subjects were female and the median (range) age was 71 (56 to 86) years. Median time since original diagnosis was 4 years. Ninety-six percent of subjects had prior use of erythropoiesis-stimulating agents. The median (range) red blood cell (RBC) transfusion burden was 6 (0-16) units in 8 weeks.

One patient in the 0.5 mg/kg dose group was excluded from efficacy analysis due to protocol violation. Of the 53 patients evaluable for efficacy, erythroid hematologic improvement was achieved in 24 patients (45%):

- 0.1 mg/kg: 0 patients (0%) (n=7)
- 0.3 mg/kg: 4 patients (67%) (n=6)
- 0.5 mg/kg: 8 patients (40%) (n=21)
- 1 mg/kg: 12 patients (60%) (n=20)

Nineteen of 45 HTB patients (42%) responded with a reduction in transfusion burden of ≥ 4 RBC units/56 days. The duration of transfusion response appeared to be dose dependent. Five HTB patients (11%) achieved RBC-transfusion independence (TI) ≥ 56 days. The duration of RBC-TI ranged from 59 to 345+ days. In the LTB group, over any 8-week transfusion-free period, 5 of 8 patients (63%) achieved both a mean Hb increase ≥1.5 g/dL sustained for ≥56 days and RBC-TI ≥56 days. The maximum mean Hb increases ranged from 1.9 to 4.4 g/dL and the duration of RBC-TI ranged from 76 to 233+ days. Sotatercept was generally well tolerated. Three patients discontinued due to treatment-emergent adverse events (TEAEs) considered suspected related to Sotatercept: 1 patient with grade 2 hemolytic anemia; 1 patient with grade 3 hypertension; and 1 patient with grade 2 muscle weakness in the 0.3, 0.5, and 1 mg/kg dose groups, respectively. Other suspected treatment-related adverse events included fatigue/asthenia (13%); headache (9%); decreased appetite (7%); nausea (7%); and dyspnea (6%). Three subjects had Grade 3-4 TEAEs, all occurring at the 0.5 mg/kg dose level: 1 patient had grade 3 pain in both thighs; 1 patient had grade 3 hypertension; and 1 patient had transformation to acute leukemia approximately 5.5 months after study treatment discontinuation. The investigator could not rule out a contributory role of Sotatercept. These data support further exploration of higher Sotatercept dose levels; longer-term treatment is ongoing in both HTB and LTB lower-risk MDS patients.

Protocol ACE-011-B-THAL-001: An Ongoing Phase 2a, Open-Label, Dose-Finding Study To Determine The Safety, Efficacy, And Tolerability Of Sotatercept (Ace-011) In Adults With Beta-Thalassemia

This ongoing phase 2a, multicenter, open-label, dose-finding study aims to determine a safe and effective dose of Sotatercept in β-thalassemia major patients with transfusion-dependent thalassemia (TDT), and β-thalassemia intermedia patients with TDT or non-transfusion-dependent thalassemia (NTDT). Patients received Sotatercept 0.1, 0.3, or 0.5 mg/kg subcutaneously once every 3 weeks; dose escalation to 0.75 mg/kg is ongoing. Efficacy is assessed by haemoglobin (Hb) increase from baseline for NTDT patients and RBC transfusion burden reduction for TDT patients.

Of the 25 patients enrolled, 72% had NTDT and 28% had TDT. Six NTDT patients were treated in each dose group (0.1, 0.3, and 0.5 mg/kg); median (range) baseline Hb was 8.7 g/dL (6.1–

10.7), 8.3 g/dL (6.0–9.5), and 8.2 g/dL (6.4–9.3), respectively. In the first 3 cycles, Hb increases of ≥ 1.0 g/dL were seen in 0, 5 (83%), and 5 (83%) patients, respectively. Hb increases of ≥ 2.0 g/dL were seen in 0, 1 (17%), and 2 (33%) patients, respectively. No appreciable transfusion burden reduction was seen for TDT patients in the 0.1 and 0.3 mg/kg groups; 0.5 mg/kg group treatment is ongoing. Increased Sotatercept exposure was associated with higher Hb increases in the first 3 cycles for NTDT patients ($n = 17$; $r = 0.77$, $P < 0.001$). Sotatercept was well tolerated: 19 (76%) patients remain on treatment. Three grade ≥ 2 treatment-related adverse events leading to discontinuation were reported; 3 patients discontinued due to lack of efficacy.

These preliminary data suggest Sotatercept every three weeks increases serum Hb in β-thalassemia and MDS patients, improving anemia; these effects appear to be dose-dependent. Sotatercept may provide clinical benefit with a favorable safety profile. Our DBA patients have already completed 0.1, 0.3 and 0.5 mg/kg/dose every 4 weeks for 4 cycles. The patients have had no Grade 4 toxicities. We are now amending this study to increase the dose further and increase the interval to every 3 weeks like the patients with beta-thalassemia and myelodysplastic syndrome have been receiving and tolerating with a positive response.

OBJECTIVES:

Primary Objective(s)

- Determine a safe and effective dose of Sotatercept in adults with DBA and RBC transfusion dependence

Secondary Objective(s)

- Determine time to response
- Determine response duration
- Evaluate the safety profile of Sotatercept in adults with DBA and RBC transfusion dependence

Exploratory Objective(s):

- Evaluate effects of Sotatercept on bone densitometry

ENDPOINTS:

Primary Endpoint(s):

- Complete response (CR): transfusion-independent and Hb > 9 gm/dL
- Partial response (PR): increase in transfusion interval from baseline and Hb < 9 gm/dL with an increase in reticulocyte count

Secondary Endpoint(s):

- Time to response
- Response duration
- Safety (type, frequency, and severity of adverse events and relationship to Sotatercept [according to the currently active minor version of National Cancer Institute (NCI) Common Terminology for Adverse Events (CTCAE) version 4.0]).

Exploratory Endpoint(s):

- Improvement of bone density as measured by bone densitometry (DEXA scan)

INDICATION:

Adults with DBA and red blood cell transfusion dependence.

STUDY DESIGN:

This study is a single-center, phase I/II, open-label, dose-escalation study to determine a safe and effective dose of Sotatercept in adults with DBA and RBC-transfusion-dependence. Three cohorts have already completed 0.1, 0.3 and 0.5 mg/kg/dose every 4 weeks for 4 cycles. The patients have had no Grade 4 toxicities. Thus this study will increase the dose further and increase the interval between the doses to that which patients with beta-thalassemia and myelodysplastic syndrome have been receiving and tolerating with a positive response. Cohorts of 3 subjects will receive Sotatercept starting with a dose of 0.75 mg/kg (dose level 4). Subsequent dose levels are specified in Table 1. Subjects will receive Sotatercept SC once every 21 days for up to 6 doses. The subsequent cohorts may begin after and only after all 3 subjects in the previous cohort have completed 28 days following their 4th dose of Sotatercept (or last dose if Sotatercept is not discontinued for safety reasons) and safety has been determined to proceed. Non-responders at lower dose-levels may receive Sotatercept at the discretion of the Investigator.

Definition of Recommended Dose:

The recommended dose of Sotatercept is defined as the lowest dose level determined safe and effective. The dose levels to be evaluated in this study are listed below (Table 1):

Table 1: Sotatercept Dose Levels

Dose Level	Dose	Frequency	Status
Dose Level 1	0.1 mg/kg	Every 4 weeks	Completed
Dose Level 2	0.3 mg/kg	Every 4 weeks	Completed
Dose Level 3	0.5 mg/kg	Every 4 weeks	Completed
Dose Level 4	0.75 mg/kg	Every 3 weeks	This study
Dose Level 5	1 mg/kg	Every 3 weeks	This study

Dose:

Three dose levels of Sotatercept have already been studied (0.1, 0.3 and 0.5 mg/kg). Dose selection was based on safety and exposure-response data from study A011-04 where subjects received up to 4 treatments of Sotatercept at 0.1, 0.3, or 0.5 mg/kg. Sotatercept was safe and exposure-dependent increases in hemoglobin were observed. There was no relationship between increased blood pressure, Sotatercept maximum concentration and maximum hemoglobin increase (Report A011-04-CP). Further increased dose levels have been used in beta-thalassemia and myelodysplastic syndrome without untoward side effects and with good response. This study has not had a response to the initial three doses and has had no significant side effects. Therefore, the study is now amended to two new dose levels of 0.75 mg/kg and 1 mg/kg. Also the previous dose levels were given every 4 weeks. New studies have shown increased effectiveness at every 3 week dosing. Thus the 4th and 5th dose levels will be given every 3 weeks.

Also as noted above there are data that corticosteroids are synergistic with the ortholog of Sotatercept. Aside from red cell transfusion, corticosteroids are a mainstay of treatment for DBA. Patients may respond to high doses of corticosteroids and then be weaned to a lower dose. The transfusion dependent patients may have been responsive in the past and “lost” their

response due to an intercurrent illness or some other unknown trigger. We postulate that patients who had a response in the past may respond to Sotatercept if given a priming dose of steroids concurrently. We therefore will stratify patients with regards to their ability to take a standing 'start-up' dose of corticosteroids as follows:

a- If a patient has no contraindication to corticosteroid therapy (as noted below), then the patient will start prednisone 1 mg/kg/day (max of 60 mg daily) for 3 weeks concurrent with first dose of Sotatercept. At the second dose (3 weeks later) the prednisone will be weaned to 0.67 mg/kg/day (max 40 mg daily) for 4 days and then 0.33 mg/kg/day (max 20mg daily) for 3 days. The prednisone will be discontinued 1 week after the 2nd dose of Sotatercept.

b- If a patient has a contraindication to corticosteroid therapy (as noted below), then the patient will begin Sotatercept without any concurrent prednisone treatment.

c- A patient is deemed to have a contraindication to corticosteroid therapy if he/she has a history of cataracts, glaucoma, pathologic fractures, diabetes mellitus, or steroid psychosis.

d- A patient can opt out of the steroid arm if he/she has had other untoward steroid effects and would otherwise refuse participation in the trial if steroids were mandatory.

The trial will therefore be structured as such:

The first patients (Dose level 4) will be stratified by whether they can tolerate a course of Prednisone and be divided into:

Cohort 4a: 3 patients on Sotatercept 0.75 mg/kg with Prednisone

Cohort 4b: 3 patients on Sotatercept 0.75 mg/kg without Prednisone

If the patients have no untoward events in the Patients in Dose Level 4 by the end of 3 of the 6 doses, then additional patients (Dose Level 5) will be enrolled at the next dose level:

Cohort 5a: 3 patients on Sotatercept 1 mg/kg with Prednisone

Cohort 5b: 3 patients on Sotatercept 1 mg/kg without Prednisone

Recruitment to Dose Level 5 can proceed independently for each of the cohorts, i.e. once the patients in Cohort 4a have completed 3 of the 6 doses without untoward events, patients can be enrolled into Cohort 5a, even if not all the patients have been recruited to Cohort 4b.

Dose Escalation / De-escalation Rules

The study follows a sequential dose-escalation design. The decision of whether to open Dose Level 5 will be made once the last of three subjects at Dose Level 4 completes the 3rd dose of Sotatercept and safety has been determined to proceed. The following dose-escalation rules will be used:

- 3 subjects are entered into each cohort at Dose Level 4 (0.75 mg/kg);
- If no subject experiences a dose-limiting toxicity (DLT) by the 3rd dose of Sotatercept, Dose Level 5 (1 mg/kg) is opened;
- If 1 of 3 subjects in a cohort in Dose Level 4 has a DLT, 3 more subjects are enrolled into that cohort at the same Dose Level 4.
- If there are no additional DLTs by the 3rd dose, Dose Level 5 is opened.
- If ≥ 2 subjects in a cohort at Dose Level 4 have a DLT (other than an increase in hemoglobin), that cohort will be discontinued.
- The cohort without DLT and with an appropriate Hb response will be chosen to be the maximum tolerated dose (MTD).
- Up to a total of 8 additional subjects will be entered into the MTD.

Definition of Dose-Limiting Toxicity

A DLT is defined as:

- Inability to deliver the scheduled doses because of toxicity. These subjects should be discontinued from the Treatment Period and continue in the Follow-Up Period for 1 month from their last dose; OR
- Any toxicity ≥ Grade 3;

Should a subject leave the study before completing 3 doses of Sotatercept during the treatment period for reasons other than a DLT, one (1) additional subject will be added to that dose level.

Dose Modifications

At each dose level the 2nd or 3rd doses can be delayed in case of hypertension > Grade 2 and/or sustained increase of hemoglobin ≥ 2 gm/dL from the previous dose except those attributed to RBC transfusions. Table 2 lists guidelines for dose modifications:

* Dose delay of Sotatercept is defined as a dose not administered > 4 days from the planned dosing dated due to Hb ≥ 10 gm/dL, hypertension ≥ SBP 150 mmHg and DPB ≥ 100 mmHg and/ or Sotatercept related toxicity.

Table 2 provides guidelines for dose modifications:

Table 2: Dose Modification, Dose Reduction and Dose Delay Guidelines

NCI CTCAE Toxicity Grade	Event		Action
≥ Grade 2	Hypertension		Dose delay[a] Hold until resolved < Grade 2
□ Grade 3	Other non-hematological AEs		Dose delay [a] Hold until resolved □ Grade 1
	Hemoglobin (Hb)		
	If Hb ≤ 12.5 g/dL[b] and:		
		- Δ Hb ≤ 2g/dL at Day 21 from last dose	Continue dosing following schedule at the same Dose Level. Hypertension should be < Grade 2.
		- Δ Hb > 2g/dL at Day 21 from last dose	Dose Reduce to the Previous Dose Level. Hypertension should be < Grade 2.
	If Hb > 12.5 g/dL[b] ≤ 14g/dL[b] for less than 4 weeks[c], and:		
		- Δ Hb ≤ 2g/dL at Day 21 from last dose	Dose delay for up to an additional 12 weeks until Hb ≤ 12.5 g/dL, and hypertension < Grade 2; continue dosing at the same dose level.
		- Δ Hb > 2g/dL at Day 21 from last dose	Dose delay for up to an additional 12 weeks until Hb ≤ 12.5 g/dL, ΔHb≤2 g/dL and hypertension < Grade 2, AND one Level Dose reduce to the previous dose level.
	If Hb > 14g/dL[b] sustained for 4 weeks (confirmed by laboratory assessment)[c]		Discontinue treatment
	If a subject experiences ≥ 3 Dose Reductions		Discontinue treatment

[a] Dose delay of Sotatercept is defined as a dose not administered > 4 days from the planned dosing date due to Hb > 12.5g/dL and/or hypertension ≥ Grade 2 according to NCI CTCAE criteria and/or Sotatercept-related toxicity ≥ Grade 3.

[b] Based on the **pre-transfusion/pre-treatment** Hb value at the time of re-treatment.

[c] If Hb > 12.5 g/dL, Hb measurement should occur every week.

If dosing of a subject is delayed for more than 12 weeks (up to a maximum of 15 weeks delay from the previous dose administered), the treatment should be discontinued.

Treatment Discontinuation

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

- Hb > 14 g/dL (not influenced by transfusions), sustained for ≥ 4 weeks, confirmed by weekly assessments.
- Hypertension DLT as defined below.
- Any other (i.e., excluding Hb 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.
- Hypersensitivity reaction to Sotatercept.
- Withdrawal of consent.
- Death.
- Lost to follow-up.
- Pattern of significant noncompliance.
- Completed study, per protocol (6 complete cycles of 21 days each). Subjects who have a sustained Hb increase or a decreased transfusion burden by end of Cycle 6 but for a period less than or equal to 8 consecutive weeks (potential late responders) may continue treatment for up to an additional two cycles (Cycles 7-8) for the purpose of meeting response criteria.

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

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, 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.

SCHEDULE OF STUDY ASSESSMENTS:

See Table 4

PHASE OF DEVELOPMENT:

Phase I/II study

SUPPORT:

Celgene

86 Morris Avenue

Summit, NJ 07901 USA

STUDY PRODUCT:

SOTATERCEPT (ACE-011)

DESCRIPTION OF STUDY TREATMENTS

Description of Investigational Product(s)

Process III Clinical Drug Product - Lyophilized Powder:

- The clinical drug product consists of Sotatercept in 10 mM citrate buffer, pH 5.8, 8% sucrose, and 0.02% polysorbate 80. It is supplied as a lyophilized powder in labeled, rubber stoppered, sealed, 3-mL glass vials.
- The recommended storage temperature for Sotatercept lyophilized drug product is 2°C to 8°C.
    - Prior to administration, the lyophilized drug product is reconstituted with 1 mL water for injection (WFI). The reconstituted drug product consists of a 50 mg/mL solution of Sotatercept. The reconstituted Sotatercept, in its original

container closure system, may be held for up to 6 hours at 2°C to 8°C. Once the reconstituted drug product is drawn into a syringe, it should be administered within one hour from the time it was drawn. The total hold time of the reconstituted drug product, including the hold time in a syringe, must not exceed 6 hours.

- Sotatercept lyophilized product will be shipped to the investigational site with a TempTale monitor in an appropriate nomadic shipper.

Shipping / TempTales

All shipments include instructions for the TempTale device within the shipper. All TempTales are to be stopped immediately upon receipt and unpacking of the shipment. Follow the TempTale Instruction Sheet in the shipper for handling of the temperature monitoring device.

- If the TempTale does not have an alarm bell showing in the screen, the IP was shipped and received in the appropriate temperature range. The temperature parameters should be checked and documented on the TempTale instruction sheet and the IP would be ready for use.
- Please note: if the alarm bell is showing on the TempTale display upon receipt of shipment and stopping of the TempTale, please store the material appropriately and quarantine it from use. Notify Celgene of the excursion right away and await confirmation that the IP is acceptable for use or is to be returned or destroyed.

Sotatercept Preparation and Administration

The clinical staff will fill out the following information on the **Sotatercept Drug Accountability Log** (see Appendix 8) on the dosing day:

- Date
- Visit
- Subject Number
- Subject Initials
- Dose
- Number of mLs used
- Lot Number
- Time Drug Removed from Refrigerator/Freezer (24 hr clock)
- Time Subject Dosed (24-hour clock)

The site personnel will confirm the lot # (for Sotatercept), the number of vials used, and the total volume of Sotatercept given and record this information in the source documents and in the pharmacy records.

Preparation of Sotatercept for Subcutaneous Dosing

Investigational Product (ACE-011) Preparation

Process III Clinical Drug Product- Lyophilized: On the day of dosing, the pharmacist/designee will:

- Pull the appropriate vial(s) from the refrigerator and allow the vial to equilibrate to room temperature.
- Add 1 mL WFI (Sterile Water for Injection) to a Lyophilized ACE-011 vial
- Let the vial sit at room temperature ~2 minutes
- Gently invert the vial to dissolve powder that may have gotten into the stopper/neck
- Gently swirl the vial for ~10 seconds (**NOTE: Do not shake and avoid prolonged or vigorous agitation)**. Allow the vial to sit at room temperature for ~ 3 minutes. This procedure will produce a clear 50 mg/mL solution for administration
- The reconstituted Sotatercept drug product is a clear to slightly yellowish opalescent solution.)

Note 1*:* The reconstituted ACE-011, in its original container closure system, may be held for up to 6 hours at 2°C to 8°C.
Note 2*:* Once the reconstituted drug product is drawn into a syringe, it should be administered within one hour from the time it was drawn.
Note 3*:* The total hold time of the reconstituted drug product, including the hold time in a syringe, must not exceed 6 hours.

- 1 mL syringes should be utilized for dispensing. Syringes need to measure up to 0.01 mL so that dose reductions can be accurately measured.
- Subcutaneous injections should be given in the following order as needed: 1) right upper arm, 2) left upper arm, 3) right upper thigh, 4) left upper thigh, 5) abdomen.
- Sufficient care should be taken so that the injection is not given intramuscularly or intravenously.
- If a dose volume is required to be split into more than 1 syringe (>1 mL dose requirement), then the volumes should be split into similar or equal volumes of 1 mL or less. For example, a subject requiring a 1.25 mL injection volume, that volume will be split into 2 syringes (one syringe can contain 0.62 mL and one syringe can contain 0.63 mL).

Treatment Administration and Schedule

Sotatercept will be administered as a SC injection to subjects by the study staff at the clinical site and will be documented in the study source record. Subcutaneous injections will be given in the upper arm, abdomen, or thigh.

Dose-escalation to the next dose level will be performed only if no side effect is reported AND if no efficacy is evidenced at the current dose level.

For treatment discontinuation, please refer to Section: Dose Escalation / De-escalation Rules

Selection of Dose for the Study

Sotatercept administered as a single dose up to 3.0 mg/kg was previously demonstrated to be safe and to have durable effects on markers of bone formation and resorption as well as red blood cells following a single IV administration. A dose-limiting pharmacodynamic effect of Sotatercept with increases in hemoglobin, hematocrit and RBCs was established in healthy

post-menopausal women at the 1.0 mg/kg dose level following multiple SC administration. This study will further delineate the hematopoietic profile of Sotatercept in subjects with Diamond Blackfan anemia.

Selection and Timing of Dosing for Each Subject
Subjects will be enrolled and receive their first dose of Sotatercept on study Day 1. Sotatercept administration should occur no sooner than 3 days after RBC transfusion. Up to a total of 6 doses will be administered every 21 days during the Treatment Period. Dose delay of Sotatercept from the planned dosing may occur due to Hb ≥ 10 g/dL, hypertension ≥ SBP 150 mmHg and DPB ≥ 100 mmHg and/or Sotatercept related toxicity.

For guidelines on dose modifications and dose delays see: Dose Modifications

Treatment / Study Discontinuation
For guidelines on Discontinuations see sections: Treatment Discontinuation and Study Discontinuation

Method of Treatment Assignment

All subjects who qualify for the study will be enrolled into the study and receive up to 6 doses of Sotatercept. A unique multi-digit subject identification number will be manually assigned by the site staff to each subject entering the Treatment Period.

Packaging and Labeling

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

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 secure and temperature-controlled location. The investigational site must maintain accurate records demonstrating dates and amounts of Sotatercept received, to whom it was administered (subject-by-subject accounting), and accounts of any Sotatercept accidentally or deliberately destroyed or returned. Accurate recording of all IP administration will be made in the appropriate section of the subject's CRF and source documents. Unless otherwise notified, all vials of Sotatercept, both used and unused, must be saved for drug accountability. The used vials may be discarded, per the institution's standard practice, after drug accountability has been completed by the monitor. The Investigator must return all unused vials of Sotatercept to the Supporter at the end of the study, or the Sotatercept may be destroyed at the clinical site with the permission of the Supporter. For either scenario, the outcome must

be documented on the drug accountability log. The Supporter will provide direction for the outcome of all unused vials.

Celgene will instruct the Investigator on the return, disposal and/or destruction of IP Investigational Product Compliance.

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

STUDY POPULATION:

Inclusion Criteria

1. ≥ 18 years of age.
2. DBA diagnosed according to the Diamond Blackfan anemia criteria (Vlachos, 2008) (Appendix 2).
3. RBC transfusion-dependence (defined as ≥ 2 units of RBC per 28 days averaged over 12 weeks prior to study entry) (Gale, 2010) (Appendix 2).
4. Creatinine clearance ≥ 30 ml/min. Renal function assessed by calculated creatinine clearance as follows (see Appendix 7: Cockcroft-Gault estimation of CrCl).
5. Karnofsky performance scale score ≥ 70 (Appendix 3).
6. Females of childbearing potential participating in the study are to use highly effective methods of birth control during study participation and for 6 weeks following the last dose of Sotatercept. Females of childbearing potential must have a negative serum or urine β-HCG pregnancy test within 3 days prior to the start of Sotatercept given on 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 (i.e., who has had menses at some time in the preceding 24 months).
7. Males must agree to use a latex condom during any sexual contact with females of childbearing potential while participating in the study and for 16 weeks 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.

8. Agreement to adhere to the study visit schedule, understand and comply with all protocol requirements.
9. Disease free of prior malignancies for >5 yrs with the exception of currently treated basal cell carcinoma, squamous cell carcinoma of the skin, or carcinoma "in situ" of the cervix or breast.
10. Understand and sign a written informed consent.

Exclusion Criteria

1. SGOT > 5X ULN, SGPT >5X ULN or bilirubin > 5X ULN.
2. Heart disease (New York Heart Association classification of ≥ 3 [Appendix 5]).
3. Uncontrolled hypertension. If hypertension is considered clinically stable, systolic blood pressure (SBP) must be < 150 mmHg or diastolic blood pressure (DBP) must be < 100 mmHg.
4. Treatment with another investigational drug or device <8 weeks pre-study entry.
5. History of severe or severe anaphylactic reaction or hypersensitivity to recombinant proteins or excipients in investigational product.
6. Pregnant or lactating females.

STUDY DURATION:

Each subject will be on the study for approximately 8 months (including the Screening Period, the Treatment Period, and the Follow-Up Period) (see Table 4). The Treatment Period is approximately 16 weeks with a post-treatment Follow-Up Period of approximately 16 weeks from the subject's last dose of Sotatercept. Subjects who discontinue from the Treatment Period early will still continue to the Follow-Up Period for 16 weeks from the last dose of Sotatercept.

NUMBER OF STUDY SITES:

This is a single center study.
Subjects will receive the treatment at:

EFFICACY EVALUATION:

Responses are defined as shown in Table 3 below. Response must be documented for ≥ 84 consecutive days (3 months).

Table 3: Response

Response	Transfusions	
	None	Reduced
Complete response (CR)	X	
Partial response (PR)		X (50% decrease)

SAFETY EVALUATION:

Side effects will be recorded at each follow-up visit.

Side effects will be graded according to the NCI-CTCAE (currently active minor version 4) (Appendix 6).

All serious adverse events will be reported to Cohen Children's Medical Center of New York and to Celgene.

TREATMENT MODIFICATIONS:

- Dose-escalation will be performed only if no side effect is reported AND if no efficacy is evidenced (see above).
- Treatment will be stopped:
  - if hemoglobin is >14 gm/dL
  - any ≥ Grade 3 adverse event related to Sotatercept

Adverse events and/or Serious Adverse events:

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 (i.e., 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 16 weeks after the last dose. AEs and serious adverse events (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.

Serious Adverse Event (SAE) Definition

A serious adverse event is one that at any dose (including overdose):

- Results in death
- Is life-threatening[1]
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity[2]
- Is a congenital anomaly or birth defect
- Is an important medical event[3]

[1]"Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

[2]"Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

[3]Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. A new diagnosis of cancer during the course of a treatment should be considered as medically important.

Adverse Event Reporting

Toxicity will be scored using CTCAE Version 4.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP homepage (http://ctep.info.nih.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

The investigator must appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the patient's outcome.

Pregnancies

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 (Investigational Product), or within (insert time-frame which must be at least 28 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 should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

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 (e.g., 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 immediately 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 immediately 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.

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.

Celgene Drug Safety Contact Information:

Celgene Corporation
Global Drug Safety and Risk Management
86 Morris Avenue
Building S12
Summit, New Jersey 07901
Fax: (908) 673-9115
E-mail: drugsafety@celgene.com

Investigator Reporting Responsibilities (IND TRIALS ONLY)

The conduct of the study will comply with all FDA safety reporting requirements.

IND Annual Reports

If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report. The Annual Report should be filed in the study's Regulatory Binder, and a copy provided to Celgene Corporation as a supporter of this study as follows.

Celgene Corporation
Attn: Medical Development
86 Morris Avenue
Summit, NJ 07901
Tel: (908) 673-9000

All adverse experience reports must include the patient number, age, sex, weight, severity of reaction (e.g. mild, moderate, severe), relationship to drug (e.g. probably related, unknown relationship, definitely not related), date and time of administration of test medications and all concomitant medications, and medical treatment provided. The investigator is responsible for evaluating all adverse events to determine whether criteria for “serious” and as defined above are present. The investigator is responsible for reporting adverse events to Celgene as described below.

Expedited Reporting by Investigator to Celgene

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours/1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (ACE-011-DBA-PI-0001) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

Report of Adverse Events to the Institutional Review Board

The principal Investigator is required to notify his/her Institutional Review Board (IRB) of a serious

adverse event according to institutional policy.

Investigator Reporting to the FDA

Serious adverse events (SAEs) that are **unlisted/unexpected, and at least possibly associated to the drug,** and that have not previously been reported in the Investigators brochure, or reference safety information document should be reported promptly to the Food and Drug Administration (FDA) by telephone or by fax. Fatal or life threatening SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 7 calendar days after awareness of the event. All other SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 15 calendar days after awareness of the event. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.

Adverse event updates/IND safety reports

Celgene shall notify the Investigator via an IND Safety Report of the following information:

- Any AE associated with the use of drug in this study or in other studies that is both serious and unexpected.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

The Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or

significant risks to subjects.

The Investigator must keep copies of all AE information, including correspondence with Celgene and the IRB/EC, on file.

STATISTICS:

All subjects who received at least one dose of study drug will be included for safety and efficacy analysis. Demographics and baseline characteristics will be summarized by dose levels.

Primary Endpoint(s):

- Complete Response and Partial Response Rate will be summarized by dose level.

Secondary Endpoint(s):

- Time to response is defined as the time from the first dose to the first date when the CR/PR criteria was met. If a subject does not have CR/PR, subject will be censored on the date of last laboratory assessment. Time to response will be listed by subject and dose level. Kaplan-Meier method will be used to estimate the median time to response by dose level.
- Duration of response is for CR/PR subjects only and is defined as the time from the first date that CR/PR criteria were met (e.g. the day following the last RBC transfusion) to the date when CR/PR criteria were not met (e.g. start date of next RBC transfusion).
- All adverse events (including non-serious and serious) will be summarized by dose levels. Key laboratory results will be summarized using CTC grade by dose levels.

SAMPLE SIZE:

Planned number of subjects is approximately 20.

Table 4: Schedule of Study Assessments:

Procedures	Screening Period*	Treatment Period								Follow-Up Period			Study DC
		Cycle 1			Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Post-Rx 1	Post-Rx 2	Post-Rx 3	Post-Rx 4
	Wk-4 to Wk0	Wk0[a] (±1d)	Wk1 (±1d)	Wk2 (±1d)	Wk3 (±2d)	Wk6 (±2d)	Wk9 (±2d)	Wk12 (±2d)	Wk15 (±2d)	Wk19 (±7d)	Wk23 (±7d)	Wk27 (±7d)	Wk 31
Obtain subject informed consent form	☒	-	-		-	-		-	-	-	-	-	
Assess inclusion/exclusion criteria	☒	-	-		-	-		-	-	-	-	-	
Obtain medical subject history	☒	-	-		-	-		-	-	-	-	-	
Record prior treatments and procedures (including transfusion history)	☒	-	-	-	-	-		-	-	-	-	-	
Physical examination	☒	☒	-	-	☒	☒	☒	☒	☒	-	-	-	☒
Vital signs including, blood pressure; weight for treatment period only; height at 1st visit only	-	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒

Procedures	Screening Period*	Treatment Period								Follow-Up Period			Study DC
		Cycle 1			Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Post-Rx 1	Post-Rx 2	Post-Rx 3	Post-Rx 4
	Wk-4 to Wk0	Wk0[a] (±1d)	Wk1 (±1d)	Wk2 (±1d)	Wk3 (±2d)	Wk6 (±2d)	Wk9 (±2d)	Wk12 (±2d)	Wk15 (±2d)	Wk19 (±7d)	Wk23 (±7d)	Wk27 (±7d)	Wk 31
Karnofsky performance status (Appendix 4)	☒	-	-	-	☒	☒	☒	☒	☒	-	-	-	☒
Hematology[b] *	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒
Blood chemistry, Hepatic function, Kidney function[c] *	☒	☒	☒	-	☒	☒	☒	☒	☒	-	-	-	☒
FSH & LH (males & females)	–	☒	-	-	-	-	☒	-	-	-	-	-	-
Testosterone (males only)	–	☒	-	-	-	-	☒	-	-	-	-	-	-
Estrogen & estradiol (females only)	–	☒	-	-	-	-	☒	-	-	-	-	-	-
Menstrual status (females only)	☒	-	-	-	-	-	☒		-	-	-	-	-
Pregnancy Test[d] *	☒	-	-	-	-	-	☒	-	-	-	-	-	-

Procedures	Screening Period*	Treatment Period								Follow-Up Period			Study DC
		Cycle 1			Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Post-Rx 1	Post-Rx 2	Post-Rx 3	Post-Rx 4
	Wk-4 to Wk0	Wk0[a] (±1d)	Wk1 (±1d)	Wk2 (±1d)	Wk3 (±2d)	Wk6 (±2d)	Wk9 (±2d)	Wk12 (±2d)	Wk15 (±2d)	Wk19 (±7d)	Wk23 (±7d)	Wk27 (±7d)	Wk 31
ECHO (within one year prior to enrollment, to be repeated if clinically indicated)	☒	-	-	-	-	-	-	-	-	-	-	-	-
DEXA scan (within one year prior to enrolment, to be repeated if clinically indicated)	☒	-	-	-	-	-	-	-		-	-	-	☒
Transfusion Assessment[e]	☒	☒	-	-	☒	☒	☒	☒	☒	☒	☒	☒	☒
Response Assessment	-	-	☒	-	☒	☒	☒	☒	☒	☒	☒	☒	☒
Adverse Events	-	☒	☒	-	☒	☒	☒	☒	☒	☒	☒	☒	☒
Concomitant therapies / procedures	-	☒	☒	-	☒	☒	☒	☒	☒	☒	☒	☒	☒
Administer study drug	-	☒	-	-	☒	☒	☒	☒	☒	-	-	-	-

*Historical clinical laboratory evaluations performed for routine medical evaluation within 28 days (prior to signing study consent) are acceptable for study entry.

a: All D1 assessments are to be done prior to Sotatercept administration.

b: Hematology laboratory evaluations (RBC count, hemoglobin, hematocrit, reticulocyte count, WBC, ANC, and platelet count) will be collected at Screening, at subsequent visits during the Treatment and Follow-Up Periods, and at Study Discontinuation visit, as referenced in the schedule above. Any laboratory evaluations may be repeated more frequently if clinically indicated.

c: Serum chemistry laboratory evaluations (sodium, potassium, chloride, CO_2 (bicarbonate), calcium, magnesium, phosphorus, BUN, creatinine, glucose, albumin, total protein, alkaline phosphatase, bilirubin [total and direct], AST, and ALT) will be collected at Screening, and at days referenced in the schedule above. Any laboratory evaluations may be repeated more frequently if clinically indicated.

d: Females of childbearing potential: A female of childbearing potential is a sexually mature woman who has not undergone a hysterectomy or who has not been postmenopausal for at least 24 consecutive months (i.e., who has had menses at some time in the preceding 24 months). A serum or urine beta-HCG test (which must be negative) must be performed not more than 3 days from the start of Sotatercept administration (Study D1) once the subject. Subjects must agree to use highly effective methods of birth control during study participation and for at least 16 weeks following the last dose of Sotatercept. Subjects must be counseled concerning measures to be used to prevent pregnancy and potential toxicities prior to the first dose of Sotatercept. Pregnancy tests will be performed according to the above schedule during study participation.

e: Subjects must have documented transfusion history for > 12 weeks before inclusion/initiation of treatment.

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Appendix 1
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Appendix 2
Diamond Blackfan Anemia Diagnosis Criteria

Diagnostic Criteria

- Age less than 1 year
- Macrocytic anemia with no other significant cytopenias
- Reticulocytopenia
- Normal marrow cellularity with a paucity of erythroid precursors

Supporting Criteria

Major

- Ribosomal protein gene mutation described in “classical” DBA
- Positive family history

Minor

- Elevated erythrocyte adenosine deaminase activity
- Congenital anomalies described in “classical” DBA
- Elevated fetal hemoglobin
- No evidence of another inherited bone marrow failure syndrome

A diagnosis of “classical” DBA is made if all the diagnostic criteria are met. When there is a positive family history, an otherwise normal individual should be considered as having “non-classical” DBA if a mutation shared by affected family members is present. Anyone suspected of having DBA, but with insufficient diagnostic criteria, should be considered as having non-classical DBA if a reported mutation is present. A patient can be assigned as having a “probable” diagnosis, with a decreasing degree of certitude if:
3 diagnostic criteria are present along with a positive family history;
2 diagnostic criteria and 3 minor supporting criteria are present; or,
a positive family history and 3 minor supporting criteria are evident, even in the absence of diagnostic criteria.

Appendix 3
Delphi Expert-Consensus Panel Definitions of RBC-Transfusion-Dependence and -Independence

Table 5: Definitions of RBC Transfusion Dependence and Independence

	RBC transfusions	Hb (gm/dL)	Surveillance Interval
RBC transfusion dependence	≥ 10 cc/kg/month	< 8	3 months
RBC transfusion independence	None	> 9	3 months
Reduced RBC transfusion dependence	50% decrease	< 9	3 months

Appendix 4
Karnofsky Performance Status Scale

The Karnofsky Performance Scale Index allows patients to be classified as to their functional impairment. This can be used to compare effectiveness of different therapies and to assess the prognosis in individual patients.

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

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Appendix 5
New York Heart Association – Classification of Heart Failure

Table 7: 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 6
Side Effects Grading and Reporting

Side effects will be graded according to the NCI-CTCAE (version 4).

Link for NCI-CTCAE version 4

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

Appendix 7

Cockcroft-Gault estimation of CrCl:

Cockcroft-Gault estimation of creatinine clearance (CrCl):
(Cockcroft, 1976; Luke 1990)

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight, kg})}{72 \times (\text{serum creatinine, mg/dL})} \quad (\textbf{Males})$$

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight, kg})}{72 \times (\text{serum creatinine, mg/dL})} \times 0.85 \quad (\textbf{Females})$$

Appendix 8

Handling and Administration Guidelines with Drug Accountability Log

Description of Investigational Product(s)

Process III Clinical Drug Product - Lyophilized Powder:

- The clinical drug product consists of Sotatercept in 10 mM citrate buffer, pH 5.8, 8% sucrose, and 0.02% polysorbate 80. It is supplied as a lyophilized powder in labeled, rubber stoppered, sealed, 3-mL glass vials.
- The recommended storage temperature for Sotatercept lyophilized drug product is 2°C to 8°C.
    - Prior to administration, the lyophilized drug product is reconstituted with 1 mL water for injection (WFI). The reconstituted drug product consists of a 50 mg/mL solution of Sotatercept. The reconstituted Sotatercept, in its original container closure system, may be held for up to 6 hours at 2°C to 8°C. Once the reconstituted drug product is drawn into a syringe, it should be administered within one hour from the time it was drawn. The total hold time of the reconstituted drug product, including the hold time in a syringe, must not exceed 6 hours.
- Sotatercept lyophilized product will be shipped to the investigational site with a TempTale monitor in an appropriate nomadic shipper.

Shipping / TempTales

All shipments include instructions for the TempTale device within the shipper. All TempTales are to be stopped immediately upon receipt and unpacking of the shipment. Follow the TempTale Instruction Sheet in the shipper for handling of the temperature monitoring device.

- If the TempTale does not have an alarm bell showing in the screen, the IP was shipped and received in the appropriate temperature range. The temperature parameters should be checked and documented on the TempTale instruction sheet and the IP would be ready for use.
- Please note: if the alarm bell is showing on the TempTale display upon receipt of shipment and stopping of the TempTale, please store the material appropriately and quarantine it from use. Notify Celgene of the excursion right away and await confirmation that the IP is acceptable for use or is to be returned or destroyed.

Sotatercept Preparation and Administration

The clinical staff will fill out the following information on the **Sotatercept Drug Accountability Log** (see Appendix 8) on the dosing day:

- Date

- Visit
- Subject Number
- Subject Initials
- Dose
- Number of mLs used
- Lot Number
- Time Drug Removed from Refrigerator/Freezer (24 hr clock)
- Time Subject Dosed (24-hour clock)

The site personnel will confirm the lot # (for Sotatercept), the number of vials used, and the total volume of Sotatercept given and record this information in the source documents and in the pharmacy records.

Preparation of Sotatercept for Subcutaneous Dosing

Investigational Product (ACE-011) Preparation

Process III Clinical Drug Product- Lyophilized: On the day of dosing, the pharmacist/designee will:

- Pull the appropriate vial(s) from the refrigerator and allow the vial to equilibrate to room temperature.
- Add 1 mL WFI (Sterile Water for Injection) to a Lyophilized ACE-011 vial
- Let the vial sit at room temperature ~2 minutes
- Gently invert the vial to dissolve powder that may have gotten into the stopper/neck
- Gently swirl the vial for ~10 seconds (**NOTE: Do not shake and avoid prolonged or vigorous agitation)**Allow the vial to sit at room temperature for ~ 3 minutes. This procedure will produce a clear 50 mg/mL solution for administration
- The reconstituted Sotatercept drug product is a clear to slightly yellowish opalescent solution.)

Note 1*:* The reconstituted ACE-011, in its original container closure system, may be held for up to 6 hours at 2°C to 8°C.
Note 2*:* Once the reconstituted drug product is drawn into a syringe, it should be administered within one hour from the time it was drawn.
Note 3*:* The total hold time of the reconstituted drug product, including the hold time in a syringe, must not exceed 6 hours.

- 1 mL syringes should be utilized for dispensing. Syringes need to measure up to 0.01 mL so that dose reductions can be accurately measured.
- Subcutaneous injections should be given in the following order as needed; 1) right upper arm, 2) left upper arm, 3) right upper thigh, 4) left upper thigh, 5) abdomen.
- Sufficient care should be taken so that the injection is not given intramuscularly or intravenously.
- If a dose volume is required to be split into more than 1 syringe (>1 mL dose requirement), then the volumes should be split into similar or equal volumes of 1 mL

or less. For example, a subject requiring a 1.25 mL injection volume, that volume will be split into 2 syringes (one syringe can contain 0.62 mL and one syringe can contain 0.63 mL).

Protocol Number - ACE-011-DBA-PI-0001
Drug Accountability Log for Drug Receipt / Drug Return

Record All Usages of Study Medication

		INVESTIGATOR NAME: Adrianna Vlachos, MD											
					Amount								
Date	Visit (Cycle/Day)	Subject No.	Subject Inits.	Dose (mg/ kg)	No. of mLs Used	No. of Vials Used	Balance (No. of Vials)	Lot No.	Time Drug Removed from Freezer/Refrig (24 hr clock)	Time Subject Dosed (24 hr clock)	RPh Inits.	CRA Inits.	Comments
									___ : ___	___ : ___			
									___ : ___	___ : ___			
									___ : ___	___ : ___			
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