A PHASE-2, PROSPECTIVE, OPEN-LABEL STUDY TO DETERMINE THE SAFETY AND EFFICACY OF SOTATERCEPT (ACE-011) IN SUBJECTS WITH MYELOPROLIFERATIVE NEOPLASM (MPN) -ASSOCIATED MYELOFIBROSIS AND ANEMIA

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1. BACKGROUND AND RATIONALE

1.1 Myeloproliferative Neoplasm (MPN)-Associated Myelofibrosis

Myelofibrosis (MPN-associated myelofibrosis) is a rare (0.4-1.3 per 100,000 in Europe, Australia and USA) cancer first described in 1879 by Henck who called it osteosclerosis. MPN-associated myelofibrosis was classified as a myeloproliferative disorder (1951) and further characterized as a clonal proliferation of a pluripotent stem cell (1978). There is some evidence of genetic transmission by a higher incidence rate in the Ashkenazi Jewish population in Northern Israel. Exposure to Thorotrast, industrial solvents (benzene and toluene) and atomic bomb radiations may be etiologic factors. The primary pathogenetic mechanism of proliferation of a pluripotent stem cell clone leads to ineffective erythropoiesis, dysplastic-megakaryocyte hyperplasia, and an increase in the ratio of immature granulocytes to total granulocytes. This clonal proliferation is characteristically accompanied by reactive bone marrow fibrosis and by extra-medullary hematopoiesis in the spleen or other organs. Typical clinical features include splenomegaly, progressive anemia, and constitutional symptoms. The terms “myeloid metaplasia” and “extra-medullary hematopoiesis” are used interchangeably to describe a pathologic process of ectopic hematopoiesis that may occur in any organ system but primarily the liver and spleen.

1.1.2 Prognosis

At the molecular level, a JAK2 tyrosine kinase mutation ($JAK2^{V617F}$) was recently described in MPN-associated myelofibrosis with mutational frequency ranging from 35% to 57% with 9-29% homozygosity. To date, however, the presence of $JAK2^{V617F}$ in MPN-associated myelofibrosis has not been shown to be a reliable prognostic variable. Presence of this mutation, change in its percent (allele burden modifications) during the course of treatment, and associations with outcomes may provide further insight into its potential use as a biologic marker to track the effectiveness of therapies for MPN-associated myelofibrosis. However, this is strictly investigational approach.

Adverse prognostic factors for survival include older age, anemia (hemoglobin < 10 g/dL) and receiving RBC-transfusions. The etiology for the latter finding is usually multi-factorial and related both to bone marrow failure and hyper-splenism. Poor prognosis is also correlated with leukocytosis or leukopenia, blood blasts, increased numbers of granulocyte precursors, thrombocytopenia, abnormal karyotype and hyper-catabolic symptoms. The course of the disease is variable. Survival from diagnosis is 2 to 20 years with median survival of about 5 years. Common causes of death are progressive bone marrow failure, blastic transformation, infection, other cancers and portal hypertension.

1.1.3 Signs and Symptoms

The clinical picture of MPN-associated myelofibrosis involves constitutional symptoms (e.g., cachexia, night sweats, bone pain, fatigue, fever), splenomegaly, anisopoikilocytosis with teardrop erythrocytes, progressive anemia, immature myeloid and erythroid precursors in the peripheral blood, elevated lactate dehydrogenase (LDH) levels, and fibrosis of the marrow (as evaluated by reticulin and trichrome [collagen] stains). The leukoerythroblastic picture is postulated to be related to both the intra-medullary sinusoidal marrow and spleen hematopoiesis.

The disease generally occurs in adults, 70% of the subjects are >50 years of age; median age is 54-62 years. Anemia is apparent in 50-70% at diagnosis and 25% will have severe anemia with hemoglobin level < 8.0 g/dL. Splenomegaly is present in 85-100% of subjects at diagnosis and is massive in 10%. Approximately one-half of the subjects present with an elevated WBC, 28% with thrombocytosis (platelets >400 x 10e9/L), and 37% with thrombocytopenia (platelets <150 x 10e9/L).

Growth factor and cytokine variations are multiple. It is unclear whether the aberrations in cytokine production and in the vasculature are pathogenic or whether they are a non-specific reaction associated with the underlying clonal activity. Increased levels of basic fibroblast growth factor (bFGF) are reported in subjects with MPN-associated myelofibrosis. Both transforming growth factor–beta (TGF-β) and bFGF regulate cell growth and differentiation. In addition to their potent fibrogenic activity, TGF-β and bFGF regulate hematopoiesis by selective actions on primitive stem cells. bFGF has been shown to augment the activity of stem cell factor (SCF), interleukin-3 (IL-3), granulocyte-macrophage colony stimulating factor (GM-CSF), andor erythropoietin on committed progenitor cells. Serum interleukin-6 (IL-6) has multiple biological effects, including the regulation of hematopoiesis, immune responses, and acute phase reactions. IL-6 appears to be a potent megakaryocytic maturation factor. Other cytokines/proteins that are dys-regulated in MPN-associated myelofibrosis include; tumor necrosis factor-alpha (TNF-α) and angiogenic molecules like vascular endothelial growth factor (VEGF).

1.1.4 Treatment of MPN-associated myelofibrosis

Two therapies are approved for MPN-associated myelofibrosis. Ruxolitinib was recently (November 2011) approved by US FDA and EMA for treatment of persons with intermediate or high-risk MPN-associated myelofibrosis, and has become standard first line therapy for patients with MF that have symptomatic splenomegaly (about 80% of patients) and/or MF-related significant systemic symptoms (fatigue, itching, night sweating, low grade fever, weight loss, decreased

performance, bone pain, and similar). Ruxolitinib improves splenomegaly and constitutional symptoms in many subjects but is associated with a worsening of anemia. The primary clinical risks with ruxolitinib treatment are the potential sequelae of decreased hematopoietic proliferation attributable to the inhibition of growth factor pathways associated with JAK inhibition. Dose-dependent, reversible thrombocytopenia has been observed in studies of patients with MF. Anemia and, less frequently, neutropenia have also been observed. Increased rates of infection and anemia are potential risks of myelosuppression, and there are multiple sequelae of anemia, including the burden and risks of transfusion.

Hydroxyurea is the most commonly used drug in the proliferative phases of the disease and is approved in Europe. It is a chemotherapy agent and controls enlarging spleen and high blood count; anemia is one of the side effects. IFNα produces hematologic responses and reduces splenomegaly in 30-50% of subjects, especially those in a proliferative phase. However, it is often poorly-tolerated. Therapies for anemia include androgens and/or erythropoietin. These are rarely effective and have important toxicities. RBC-transfusions are given for severe anemia. Splenectomy and/or spleen radiation are sometimes used to manage splenomegaly. Splenectomy is associated with an increased risk of leukemia transformation in some series. Spleen radiation can result in severe bone marrow suppression. No medical therapy is proved to prolong survival. Subjects with an intact quality of life and no threatening hematologic abnormalities, like erythrocytosis or thrombocytosis, are often observed without therapy.

Advances in the pathogenesis of MPN-associated myelofibrosis are expected to facilitate the development of molecularly targeted therapy. In the meantime, current management strategies include observation for low-risk cases, ruxolitinib, hydroxyurea, androgens, at the intermediate and high-risk level, and allo transplants for high-risk disease in <5% of suitable candidates. Benefit to a subset of subjects is reported immune-modulating drugs (IMiDs) like thalidomide, lenalidomide and pomalidomide. There is an unmet medical need for pharmacologic therapies to improve anemia in persons with MPN-associated myelofibrosis.

1.2 Rationale for ACE-011 in MPN-associated myelofibrosis

1.2.1 Background

1.2.1.1 Activin Biology

The activins (A-E) are proteins that form dimers and heterodimers. All are part of the TGF-β protein super-family. The first described activin, Activin A was initially identified as a gonad differentiation factor involved in modulating follicle stimulating hormone (FSH) secretion 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 initially described as erythroid differentiation factor (EDF), effecting the maturation and differentiation of RBC's (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; 1989) and erythropoiesis-inhibitory effects (Nakao, 1991).

At the cellular level, activins bind initially to the high-affinity Type-II receptor (ActRIIA). The ligand-bound ActRIIA then recruits the low-affinity Type I receptor (ActRIA or ALK-4). The receptor hetero-complex, through its cytoplasmic protein kinase activity, then activates the Smad signaling cascade to eventually influence nuclear transcriptional factors (Chen, 2002; Mathews, 1994). Competitive binding of activins in the blood by the sotatercept (ACE-011) soluble fusion protein can result in inhibition of the ActRIIA receptor signaling pathway by impeding biological processes attributed to these pleiotropic proteins.

The activin signaling pathway has been shown to induce terminal erythroid differentiation in some preclinical models. Inhibition of activin may indirectly lead to increases in proliferation or differentiation of the erythroid lineage. Based on its pharmacologic effects, sotatercept (ACE-011) is being developed for the treatment of anemia associated with a variety of disorders, such as in chronic kidney disease and CIA.

In a retrospective study (Seder, 2009) activin immune reactivity was detected in about 80% of lung adenocarcinomas surveyed (N=164). Expression ranged from moderate in most samples to high in about 20%. Gene expression profiling was also used to measure activin mRNA in 86 lung adenocarcinomas and 10 normal lung samples. An average of three-fold more activin transcript was detected in cancer tissue relative to normals samples and particularly high over-expression were associated with worse overall survival in stage I persons with NSCLC.

Additionally, in the NIH "directors challenge" study for NSCLC adenocarcinoma (Shedden, 2008), three of 12 molecular subgroups, including the subgroup with the worst survival prognosis, showed over-expression of activin A. Thus, over-expression of activin may play a role in NSCLC tumor progression.

1.2.1.2 Sotatercept (ACE-011)

Sotatercept (ACE-011) (ActRIIA-IgG1Fc) is a human fusion protein consisting of the extracellular domain (ECD) of activin receptor IIA (ActRIIA) linked 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 (ACE-011). However, in order to reduce the potential immunogenicity of the human molecule, sotatercept (ACE-011), and to maximize the opportunity to maintain exposures in chronic models, a murine surrogate molecule was constructed by exchanging the human immunoglobulin Fc sequence portion of sotatercept (ACE-011) with its murine IgG2a homolog. The resultant construct is referred to as RAP-011 (ActRIIA-mIgG2aFc), and is described in the pharmacology studies below. Both ACE-011 and RAP-011 bind with high affinity to activin A/B, GDF-11 and, with slightly lower affinity, to BMP-10.

1.2.1.3 Pharmacology

RAP-011 was evaluated in a range of animal pharmacology studies to assess the effects of inhibition of Activin A on the biological processes attributed to that regulatory protein. RAP-011 has been shown to have significant effects on the red cell compartment. RAP-011 treatment of mice at 10, 30 and 50 mg/kg by intra-peritoneal injection (IP) twice per week for 3 months resulted in a 16-26% increase in RBC counts compared to control animals. Rats treated with sotatercept (ACE-011) at 0.3, 3 and 30 mg/kg once per week for 3 months showed RBC increases of 6-15% over control animals. Finally, in cynomolgus monkeys treated with 10, 30 or 50 mg/kg of sotatercept (ACE-011) twice per month for 3 months, there was a 20-25% increase in RBC counts compared to control animals. In this study, RBC level increases were apparent as early as 2 weeks following the initial dose of sotatercept (ACE-011).

RAP-011 administered at 10 mg/kg to mice three days prior to administration of paclitaxel at 30 mg/kg was sufficient to prevent decreases in RBC parameters typically seen three days later. Mice receiving paclitaxel alone had decreased hematocrit levels from 43% to 38% three days following treatment. RAP-011 administered three days prior to paclitaxel injection was sufficient to keep the hematocrit levels above 42% at three days and up to two weeks following paclitaxel administration. Therefore, prophylactic treatment with RAP-011 was able to prevent paclitaxel-induced anemia in mice.

RAP-011 has also been shown to significantly increase bone mineral density (BMD) and strength in normal animals and in a variety of animal models of bone loss (Chantry, 2008; Lotinun, 2008; Pearsall, 2008). In a murine ovariectomy (OVX)-induced model of osteopenia, RAP-011 (10 mg/kg intravenous [IV], twice per week x 12 weeks) increased trabecular BMD > 25% in 6-12 weeks compared to the phosphate buffered saline (PBS)-treated controls ($p<0.002$). RAP-011 treatment was able to reverse the accelerated bone loss associated with ovariectomy. As expected, sham-operated (SHAM) mice (i.e., intact ovaries) started the study with a greater trabecular BMD than OVX mice. PBS-treated SHAM mice showed a 10% decrease in trabecular BMD after 12 weeks of treatment compared to baseline, while SHAM-RAP-011 mice had a 32% increase in trabecular BMD over the same period. These data demonstrate that RAP-011 is able to increase trabecular BMD in both the normal state and in a model of established bone loss. The femurs of both the RAP-011 treated OVX and SHAM mice showed statistically significant increases in all measured parameters of bone strength (i.e., maximum load, stiffness, energy, ultimate strength, and elastic modulus). In summary, treatment with RAP-011 produced bone of superior quality consistent with an anabolic agent.

RAP-011 was evaluated in a mouse model of skeletal metastasis using luciferase-tagged, human MDA-MB-231 breast cancer cells (estrogen receptor negative). Mice were pretreated for 2 weeks with RAP-011 (10 mg/kg, biweekly, subcutaneous [SC]) prior to intra-cardiac injection of tumor cells. Treatment with RAP-011 was continued for an additional 5 weeks following tumor implantation. A parallel study was conducted to examine the effect of RAP-011 treatment, as described above, on survival of MDA-MB-231 bearing mice.

The data suggest that RAP-011 treatment may decrease the incidence of MDA-MB-231 metastasis to bone and may also play a role in inhibiting tumor growth in the bone marrow environment. Furthermore, in the presence of tumor cells, RAP-011 is able to prevent lytic disease through an anabolic mechanism of bone formation. Lastly, treatment with RAP-011 resulted in an approximately 25% survival benefit in this model.

RAP-011 was also evaluated in osteolytic bone disease of multiple myeloma. Multiple myeloma is associated with the development of bone disease characterised by increased osteoclast activity and a suppression of osteoblastic bone formation. Results obtained in the 5T2MM murine model demonstrated that RAP-011 could prevent the development of osteolytic bone disease in a preventative setting. 5T2MM cells promoted the development of osteolytic bone lesions ($p<0.001$), a reduction in trabecular volume ($p<0.001$) and cortical volume ($p<0.005$). RAP-011 completely prevented 5T2MM-induced decreases in trabecular volume and number in both tibia ($p<0.001$ and $p<0.01$), femur ($p<0.001$ and $p<0.001$) and vertebrae ($p<0.01$ and $p<0.01$) when compared to vehicle treated mice. Bone volume was 19% higher in the tibia, 35% higher in the femur

and 12% higher in vertebrae of RAP-011 treated mice than naïve non-tumour bearing mice. This study showed that, in the preclinical murine model for myeloma, RAP-011 stimulates bone formation by increasing osteoblast perimeter and number, mineralisation and bone formation rate but had no effect on osteoclast activity. RAP-011 also appeared to inhibit tumor growth as demonstrated by decreased serum M protein, indicative of decreased tumor burden.

The efficacy of RAP-011 was also examined in two orthotopic metastatic models of breast cancer using luciferase-tagged human MCF-7 and MDA-MB-231 breast cancer cells (estrogen receptor positive and negative, respectively). Mice were pretreated for 2 weeks with RAP-011 (10 mg/kg, biweekly, SC) prior to the intra-cardiac implantation of tumor cells into female nude mice. Treatment with RAP-011 was continued for an additional 7 weeks following tumor implantation at which time mice were sacrificed and assessed for tumor burden. RAP-011 either modestly decreased the tumor burden (in the case of mice bearing MCF-7 tumors) or delayed tumor growth by approximately 3 weeks (MDA-MB-231 model) as measured by bio-luminescence.

The ability of RAP-011 to repair osteolytic lesions caused by metastatic disease was investigated in mice. In this model, MDA-MB-231-Luc cells were intratibially implanted in athymic nude mice to mimic bone metastasis. Mice were treated with a chemotherapy regimen of paclitaxel (20 mg/kg, IP, every three days) starting seven days after tumor injection and continuing for the duration of the study. On study day 42, mice with detectable but minimal tumor burden, as measured by bioluminescent imaging, were divided into two groups and treated with either RAP-011 (10 mg/kg, SC, biweekly) or vehicle. Prior to dosing, µCT scans of the tumor bearing tibia were conducted to identify osteolytic lesions. RAP-011 treatment continued for four weeks (to study day 70) and a final µCT scan of the tibia was performed. On study day 70 there was a trend toward decreased number and size of osteolytic lesions in RAP-011-treated mice compared to control animals. Although osteolytic disease (most likely related to tumor burden) did progress in some of the treated mice, the majority of mice treated receiving RAP-011 developed less severe or no bone lesions compared to the untreated group. Finally, treated animals also demonstrated an increased hematocrit, confirming the ability of RAP-011 to prevent CIA. To summarize, treatment with RAP-011 has the ability to inhibit osteolytic lesions caused by tumors and to build new bone after cytotoxic chemotherapy with paclitaxel.

1.2.1.5 Toxicology

Sotatercept (ACE-011) has been evaluated for toxicological effects in two species, Sprague-Dawley rats and cynomolgus monkeys. The dose levels ranged from 0.3

to 30 mg/kg in rats and from 1 to 50 mg/kg in monkeys. These dose ranges were designed to support phase 1a single-dose levels of 0.01 to 3.0 mg/kg IV and phase 1b multiple doses of 0.1 to 2 mg/kg (monthly, SC). Weekly (rat and IV monkey studies) or every 2 week (SC monkey studies) dosing in animals was designed to provide continuous, but fluctuating serum concentrations of sotatercept (ACE-011), which would be mimicked by a one-month dosing interval in humans.

Sotatercept-related hematological (increase in RBC parameters) and reproductive (epididymal granulomas, testicular degeneration, decreased sperm counts and motility, and change in ovarian/uterine weights) findings were expected pharmacodynamic effects of ActRIIA signal inhibition, likely mediated via modulation of erythropoiesis and FSH secretion, respectively. Unique to rats were adrenocortical and pancreatic findings. Neither finding was associated with any clinical signs of adrenocortical (anorexia, weakness, gastrointestinal disturbances, serum electrolyte disturbances) or pancreatic (abnormal stool, weight loss) insufficiency. Kidney findings include membranoproliferative glomerulonephritis and/or tubulointerstitial nephritis in rats and monkeys. Although assessment by immunohistochemistry demonstrated deposition of immunoglobulin and complement associated with glomerular changes in monkeys, only rare monkeys tested positive for anti-drug antibodies (ADA). Additionally, in a three-month toxicity study in rats, kidney findings were seen primarily in rats that did not exhibit an ADA response. Therefore, although anti-sotatercept antibody deposition in the kidney cannot be ruled out as a contributing cause, the kidney findings are presumed to be primarily a direct effect of the drug.

Related to the kidney findings in monkeys was the observation of perivascular accumulation of foamy macrophages and intimal thickening of small arteries and arterioles in the choroid plexus at doses of ≥ 2.6 mg/kg every 4 weeks, as well as mononuclear cell infiltrate at all dose levels, in the 9-month study. Like the kidney, these findings were associated with deposition of immunoglobulin M (IgM) and complement. Similar findings were not seen in rats.

The no-observed-adverse effects levels (NOAELs) from the 3-month rat and 9-month monkey SC studies were 3 and 1 mg/kg, respectively. Anticipated plasma exposure in humans at 2.0 mg/kg every 3 weeks will exceed the exposure attained at these NOAELs. Plasma exposures (area under the concentration curve [AUC]) at these doses are estimated to be approximately 0.7- and 0.3-fold, in rats and monkeys, respectively, that of the exposure in humans at the proposed maximum dose of 2.0 mg/kg.

1.2.1.6 Summary of Clinical Experience

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

Sotatercept (ACE-011) was first studied in a randomized, phase 1a, single dose, dose escalation study in healthy, postmenopausal females (Ruckle, 2009). Sotatercept (ACE-011) was diluted in normal saline 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; 5 active and 1 placebo at each of the IV and SC dose levels. All subjects were followed for 4 months following a single dose administration.

The pharmacokinetics (PK) of sotatercept (ACE-011) was linear. The overall mean exposure (AUC) was proportional to doses (0.01-3 mg/kg IV, 0.03-0.1 mg/kg SC). Across IV doses ranging from 0.1 through 3.0 mg/kg, the mean clearance (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 (ACE-011) was completely absorbed, and the mean $t_{1/2,}$ z was approximately 30 days, with no apparent dependence on dose.

The most commonly occurring treatment-emergent adverse events (AEs; i.e., those occurring in more than 1 subject in any treatment group) 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 was mild in severity and were judged to be unrelated to sotatercept (ACE-011). No deaths, serious AEs (SAEs), or AEs leading to discontinuation were reported. Changes in RBCs, hemoglobin, reticulocytes, liver function tests, glucose, uric acid, amylase and lipase occurred in some subjects. Mild, transient elevations in pancreas 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) data. Preservation of adrenal cortical function was monitored through evaluation of serum electrolytes (sodium and potassium levels) and through cortisol response to adrenocorticotropic hormone (ACTH) stimulation.

No clinically significant findings were observed at doses up to 3.0 mg/kg IV, and sotatercept (ACE-011) was well tolerated in healthy, postmenopausal female volunteers in single dose levels up to 0.1 mg/kg SC and 3.0 mg/kg IV, the highest dose levels tested in this study.

1.2.1.6.2 A011-02: A Phase-1b Study in Healthy Postmenopausal Women (Multiple Dose)

Sotatercept (ACE-011) was studied in a phase 1b, single-center, randomized, double-blind, placebo-controlled, multi-dose, dose-escalating study to evaluate the safety, tolerability and pharmaco-dynamics of sotatercept (ACE-011) in healthy postmenopausal women. Four cohorts of 10 subjects each were planned at the following dose levels: 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 (ACE-011) or placebo every 28 days for a total of 4 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 dose-limiting pharmacodynamic effect was observed. 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 rise in hemoglobin levels, up to 20 g/dL and hematocrit levels, up to 57.3%. Due to symptoms of headaches, nausea, eye pain, dizziness and vomiting approximately one week following the second dose, the subject was hospitalized for monitoring and evaluation of her hypertension. The head MRI, fundoscopy, and ECG performed were reported as normal and headache symptoms resolved following corrective treatment by phlebotomy. The SAE resolved and the subject was discharged from the hospital the following day. The hypertension was monitored closely and managed initially with antihypertensive medication. The hypertension resolved by the end of the study without need of any antihypertensive medication. The subject received aspirin prophylactically until the end of the study and continued taking ibuprofen as needed for headaches. Further details can be found in the Investigator's Brochure.

Based on the magnitude of the hematopoietic response, the Sponsor suspended dose escalation to the 2.0 mg/kg dose level and further dosing in all cohorts as a result of this dose-limiting pharmaco-dynamic effect at the 1.0 mg/kg dose level. In total, 31 subjects were enrolled and treated. Dose levels of sotatercept (ACE-011) 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 4 planned doses of sotatercept (ACE-011). Due to early discontinuation of study drug, subjects randomized to active treatment in Cohort 2 received 3 doses of sotatercept (ACE-011), and subjects randomized to active treatment in Cohort 3 received 2 doses of sotatercept (ACE-011). Subjects randomized to placebo treatment received between 1 and 4 doses of study treatment. In the analysis of the data, after the administration of the first dose, a dose and time dependent increase in hemoglobin, HEMATOCRIT and RBC numbers were observed (see

Table 1 below for changes in hemoglobin levels).

Table 1: A011-02: A Phase-1b Study in Healthy Postmenopausal Women, Hemoglobin Evaluation After Different Doses of Sotatercept

Time Point	Mean Change from Baseline (g/dL)			
	Placebo N=7[a]	**0.1mg/kg N=8**	**0.3mg/kg N=8**	**1.0mg/kg N=8**
Baseline	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] N placebo subjects with data decreases over time as a result of the early discontinuation of the study (i.e., 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; 5 subjects with data on Days 71 and 113; 4 subjects with data on Day 64; 3 subjects with data on Day 141; two subjects with data on Day 99; and one subject with data on Days 92 and 169.

[b] N doses given per treatment group: 0.1 mg/kg 4 doses; 0.3 mg/kg 3 doses; 1.0 mg/kg 2 doses. Data beyond this study day are considered follow-up results.

[c] N=1

Other than the serious case of hemoglobin increase, no life-threatening events were reported. The most notable AEs were those related to increases in hematologic laboratory measures in the 1.0 mg/kg dose group: hematocrit, hemoglobin and RBC numbers. The AEs of increased hemoglobin and/or hematocrit 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 Hemoglobin levels underwent phlebotomies and all Hemoglobin

elevations were 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.

Paresthesia and dizziness were reported more frequently in the sotatercept (ACE-011) groups, though the events were < G 2 and generally not considered drug related. Other frequently reported events (e.g. fatigue, upper respiratory infection) did not appear to increase with dose and were generally mild.

Hemoglobin levels for all subjects with elevations had returned to within normal limits by the end of the study.

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

The PK of sotatercept (ACE-011) were linear after SC administration. Both AUC28d and Cmax were proportional to dose from 0.1 to 1 mg/kg following the first SC administration. The $t_{1/2,}$ z of sotatercept (ACE-011) following the last dose in all three dose groups was identical, with mean $t_{1/2,}$ z being approximately 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 ((apparent) volume of distribution) 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. BMD 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.

1.2.1.6.3 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, tolerability and efficacy of sotatercept (ACE-011) in subjects with osteolytic lesions of multiple myeloma (MM). In this study, subjects were randomized in a 4:1 ratio to one of three dose levels of sotatercept (ACE-011) (0.1, 0.3 and 0.5 mg/kg) or placebo, administered to subjects every 28 days by SC injection, for up to four doses over a 3-month period. Sotatercept (ACE-011) was evaluated in combination with the anti-myeloma therapy of melphalan (4 mg/m^2 on days 1-7), prednisolone (40 mg/m^2 on days 1-7) 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 medication: 6 subjects received placebo, 8 subjects received 0.1 mg/kg sotatercept (ACE-011), 8 subjects received 0.3 mg/kg sotatercept (ACE-011), and 8 subjects received 0.5 mg/kg sotatercept (ACE-011). Twenty six (86.7%) 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, 50.0% 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 disease at screening (83.3%) and had received prior chemotherapy (93.3%). Approximately 43.3% of subjects were receiving bisphosphonates at screening, which continued during the study. Fourteen out of 24 subjects (58%) who received study treatment (sotatercept [ACE-011]) did receive 3 doses or more (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).

Safety: Overall, 22 (91.7%) subjects receiving sotatercept (ACE-011) and 4 (66.7%) subjects receiving placebo reported at least one AE. Among subjects receiving sotatercept (ACE-011), AEs were reported in 87.5%, 87.5%, and 100% of subjects in the 0.1 mg/kg, 0.3 mg/kg, and 0.5 mg/kg dosing cohorts, respectively. Treatment-related AEs (i.e., those assessed by the Investigator as possibly, probably, or definitely related to treatment) were reported by 21 (87.5%) subjects receiving sotatercept (ACE-011) and 4 (66.7%) receiving placebo. Most subjects had AEs that were assessed as related to MPT: 21 (87.5%) subjects receiving sotatercept (ACE-011) and 4 (66.7%) subjects receiving placebo. No AEs were assessed by the Investigator as related to the study medication alone (sotatercept (ACE-011) 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 (ACE-011) dose group (increased blood pressure; sudden death) and one subject in the 0.5 mg/kg sotatercept (ACE-011) dose group (hypertension). Four subjects had SAEs, 1 (12.5%) subject in the 0.1 mg/kg sotatercept (ACE-011) group and 3 (37.5%) subjects in the 0.5 mg/kg sotatercept (ACE-011) 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 (ACE-011), and 1 SAE (sudden death) was assessed as probably related to MPT and possibly related to sotatercept (ACE-011). One subject in the 0.5 mg/kg sotatercept (ACE-011) dose group discontinued study drug due to episodes of atrial fibrillation assessed as possibly related to MPT and unrelated to sotatercept (ACE-011).

Table 2: Summary of Adverse Events Reported in Greater Than or Equal To 5 Percent of Patients Overall

			Sotatercept (ACE-011) Treatment Group							
Preferred Term[a]	**Placebo (N=6)**		**0.1 mg/kg (N=8)**		**0.3 mg/kg (N=8)**		**0.5 mg/kg (N=8)**		**All Sotatercept (ACE-011) (N=24)**	
	Any Grade	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**
Neutropenia	4 (66.7%)	1 (16.7%)	4 (50.0%)	2 (25.0%)	6 (75.0%)	2 (25.0%)	6 (75.0%)	3 (37.5%)	16 (66.7%)	7 (29.2%)
Leukopenia	0	0	3 (37.5%)	1 (12.5%)	1 (12.5%)	0	1 (12.5%)	1 (12.5%)	5 (20.8%)	2 (8.3%)
Granulo-cytopenia	0	0	2 (25.0%)	1 (12.5%)	1 (12.5%)	1 (12.5%)	1 (12.5%)	1 (12.5%)	4 (16.7%)	3 (12.5%)
Anaemia	0	0	1 (12.5%)	1 (12.5%)	1 (12.5%)	1 (12.5%)	2 (25.0%)	1 (12.5%)	4 (16.7%)	3 (12.5%)
Respiratory tract infection	0	0	1 (12.5%)	1 (12.5%)	1 (12.5%)	0	1 (12.5%)	0	3 (12.5%)	1 (4.2%)
Thrombo-cytopenia	0	0	1 (12.5%)	0	0	0	2 (25.0%)	1 (12.5%)	3 (12.5%)	1 (4.2%)
Pyrexia	0	0	1 (12.5%)	0	1 (12.5%)	0	1 (12.5%)	0	3 (12.5%)	0
Blood pressure increased	0	0	1 (12.5%) *	1 (12.5%) *	0	0	1 (12.5%)	0	2 (8.3%)	1 (4.2%)
Bronchitis	1 (16.7%)	0	0	0	1 (12.5%)	0	1 (12.5%)	0	2 (8.3%)	0
Compression fracture	0	0	0	0	1 (12.5%)	0	1 (12.5%)	0	2 (8.3%)	0
Pathological fracture	0	0	1 (12.5%)	0	0	0	1 (12.5%)	1 (12.5%)	2 (8.3%)	1 (4.2%)

[a]Adverse events were those that were treatment-emergent, defined as newly acquired or worsened during or after administration of first dose of study medication. A person 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 (ACE-011) or placebo).

Table 3: Summary of SAEs Reported

Study Treatment	Age (y) / Sex / Race	Preferred Term (Verbatim Term) [Severity / Grade[a]]	Study Day[b] at Onset	Outcome (duration)	Relationship to Study Treatment
0.1 mg/kg Sotatercept (ACE-011) and MPT	61 / M / White	Sudden death (sudden death)	103	Death	Sotatercept (ACE-011): possibly MPT: probably
0.5 mg/kg Sotatercept (ACE-011) and MPT	68 / M / White	Pain in extremity (pain in leg) [severe / G 3]	128	Ongoing at end of study	Sotatercept (ACE-011): not related MPT: not related
		Pathological fracture (pathological fracture of femur) [severe / G 3]	130	Ongoing at end of study	Sotatercept (ACE-011): not related MPT: not related
0.5 mg/kg Sotatercept (ACE-011) and MPT	45 / M / White	Pneumonia (pneumonia) [moderate / G 2]	9	Resolved (12 days)	Sotatercept (ACE-011): not related MPT: possibly
0.5 mg/kg Sotatercept (ACE-011) and MPT	78 / F / White	Atrial fibrillation (atrial fibrillation) [life-threatening / G 4]	6	Resolved (1 day)	Sotatercept (ACE-011): not related MPT: possibly

F= female; M = male; MPT = melphalan, prednisolone, and thalidomide; NCI CTCAE, v3.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0; y = years

[a]based on NCI CTCAE, v3.0.

[b]Relative to first dose of study drug.

Following analysis of the central laboratory data, increases in Hemoglobin values were observed within 28 days after administration of the first dose of sotatercept (ACE-011)/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 Hemoglobin from Baseline at Any Time and Sustained for Greater ≥28 Days

Increase in Hemoglobin	Dose Sotatercept (ACE-011)/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	4	3	7	2	16
≥ 1.5 g/dL	2	3	3	1	9
≥ 2.0 g/dL	1	3	2	0	6

Taken together, these data, suggest a beneficial pharmaco-dynamic effect of sotatercept (ACE-011) on erythropoiesis in a person population with cancer CIA.

A011-08: A Phase 2 Study in Women with Metastatic Breast Cancer with Chemotherapy Induced Anemia (Preliminary results)

The results presented in this section are preliminary. Study A011-08 is clinically completed and the writing of the clinical study report is in progress.

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 chemotherapy-induced anemia (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 subcutaneous injection every 28 days for up to 4 treatments (Days 1, 29, 57, and 85). Subjects were administered concurrent treatment with a bone marrow suppressive chemotherapy regimen for metastatic breast cancer per standard of care at the study site.

Because of changes in guidance for the treatment of CIA and a slower than expected rate of enrollment the study was terminated after 30 subjects enrolled. All 30 received ≥1 dose of treatment: 5 subjects in the placebo cohort, 8 subjects in the sotatercept 0.1 mg/kg cohort, 10 subjects in the sotatercept 0.3 mg/kg cohort and 7 subjects in the sotatercept 0.5 mg/kg cohort. 29 subjects were white, all were female with a median age of 51 y (range, 32-74 y). Demographic characteristics were similar across the cohorts.

Fourteen subjects completed treatment. Fourteen 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 disease progression, four subjects (25.0%) withdrew consent, three subjects (18.8%) discontinued due to an AE, and one subject discontinued because of receiving an ESA.

Of the 25 subjects in the three sotatercept cohorts combined, four received the planned four doses of 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 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 with a hemoglobin increase ≥ 10 g/L from baseline for 28 consecutive d up to 2 mo after the last dose of study treatment, in the absence of RBC transfusion or treatment with an ESA (Table 5).

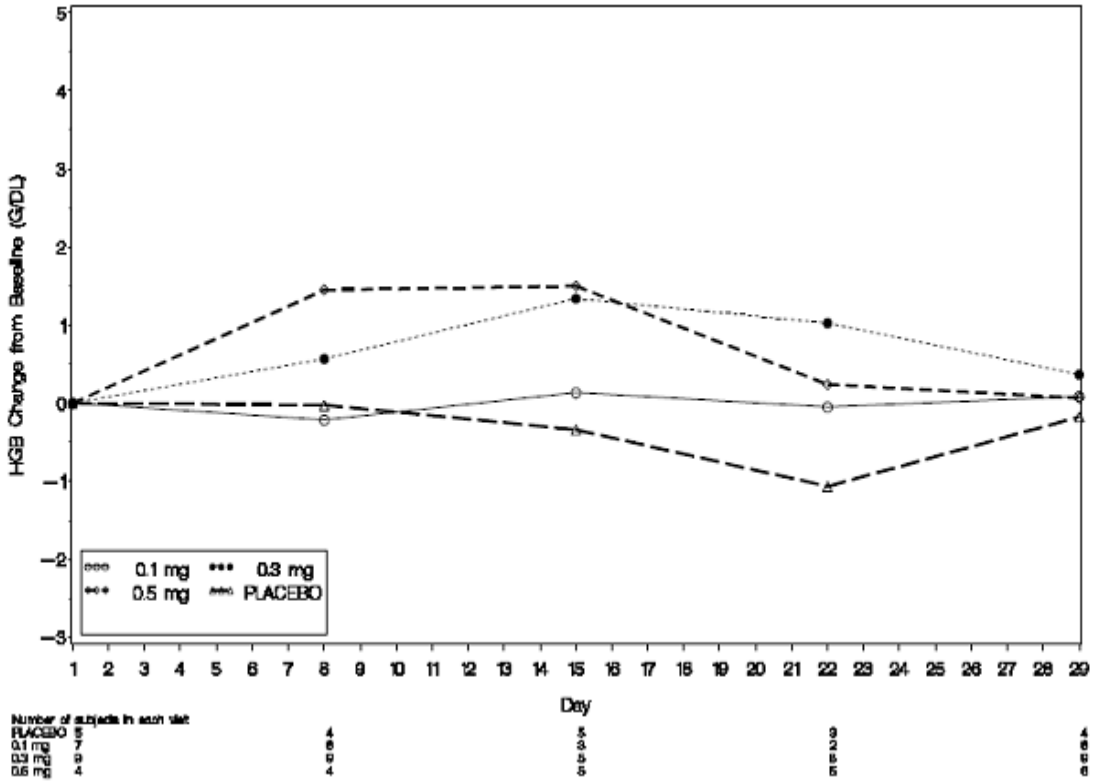
Table 5: Primary Efficacy Analysis: Subjects with Hemoglobin Increase from Baseline of ≥10 g/L for 28 Consecutive Days – Per Protocol Set, Central Laboratory Results (Study A011-08)

		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	3 (33.3%)	2 (50.0%)	5 (27.8%)
Non-responder	4 (80.0%)	5 (100%)	6 (66.7%)	2 (50.0%)	13 (72.2%)

Five of 18 subjects in the three sotatercept (0.1, 0.3, and 0.5 mg/kg) treatment groups combined responded. One of five subjects in the placebo group responded. 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 dose-response relationship.

Among the 13 subjects in the three sotatercept treatment groups combined who were non-responders, five subjects skipped a dose and/or had at least one dose reduced during treatment. Four had achieved a hemoglobin increase ≥1 g/dL and one subject achieved an elevated hemoglobin of ≥ 11 g/dL Mean changes from baseline hemoglobin levels during the 28-day period after the first dose are presented in Figure 1. Mean changes from baseline hemoglobin levels during the 28-day period after the first dose in subjects in the sotatercept 0.1 mg/kg group were similar to those in the placebo group. Mean increases in hemoglobin during that period in the sotatercept 0.3 mg/kg and 0.5 mg/kg groups were greater those in the sotatercept 0.1 mg/kg and placebo treatment groups, and support a sotatercept dose-response relationship.

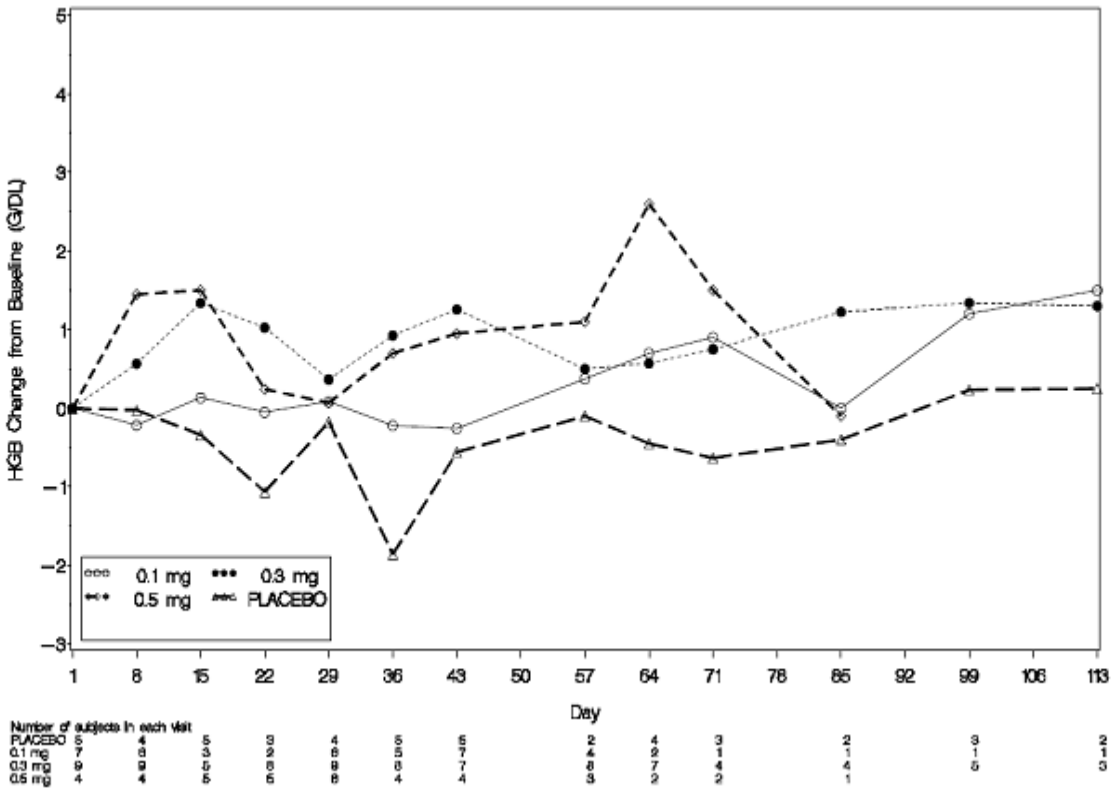
Figure 1: Mean Change from Baseline Hemoglobin during 28 Days Following First Treatment – All Subjects, Central Laboratory Results (Study A011-08)



Note: Subjects were administered their assigned treatment on Day 1.

Mean changes from baseline hemoglobin over the extended period from first dose to 28 days after the last dose are presented in Figure 2. Increases in Hemoglobin concentrations were achieved in all sotatercept treatment groups. Mean changes in Hemoglobin during the 28-day period showed greater increases in Hemoglobin concentrations among subjects in the sotatercept 0.3 mg/kg and 0.5 mg/kg groups than those of subjects in the sotatercept 0.1 mg/kg and placebo treatment groups, and provide additional evidence of a dose-response relationship. Mean increases following repeated doses of sotatercept declined over the 28-day interval between treatments.

Figure 2: Mean Change from Baseline Hemoglobin during Period from First Dose to 28 Days Following the Last Treatment – All Subjects, Central Laboratory Results (Study A011-08)



Note: Subjects were administered their assigned study treatment on Days 1, 29, 57, and 85.

Assessments of safety in this study were consistent with the known safety profile 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.

Observed increases in Hemoglobin, hematocrit, and RBCs and decreases in FSH were consistent with results from prior clinical studies and are consistent with the known pharmacologic profile of sotatercept. There were no notable differences between treatment groups in the emergence of Grade 3 or 4 toxicities. Five of seven subjects in the sotatercept 0.5 mg/kg group demonstrated shifts in creatinine from normal (at baseline) to Grade 1 (worst post baseline value). All observations of creatinine concentrations in the other treatment groups remained within the normal range. Mean changes in vital signs were generally small with no trends over time over treatment groups. There were no clinically significant abnormal findings on ECG, and no notable differences among treatment groups in QTc.

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 SC 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.

ACE-011-MDS-001: A phase 2 dose-ranging study of sotatercept for the treatment of patients with anemia and low- or intermediate-1 risk myelodysplastic syndromes or non-proliferative chronic myelomonocytic leukemia (Preliminary results)

This is an ongoing open-label, randomized, phase 2, parallel dose-ranging, multicenter study of sotatercept for the treatment of patients with anemia (hemoglobin ≤ 9.0 g/dL requiring transfusion of ≥ 2 units of RBCs in the 84 days prior to enrollment) and low- or intermediate-1 risk myelodysplastic syndromes or non-proliferative chronic myelomonocytic leukemia (CMML). Patients received subcutaneous sotatercept at dose levels of 0.1, 0.3, 0.5, or 1.0 mg/kg once every 3 weeks.

A preliminary safety analysis from this ongoing Celgene-sponsored MDS study (Komrokji 2014) indicates that administration of sotatercept is generally well-tolerated at the dose levels tested (N=54, as of May 22, 2014).

ACE-011-REN-001: Safety and hemoglobin effect of the first 28-day dose cycle of sotatercept 0.7 mg/kg compared with lower doses and placebo for correction of anemia in hemodialysis subjects (Interim analysis)

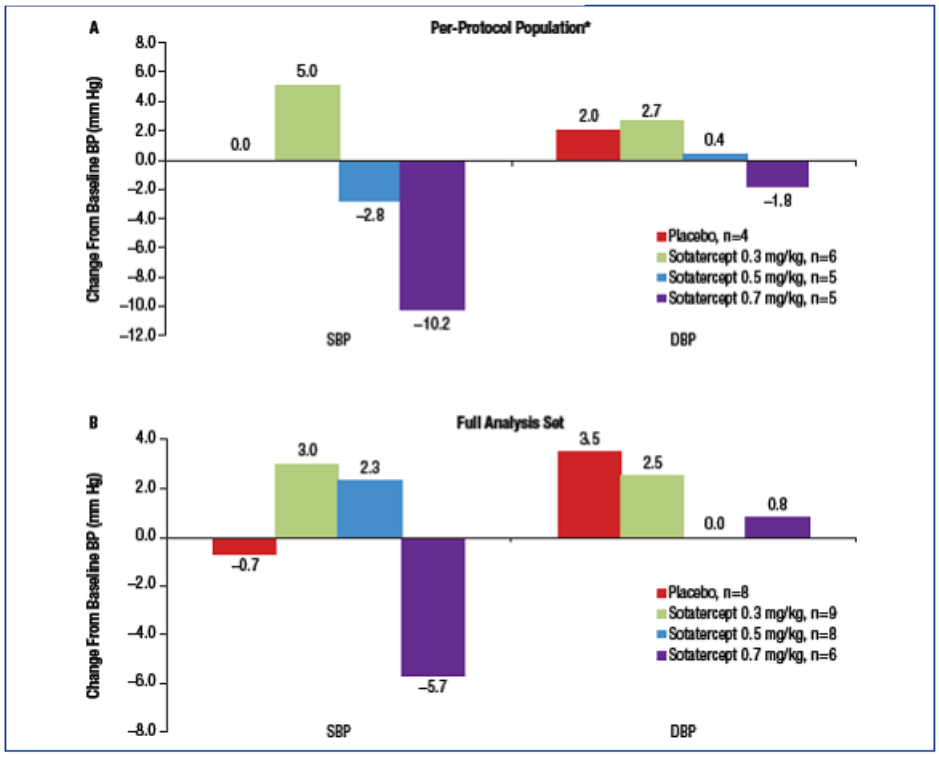
This is ongoing randomized, single-blind, placebo-controlled, sequential dose-escalation study in subjects with end-stage kidney disease on hemodialysis.

At the end of the first dose cycle, home blood pressure (BP) measurements revealed small changes from baseline in systolic BP (SBP) and diastolic BP (DPB) that were generally similar in magnitude in subjects receiving placebo or sotatercept 0.3, 0.5, and 0.7 mg/kg in the safety population (N=23) (Figure 3).

During the 225-day, long-term treatment phase, home BP measurements showed no consistent or dose-dependent change from baseline among subjects in any of the treatment groups (N=17).

In order to ensure the safety of the study subjects, this protocol includes the monitoring of blood pressure and hemoglobin, and treatment discontinuation rules in order to mitigate the risk of blood pressure increases.

Figure 3. Change from baseline in home blood pressure (BP) at the end of dose cycle 1.



*The per-protocol population excludes data from those subjects with protocol violations and are censored for those subjects who had treatment failure requiring rescue in the first dose cycle.

Potential Risks for Human Use

Nonclinical studies to determine the safety of sotatercept (ACE-011) have been conducted in cynomolgus monkeys and Sprague-Dawley rats. Many of the observed effects in these studies were as a result of the expected biologic activity of TGF-β superfamily inhibition and can be summarized as a dose-dependent decrease in sperm count and motility secondary to FSH suppression as well as reversible increases in RBC parameters due to the effects on erythroid differentiation factor (activin).

The most significant toxicity findings are listed below:

Hematological findings (increase in RBC parameters – RBCs, hemoglobin, hematocrit) were observed across all studies. Associated with the increase in RBC parameters were increases in reticulocytes and decreases in mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC). The increase in RBC parameters is an anticipated effect of sotatercept (ACE-011) treatment and is being targeted as a therapeutic intervention for conditions associated with anemia.

In the 6- and 9-month monkey studies, glomerulonephritis and/or tubulointerstitial nephritis were observed in monkeys administered ≥ 10 mg/kg administered subcutaneously (SC) every 2 or 4 weeks. At 2.6 mg/kg administered SC every 4 weeks for 9 months, kidney findings were limited to a single incidence of tubulointerstitial nephritis. The NOAEL in the 9-month study was considered to be 1 mg/kg every 4 weeks. Serum exposure in monkeys at the 1 mg/kg dose is estimated to be ~0.9-fold the projected serum exposure in humans at the maximum dose of 2 mg/kg every 3 weeks proposed in humans. In the single- and multiple-dose studies in healthy postmenopausal women, there have been no changes in serum chemistry or urinalysis profiles suggestive of kidney injury. Subjects administered sotatercept should be monitored closely.

In the 9-month monkey study, treatment-related findings in the choroid plexus included: peri-vascular accumulations of foamy macrophages and intimal thickening of small arteries and arterioles primarily at 10 mg/kg administered every 2 weeks as well as an increased incidence of small, focal aggregates of mononuclear inflammatory cells at all dosages. Findings at 1 mg/kg were limited to mononuclear cell infiltrates and were not adverse.

Anti-drug antibodies (ADA) have been observed in toxicology studies. Adrenal gland congestion or necrosis was observed in rats but not in monkeys. The finding was more pronounced in female rats and appeared following either one month of IV dosing or 3 months of SC dosing. Although the current data suggest adrenal toxicity may be specific to rats, the relevance of the adrenal findings to humans is uncertain.

Elevations in liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and/or alkaline phosphatase) and triglycerides, were observed sporadically in rats and monkeys receiving sotatercept (ACE-011). There were no histological correlates in the liver, and often a dose-response relationship was not observed. The relevance of these findings to sotatercept (ACE-011) treatment is uncertain; however, liver enzymes will continue to be monitored in this study.

Pregnancy and Lactation

Because of the potential for effects on hormones in the pituitary, including FSH, in addition to possible direct effects on fetus, there may be potential indirect effects on the fetus. Delays in fetal development (decreased fetal weights and delays in ossification) were observed at doses ≥ 15 mg/kg (1.6-fold of the projected exposure at the maximum proposed human dose of 2.0 mg/kg every 3 weeks). In addition, at 50 mg/kg (3.8-fold the exposure at the maximum proposed human dose), there was an increase in late fetal death coupled with an overall increase in post implantation loss and a reduction in live litter size, as well as an increase in the incidence of developmental variations of supernumerary ribs with corresponding increases and decreases in thoracic and lumbar vertebrae, respectively. No fetal malformations were observed in this study at dosages up to 50 mg/kg. The NOAEL for embryofetal development effects was 5 mg/kg (~1.0-fold the projected exposure at the maximum proposed human dose of 2.0 mg/kg every 3 weeks) based on reduced fetal weights and associated delays in ossification.

- In an embryo-fetal development study in rabbits, post-implantation loss was increased and average litter size and live fetuses were reduced at 15 and 50 mg/kg. In addition, fetal body weights were reduced in all sotatercept dosage groups. Abortions occurred in one rabbit in the 5 mg/kg dosage group and two rabbits in the 50 mg/kg dosage group. Based on these findings, an NOAEL was not identified in this study and was therefore less than 5 mg/kg (1.0-fold the exposure at the maximum proposed human dose of 2.0 mg/kg every 3 weeks).
- Precautions should still be taken to protect females of childbearing potential. Nonclinical studies on breast milk have not been done.
- If sotatercept (ACE-011) is taken during pregnancy, a teratogenic effect in humans cannot be ruled out. Therefore, all sotatercept (ACE-011) protocols describe pregnancy prevention requiring females of child-bearing potential to use highly effective methods of birth control. In addition, since it is unknown if sotatercept (ACE-011) is found in breast milk, breast feeding is prohibited in all protocols.

Fertility

- In male rats, sperm granulomas and testicular degeneration were observed histologically. In addition, sperm analysis revealed a reduction in sperm counts and motility as well as sperm fragmentation in isolated animals (2/10 males) at doses of 30 mg/kg IV. Sperm fragmentation was also noted in 2/5 males administered 10 mg/kg IV at the end of the recovery period. Overall, there was some evidence of recovery (motility similar to controls) at the end of the 4-week recovery period. There was no evidence of a treatment-related impact on reproductive organs (testes, ovary, uterus) of monkeys in the toxicity studies; however, the monkeys on these

studies, were too immature to fully assess the potential impact on reproductive organs. The NOAEL for reproductive effects (testicular or ovarian) was 1 mg/kg IV. Serum exposure ($AUC_{0\text{-}28d}$) in rats at the NOAEL was estimated to be ~ 10,940 µg·hr/mL, ~ 0.5-fold the projected serum exposure in humans at the maximum proposed dose of 2.0 mg/kg every 3 weeks (estimated $AUC_{0\text{-}28d}$ ~ 20,928 µg·hr/mL).

- In summary, in view of the potential risks sotatercept (ACE-011) treatment has on fertility, sotatercept (ACE-011) is targeted toward person groups for whom the potential benefits outweigh the perceived risks.

Because of the potential risks sotatercept treatment has on fertility, sotatercept was first studied in healthy postmenopausal in two completed phase-1 clinical trials. In addition, due to the potential for effects on hormones in the pituitary, levels of growth hormone, ACTH, and thyroid stimulating hormone (TSH) were monitored closely in the phase 1 studies.

Completed studies in humans carried out in postmenopausal females showed a dose-dependent decrease in circulating levels of FSH, with mean levels in the multi-dose study in the two higher dose groups remaining below baseline at study end. No effect of sotatercept on growth hormone, ACTH, TSH or kidney was observed.

To date, anti-sotatercept binding antibodies were detected in approximately 6.3% (9 of 143) of evaluable subjects receiving sotatercept, with one-third (3 of 9) of them having pre-existing positive titers before the start of sotatercept treatment. Preliminary review of data available, including AEs, SAEs, and laboratory results, did not show immune mediated allergic effect or other safety consequence.

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

1.2.1.7. Potential Risks of the Combination of Ruxolitinib and Sotatercept

RUXOLITINIB AND SOTATERCEPT APPEAR NOT TO HAVE OVERLAPPING SIDE EFFECTS IN CLINICAL STUDIES CONDUCTED SO FAR. THEREFORE, A COMBINATION OF RUXOLITINIB AND SOTATERCEPT IS NOT EXPECTED TO RESULT IN ANY NEW CLINICALLY RELEVANT ISSUES. OF NOTE, AS PER THE DESIGN OF THE STUDY, ONLY PATIENTS THAT ARE ON RUXOLITINIB FOR AT LEAST FOR 6 MONTHS, AND ON STABLE DOSE FOR THE LAST 2 MONTHS, WOULD POTENTIALLY BE ELIGIBLE FOR PARTICIPATION IN THIS STUDY, WHERE SOTATERCEPT WOULD BE ADDED TO THEIR THERAPEUTIC REGIMEN.

2.0 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objective

Determine safety and efficacy of sotatercept as therapy for persons with MPN-associated myelofibrosis and anemia

2.2 Endpoints

2.2.1 Primary

Safety

Anemia response

2.2.2 Secondary

Time to anemia response

Duration of anemia response

3.0 INVESTIGATIONAL PLAN

3.1. Design

Phase-2, open-label study to determine safety and efficacy of sotatercept in persons with MPN-associated myelofibrosis and anemia

Screening Phase:

Potential subjects will enter screening and be evaluated for the inclusion and exclusion criteria for the Treatment Period of this study. The screening period will not last more than 28 days (except for bone marrow biopsy which can be done within 6 months). The assessments and procedures that will be performed during screening are outlined in Appendix: Schedule of Events. Screening assessments will include an informed consent, medical history, transfusion history for previous 84 days, review of prior MF-directed medications, complete physical exam, vital signs, ECOG performance status assessment, complete blood count (CBC) with differential, serum chemistries, erythropoietin level, 12-lead ECG, bone marrow biopsy and aspirate to confirm diagnosis, spleen and liver measurements, and pregnancy test in females of childbearing potential (FCBP) will have to be obtained.[1]

Treatment Period:

Subjects meeting study-entry-criteria will be enrolled and receive sotatercept. Twenty-one days is considered one cycle of therapy. Subjects may be taken off study after 8 cycles if there is no anemia-response. Those patients experiencing clinical benefit may remain on study treatment as long as they derive benefit in the judgment of treating physician, in the absence of disease progression or toxicity warranting discontinuation of therapy.

Initially patients not on any therapy for MF, will be assigned alternately into two treatment cohorts of 5 subjects each: (1) 0.75 mg/kg dose SC every 3 weeks; and (2) 1.0 mg/kg dose SC every 3 weeks. Response will be analyzed after each cycle, starting with cycle 5 of therapy. The cohort with at least one responder (out of 5 treated patients) will be expanded with an additional 15 subjects. If none of the 5 subjects in a cohort responds by cycle 8, enrollment into that cohort may be closed. If a cohort is closed for lack of efficacy, ongoing subjects in the cohort may have their dose changed to that of the other cohort dose, if there was a response in the other cohort. If there is no responder in either cohort additional dose cohorts of 5 subjects each may be considered at lower or higher doses of sotatercept (this will require protocol amendment); the same rules for cohort expansion will apply. After the 5th subject in each cohort has been evaluated for response, then a cohort-

[1] A female of childbearing potential is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

summary will be completed and submitted to the IND Office's Clinical Research monitor.

Separate cohort for patients that are already on therapy with ruxolitinib (for at least for 6 months, and on stable dose for last 2 months) will be enrolled. These patients will be given 0.75 mg/kg dose of sotatercept SC every 3 weeks and the same statistical analysis for efficacy will apply as described for cohorts above. Specifically, response will be analyzed after each cycle, starting with cycle 5 of therapy. If there is at least one responder out of 5 treated patients, this cohort will be expanded with an additional 15 subjects. If none of the first 5 subjects in this cohort responds by cycle 8, enrollment into the cohort may be closed.

Study assessments and serial measurements of safety and efficacy will be performed as outlined in Appendix: Schedule of Assessments. All scheduled visits will have a ±4-day window unless otherwise stated. Vital signs will be measured at the start of each cycle but monitoring of blood pressure may be done at home on non-dosing days. Blood pressure will be measured at a minimum every week for first 3 weeks during cycles 1-5. Patients will be instructed to call treating physician and his staff if systolic blood pressure [SBP] ≥ 140 or diastolic blood pressure [DBP] ≥ 90. In the absence of clinically significant changes in blood pressure after 5 cycles of treatment, monitoring frequency may decrease to once per cycle at the investigator's discretion. Hematologic parameters will be measured at a minimum every week for first 3 weeks during courses 1-5, then every 2-3 weeks thereafter. Serum chemistry parameters, including erythropoietin level, will be measured at minimum every 3-6 weeks.

Blood samples will be collected for assessment of antidrug antibody (ADA) and pharmacokinetics (PK) in all subjects as described in Appendix: Instruction for collection of samples for sotatercept ADA and PK. The sample will be collected prior to administration of sotatercept on the first day of cycles 1-5, then every other cycle for cycles 7-12 (i.e., cycles 7, 9 and 11), then every 6 months for cycles 12+; samples will be stored in Dr. Verstovsek's laboratory at MD Anderson Cancer Center. Upon completion of clinical study, ADA samples will be shipped to QPS, LLC in Newark, DE; PK samples will be shipped to supporter of the study, Celgene Corporation.

Occasional missed PK and ADA samples not completed due to patient schedule will not be considered as deviations.

An unscheduled visit can occur at any time during the study. The date for the visit and any data resulting there from will be recorded on the appropriate source. Source documents for these unscheduled visits must be maintained. At treatment discontinuation, subjects will undergo off study evaluations as outlined in Appendix: Schedule of Assessments. In addition, a safety assessment will be done

approximately 30 days post the last dose of study drug (the person will be contacted by the PI or his staff to assess for AE's).

Women of childbearing potential and men must agree to using medically approved contraceptive measure for at least 112 days following the last dose of sotatercept (ACE-011), Males must agree to use a latex condom or non-latex condom NOT made of natural (animal) membrane during any sexual contact with females of childbearing potential or a pregnant female while participating in the study and for at least 112 days following the last dose of sotatercept (ACE-011), even if he has a vasectomy. The two methods of reliable contraception must include one highly effective method (i.e. intrauterine device [IUD], hormonal [birth control pills, injections, or implants], tubal ligation, or partner's vasectomy) and one additional effective (barrier) method (i.e. latex condom, diaphragm, cervical cap). Females of childbearing potential (FCBP) must be referred to a qualified provider of contraceptive methods if needed.

Males must tell the doctor right away if his partner becomes pregnant or suspects pregnancy.

3.1.1 Investigational Drug

Celgene Corporation will supply sotatercept to study-subjects at no charge. Sotatercept clinical drug product will be provided as a lyophilized powder (lyophilized ACE-011 drug product process 3 Formula). 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 stopper, 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. The reconstituted drug product consists of a 50 mg/mL solution of sotatercept. The reconstituted sotatercept should be used immediately after reconstitution, and if not used immediately, the reconstituted sotatercept, in its original package, 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 immediately (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. Accurate recording of all study drug administration (including dispensing and dosing) will be made in the appropriate source documents.

The Investigator or designee is responsible for taking an inventory of each shipment of study drug received, and comparing it with the accompanying study drug accountability form. The study staff will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and return a copy to Celgene or its representative. At the study site, all investigational study drugs will be stored in a locked, safe area to prevent unauthorized access. Celgene will instruct the Investigator on the return or destruction of unused study drug. If any

study drug is lost or damaged, its disposition should be documented in the source documents. Study drug will be destroyed per MDACC destruction policies.

Treatment Administration and Schedule
Sotatercept should be given every 3 weeks as a SC injection to subjects at the clinical site and will be documented in the source record. SC injections will be given in the upper arm, abdomen, or thigh. Each subject will return to the site on each scheduled clinic visit. All adverse events/toxicities are to be graded according to the Common Terminology Criteria for Adverse Events (CTCAE Version 4.0). In a case of clinically relevant grade 4 drug-related toxicity, therapy will be stopped and person's participation in a study discontinued. In other instances, any sotatercept-related adverse event that may have occurred has to resolve to ≤ grade 2 for the next scheduled injection to be given. Delay in giving sotatercept because of drug-related adverse effects is ≤ 56 days; after that patient will have to be taken off the study. Once the therapy restarts, 21-day cycles will resume.

Sotatercept will be held if there is an increase in hemoglobin level to ≥11.5 g/dL and may restart if/when hemoglobin level decreases to ≤11.0 g/dL. Once therapy restarts 21-day cycles resume.

3.3 Inclusion and Exclusion Criteria

Subjects are to be assessed for suitability for entry into the study based on the following inclusion and exclusion criteria.

3.3.1 Key Inclusion criteria

Subjects must meet the following inclusion criteria:

1. MPN-associated myelofibrosis;
2. Anemic patient OR RBC-transfusion-dependent patient
3. ≥18 years of age
4. ALT (SGPT) and AST (SGOT) ≤ 2.5x upper limit of normal (ULN), or ≤ 4x ULN (if upon judgment of the treating physician, it is believed to be due to extramedullary hematopoiesis [EMH] related to MF)
5. Direct bilirubin ≤ 1.5 x ULN; or ≤ 2x ULN (if upon judgment of the treating physician, it is believed to be due to extramedullary hematopoiesis related to MF)
6. Creatinine clearance > 50 mL/min.
7. Treatment-related toxicities from prior therapies must have resolved to Grade ≤ 1
8. Women of childbearing potential and men must agree to using medically approved (i.e., mechanical or pharmacological) contraceptive measure for at least 112 days following the last dose of sotatercept (ACE-011), Males must agree to use a latex condom or non-latex condom NOT made of natural (animal) membrane during any sexual contact with females of

childbearing potential or a pregnant female while participating in the study and for at least 112 days following the last dose of sotatercept (ACE-011), even if he has a vasectomy.

9. For cohort of patients that are already on ruxolitinib therapy: on therapy with ruxolitinib for at least for 6 months, and on stable dose for last 2 months, before starting therapy with sotatercept

3.3.2. Key Exclusion Criteria

1. Serious medical condition or psychiatric illness that would prevent, (as judged by the treating physician) the subject from signing the informed consent form or any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study;
2. Pregnant or lactating female;
3. Known positive for human immunodeficiency virus-1 (HIV-1), or active infection with hepatitis-B or -C;
4. Use of any MPN-associated myelofibrosis-directed therapy within 2 weeks prior to study Day 1 (other than Ruxolitinib at a stable dose for patients in the combination cohort as stated in inclusion criteria).
5. Symptomatic congestive heart failure (New York Heart Association Classification >Class II), unstable angina, or unstable cardiac arrhythmia
6. Prior sotatercept
7. Major surgery within 4 weeks prior to Day 1
8. Severe allergic or anaphylactic reactions or hypersensitivity to recombinant proteins or excipients in the investigational product
9. Uncontrolled hypertension (systolic blood pressure [SBP] ≥ 140 or diastolic blood pressure [DBP] ≥ 90).

3.7 Concomitant therapy

3.7.1 Recommended concomitant therapy

All supportive measures consistent with optimal subject care will be given throughout the study. Packed red blood cell transfusions are allowed when necessary. Growth factor use (including erythropoietin) is not allowed with the exception of the use of filgrastim (G-CSF) or pegfilgrastim, which is permitted at the investigators discretion when used to treat febrile neutropenia or grade 3-4 prolonged neutropenia.

3.7.3. Prohibited concomitant therapy

Concomitant use of growth factors (including erythropoietin and excluding G-CSF and pegfilgrastim), cytotoxic chemotherapeutic agents (e.g. hydroxyurea), or

other experimental drug or therapy for myelofibrosis while the subject is on study is prohibited. Chronic use (>2 weeks) of greater than physiologic doses of a corticosteroid agent (dose equivalent to >10 mg/day of prednisone) is not permitted during the study. Anagrelide is allowed to be used during the study to control elevated platelet count.

3.8 Discontinuation of Study Treatment

Subjects should have blood pressure (systolic and diastolic) measured after approximately 10 minutes seated, before each dose of study drug. If SBP ≥140 mmHg or DBP ≥90 mmHg, blood pressure should be re-checked. If unable to control it, dosing should be postponed (Table 6).

Treatment with study drug is to be discontinued when any of the following occurs:

- Lack of therapeutic effect
- Adverse event(s) which in the judgment of the PI may cause severe or permanent harm or which rule out continuation of study drug.
- Hypertension (Table 6)
- Withdrawal of consent
- Lost to follow-up
- Death
- Suspected pregnancy

Table 6. Management of hypertension

Event		Action
Hypertension		
	-If Systolic blood pressure (SBP) ≥140 OR Diastolic BP (DBP) ≥ 90 mm Hg AND SBP increase ≥ 20 mmHg over baseline OR DBP increase ≥ 20 mmHg over baseline	Dose delay (no more than 2 dose delays allowed) Hold until resolved SBP and DBP should be < 140 and < 90 mmHg Initiation of anti-hypertension is allowed after one week if the BP is Systolic blood pressure (SBP) ≥140 OR Diastolic BP (DBP) ≥ 90 mmHg AND SBP increase ≥ 20 mmHg over baseline OR DBP increase ≥20 mmHg over baseline
	-If 2 Dose delays due to BP increase, ie SBP ≥140 OR DBP ≥ 90 mmHg AND SBP increase ≥ 20 mmHg over baseline OR DBP increase ≥ 20 mmHg over baseline	Dose delay until SBP and DBP should be < 140 and < 90 mmHg
	-If SBP > 160 mmHg OR DBP > 100 mmHg, sustained (ie confirmed by two measurements within 7 days)	Discontinue treatment

4.0 Serious Adverse Event reporting

4.1 Serious Adverse Event Reporting (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.
  Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical 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 (21 CFR 312.32).
- **Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.**
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- **Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.**
- **Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug,**

unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

- **Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.**

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Leukemia Guidelines for AE reporting will be followed.

Adverse Events and Protocol specific data will be entered into PDMS/CORe. PDMS will be used as the electronic case report form.

4.1.1 Expedited reporting by investigator to Celgene

Investigator Communication with Supporting Companies:

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form, MD Anderson 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-MPN-associated myelofibrosis-PI-0005) 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 person records.

The Celgene Study Identifying number: ACE-011-MPN-associated myelofibrosis-PI-0005 ***should be written on the top of the form.***

Celgene Drug Safety Contact Information:

Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporate Park
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922
Fax: (908) 673-9115
E-mail: drugsafety@celgene.com

4.1.2 Pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject or the female partner of a male subject occurring while the subject is on study drug, or within 30 days of the subject's last dose of study drug, are considered immediately reportable events. Study drug is to be discontinued immediately and the subject instructed to return any unused portion of the study drug to the investigator(s). The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Celgene Safety immediately by phone and facsimile using the SAE Report Form.

The female should be referred to an obstetrician-gynecologist experienced in reproductive toxicity for further evaluation and counseling.

The Investigator(s) will follow the female subject until completion of the pregnancy, and must notify Celgene Safety of the outcome of the pregnancy as a follow-up to the initial SAE report.

If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the Investigator(s) should follow the procedures for reporting SAEs (i.e., report the event to Celgene Safety by telephone and facsimile within 24 hours of the Investigator's knowledge of the event).

In the case of a live "normal" birth, Celgene Safety should be advised by telephone and facsimile within 24 hours of the Investigator's knowledge of the event.

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator(s) suspects is related to the in utero exposure to the study drug should also be reported to Celgene Safety by telephone and facsimile within 24 hours of the Investigators' knowledge of the event.

If the female is found not to be pregnant, any determination regarding the subject's continued participation in the study will be determined by the Investigator.

5.0 STATISTICS

5.1 Overview

This is a phase-2 open-label, non-comparative study to determine safety and efficacy of sotatercept in persons with MPN-associated myelofibrosis and anemia. Efficacy will be assessed as anemia-response. Two dose cohorts (0.75 and 1.0 mg/kg) will be studied in patients not on any MF-directed therapy. Additional cohort of MF patients, currently on therapy with ruxolitinib (for at least for 6 months, and on stable dose for last 2 months) will be studied. Up to 60 persons will be enrolled (20 per cohort), at a rate of 1 subjects per month. Additional patients may be enrolled in case of early discontinuation (<8 cycles of therapy given) due to unrelated reasons (i.e. replacement patients). The study is not designed for statistical comparisons between the dose cohorts.

5.2 Datasets to be analyzed

All subjects receiving ≥1 dose of sotatercept are evaluable for safety.

5.3 Statistical Methodology

5.3.1 Primary Endpoint

The primary endpoints are safety and anemia-response. Primary analysis of a response for each dose cohort will be performed once all 20 patients have been accrued to that dose cohort and treated for at least 5 cycles (unless therapy is stopped in a given patient earlier due to toxicity).

5.3.2 Study-Design

This is an open-label, 2 dose level trial to evaluate the efficacy and safety of sotatercept in patients with MPN-associated myelofibrosis (PMF or post ET/PV MF) and significant anemia. Clinical efficacy will be assessed as anemia-response with a target rate of greater than or equal to 30% at either dose level. Initially patients not on any MF-directed therapy will be assigned to two different treatment groups alternatively: 5 patients will be treated with 0.75 mg/kg dose SC every 3 weeks, and 5 patients will be treated with 1.0 mg/kg dose SC every 3 weeks. Assignment of the following 15 patients per dose level (if both dose levels require expansion) will be done alternatively. Each 3-week period will be defined as one cycle. Additional cohort of MF patients, currently on therapy with ruxolitinib (for at least for 6 months, and on stable dose for last 2 months) will be studied: these patients will be treated with 0.75 mg/kg dose SC every 3 weeks of sotatercept. Same design will be applied to this cohort of patients: if there is at least one responder out of 5 treated patients, this cohort will be expanded with an additional 15 subjects.

5.3.3 Interim Futility and Safety Monitoring

The method of Thall, Simon, Estey (1995, 1996) as extended by Thall and Sung (1998) will be used for interim futility and safety monitoring.

5.3.3.1 Futility Monitoring:
We assume a non-informative beta (0.6, 1.4) prior for the anemia-response rate and we will apply the following futility stopping rule for each dose cohort separately. The futility stopping rule will be applied every 5 patients, starting with the 5th patient per dose cohort. Specifically, we will stop enrollment to a dose cohort if at any time during the study,

Pr{anemia-response rate > 30% | data from patients evaluated} < 0.05

In other words, if at any time during the study, we determine that there is less than 5% chance that the anemia-response rate for a given dose cohort is greater than 30%, we will stop enrollment into that dose cohort. Stopping boundaries corresponding to this probability criterion are as follows:
[# of patients with anemia-response/ # of evaluable patients] </= 0/5, 1/15, 2/20.

The operating characteristics corresponding to this stopping rule is as follows:

True anemia-response rate	Prob(early stopping)
0.05	0.90
0.1	0.70
0.2	0.37
0.3	0.18
0.4	0.08
0.5	0.03

At the end of the trial, if for a given dose cohort, Pr (anemia-response rate > 30% | data) >0.95, then that dose cohort will be considered a success. If a dose cohort is closed at the interim for a lack of efficacy, ongoing patients from that treatment group may have their dose regimen changed to the other treatment group (if there was a response in the other cohort).

With a total of 20 patients in a dose cohort, if we observe 6 confirmed responders, the 95% credible interval will be (0.132, 0.502).

5.3.4. Safety evaluation

Data from all subjects who receive ≥1 dose of study drug are included in the safety analysis. Severity of the toxicities will be graded according to the NCI CTCAE v4.0 whenever possible. Toxicity is defined as an adverse event and classified as possibly, probably, or definitely related to study drug. Such adverse events will be recorded by the PI in a database. The maximum grade for each type of toxicity will be recorded for each subject, including start/stop dates, and frequency tables for each group will be reviewed to determine toxicity patterns.

Toxicity Stopping Rule:

For safety monitoring, we define toxicity as any Grade 4 non-hematologic adverse event that is considered to be at least possibly related to treatment. We assume a non-informative beta prior (0.4, 1.6), which has a mean of 20%; and we will apply the following toxicity stopping rule-in each dose cohort separately. For practical reasons, we will monitor the toxicity in cohort of 5. Specifically, we will stop a dose cohort if

$$\Pr\{\text{toxicity rate} > 20\% \mid \text{data from patients evaluated}\} > 0.85$$

In other words, if we determine that there is more than 85% chance that the toxicity rate is greater than 20% in a given dose cohort, that dose cohort, will be terminated. In addition, the higher dose cohort will be stopped once the lower dose cohort is terminated according to the above stopping rule. Stopping boundaries for each dose cohort corresponding to this probability criterion are as follows:
[# of patients with Grade 4 non-hematologic AEs/ # of evaluable patients] >/=3/5, 4/10, 5/15, 7/20.

The operating characteristics corresponding to this toxicity stopping rule is as follows:

True overall toxicity rate	Prob(early stopping)
0.05	0.002
0.1	0.024
0.2	0.206
0.3	0.530
0.4	0.808

5.3.5. Analysis Plan

The primary analysis will be based on the intent-to-treat (ITT) principle. Patients who drop off the study early before being able to be evaluated for the 84-day interval will not be counted as having anemia response

Anemia response is a composite endpoint defined as an increase in hemoglobin (hemoglobin response; defined below) in a subject with anemia (anemic patient as defined below) OR becoming RBC-transfusion-independent in a subject who is RBC-transfusion-dependent (defined below):

1. **Hemoglobin-response** is defined as an increase in hemoglobin level of ⩾1.5 g/L (compared to baseline) on every determination consecutively for a ⩾84 d interval, without RBC-transfusions.
2. **RBC-transfusion-independence** is defined as no RBC-transfusion in any "rolling" 84 day interval during the treatment period, in patients who were RBC-transfusion dependent at enrollment.

Definitions:

Anemic patient is defined for the purpose of this protocol as 1. a patient with a hemoglobin level <10 g/L on every determination over 84 days before study-entry, without RBC-transfusions, and 2. a patient with a hemoglobin level <10 g/L that is receiving RBC-transfusions periodically but not meeting criteria for transfusion-dependent patient as defined below. The baseline hemoglobin value for these subjects is the lowest hemoglobin level during the antecedent 84 days.

RBC-transfusion-dependent patient is defined as a patient with an RBC-transfusion-frequency of ≥2 units PRBC/28 days averaged over 84 days immediately pre-study-entry. There must not be any consecutive 42 days without an RBC-transfusion during this interval

Secondary Endpoints

Duration of response: duration of response is defined as the date at which the subject's objective status is first noted to be a response, to the date progression is documented (if one has occurred) or to the date of last follow-up (for those subjects who have not progressed).

Time to response: The time to response is defined as interval from 1st dose of study drug to 1st day of a response. Non-responders are censored on the last evaluation date.

The distribution for each of these event-time variables (duration of response and time to response) will be estimated by Kaplan-Meier curves.

6.0 REGULATORY CONSIDERATIONS

6.1 Institutional Review Board/Ethics Committee approval

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the IRB/EC and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards.

The Investigator will be responsible for preparing documents for submission to the relevant IRB/EC and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study.

The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number.

Any amendments to the protocol after receipt of IRB/EC approval must be submitted by the Investigator to the IRB/EC for approval. The Investigator is also responsible for notifying the IRB/EC of any serious deviations from the protocol, or anything else that may involve added risk to subjects.

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

6.2 Informed consent

The PI must obtain informed consent of a subject or his/her designee prior to any study related procedures as per GCPs as set forth in the CFR and ICH guidelines.

Documentation that informed consent occurred prior to the subject's entry into the study and the informed consent process should be recorded in the subject's source documents. The original consent form, signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the medical records.

6.3 Subject confidentiality

Celgene affirms the subject's right to protection against invasion of privacy. In compliance with United States federal regulations, Celgene requires the Investigator to permit Celgene's representatives and, when necessary, representatives of the FDA or other 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 statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

6.4 Study records requirements

The PI must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug, that is copies of eCRF and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study; documents regarding subject treatment and study drug accountability; original signed informed consents, etc.]) be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). The PI agrees to adhere to the document/records retention procedures by signing the protocol.

6.5 Premature discontinuation of study

6.5.1 Single center

The responsible local clinical Investigator, MDACC as well as Celgene have the right to discontinue this study at any time for reasonable medical or administrative reasons in any single center. Possible reasons for termination of the study could be but are not limited to:

Unsatisfactory enrollment with respect to quantity or quality.

Inaccurate or incomplete data collection.

Falsification of records.

Failure to adhere to the study protocol.

6.5.2 Study as a whole

Celgene and MDACC reserve the right to terminate this clinical study at any time for reasonable medical or administrative reasons.

Any possible premature discontinuation would be documented adequately with reasons being stated, and information would have to be issued according to local requirements (e.g., IRB/EC, regulatory authorities, etc.).

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