Official Protocol Title:	A Phase 2, Open-Label, Pharmacodynamic Study to Evaluate the Effect of Sotatercept (ACE-011) on Red Blood Cell Mass and Plasma Volume in Subjects With Solid Tumors
NCT number:	NCT01190644
Document Date:	05-Mar-2012

– SUMMARY OF CHANGES –

AMENDMENT NO. 3

A PHASE 2, OPEN-LABEL, PHARMACODYNAMIC STUDY TO EVALUATE THE EFFECT OF SOTATERCEPT (ACE-011) ON RED BLOOD CELL MASS AND PLASMA VOLUME IN SUBJECTS WITH SOLID TUMORS

INVESTIGATIONAL PRODUCT (IP):	**SOTATERCEPT (ACE-011)**
PROTOCOL NUMBER:	**ACE-011-ST-001**
ORIGINAL DATE:	**01 FEBRUARY 2010**
AMENDMENT No. 1 DATE	**18 APRIL 2011**
AMENDMENT No. 2 DATE	**15 NOVEMBER 2011**
AMENDMENT No. 3 DATE	**05 MARCH 2012**
EudraCT NUMBER:	**Not Applicable**
CELGENE IND NUMBER:	**103362**

Contact Information:

PPD

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1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

1. An ACE-011-ST-001 Investigator Update meeting was held on 12DEC11. Attendees included all 3 current Investigators (Drs. D. Henry, S. Noga, C. Miller) as well as Dr. Jerry Spivak from Johns Hopkins University, along with representatives from both Celgene and collaborating partner Acceleron.

   The group discussed whether it is necessary to continue requiring a chemotherapy 'holiday' during the first dosing cycle with sotatercept while the pre-/post-dose Red Blood Cell / Plasma Volume (RBC/PV) testing is performed. Under the current protocol (Amendment #2: Final 15NOV11), at the time of enrollment into the study (Day 1) through Day 28 of the Treatment Period, subjects must not be receiving any other concurrent cytotoxic chemotherapy for their cancer. Once both RBC/PV tests have been completed, subjects can initiate chemotherapy as directed by the Investigator.

   The original design strategy was to have the RBC/PV test conducted during this break in chemotherapy dosing, minimizing the possible impact of how responsive the bone marrow might be due to chemotherapy; however, many patients pre-screened for the study have not developed anemia during this post-chemotherapy window in the range required for entry into the study (i.e., hemoglobin value between ≥ 8.0 to < 11.0 g/dL). Also, it was initially thought that the study would produce more uniform results across subjects by not allowing concomitant chemotherapy during the RBC/PV testing. Dr. Spivak has advised that the administration of concomitant chemotherapy will not impact analysis on RBC/PV activity and changes in RBC mass or plasma volume will either be evident or not.

   The group agreed that the study should be opened up to all metastatic solid tumor patients (whether or not receiving chemotherapy).

2. Other administrative changes were also incorporated and are outlined in Section 2 Itemized Changes.

2. ITEMIZED CHANGES

Text Modification Key:

~~Deleted Text~~

Added Text

Unchanged Text

2.1. Section: PROTOCOL SUMMARY (Pages 5-6)

Revised Text:

Objectives

– – – – – – – – – – –

The exploratory objectives are:

- To evaluate treatment-related biomarkers
- To evaluate the change in precursors in the bone marrow ~~precursors~~and blood
- To measure gene expression levels in hematopoiesis
- To evaluate pharmacokinetics of ACE-011

Study Design

– – – – – – – – – – –

ACE-011 (35 mg subcutaneous [SC] dose) will be administered to each subject who will be their own internal control with a pre-ACE-011 and post-ACE-011 RBC/PV test. The measures for analysis of the RBC and hematopoietic effect are lab-related and nuclear scan-related and therefore not subject to biased results. Subjects may receive up to a total of three doses of ACE-011 during the study~~.~~ (Study Day 1, 43, and 85).

~~At the time of enrollment into the study (Day 1) through Day 28 of the Treatment Period, subjects must not be receiving any other concurrent cytotoxic chemotherapy for their cancer. Once both RBC/PV tests have been completed, subjects can initiate chemotherapy as directed by the Investigator. Subjects can then continue to receive up to two additional doses of ACE-011 at Day 43 and Day 85.~~

– – – – – – – – – – –

Study Treatments

Each 35 mg dose of ACE-011 will be administered as a subcutaneous injection given in the upper arm or thigh.

Subjects will be enrolled and receive their first dose of ACE-011 on study Day 1. Up to two additional doses of ACE-011 will be administered every 42 days during the Treatment Period

(Day 43 and Day 85). ~~At the time of enrollment into the study (Day 1) through Day 28 of the Treatment Period, subjects must not be receiving any other concurrent cytotoxic chemotherapy for their cancer. Once both RBC/PV tests have been completed, subjects can initiate chemotherapy as directed by the Investigator. Subjects can then continue to receive up to two additional doses of ACE-011 at Day 43 and Day 85.~~

Rationale:

Language removed from protocol requiring no concurrent cytotoxic chemotherapy at the time of enrollment (Day 1) through Day 28 of the Treatment Period. This will allow all metastatic solid tumor patients (whether or not receiving chemotherapy) to be evaluated for inclusion in the study.

Administrative change regarding precursor evaluation in bone marrow and blood.

2.2. Section 1: INTRODUCTION (Page 14)

Revised Text:

The chemical structure of ACE-011 is composed of a disulfide-linked, glycosylated, dimeric protein. ACE-011 competes with the activin receptor IIA that binds a number of TGF-β superfamily ligands including activin, myostatin (growth differentiation factor [GDF]-8), and GDF-11, preventing the biological activities of these ligands.

~~ACE-011 avidly binds to activin A with a binding coefficient (Kd) of approximately 8.9 pM and prevents its binding to endogenous receptors, thereby inhibiting biological effects of activin.~~

– – – – – – – – – – –

While the mechanism(s) underlying the stimulation effect of ACE-011 on erythropoiesis are not yet fully understood, it is hypothesized that a blockade of ActRIIA receptor signaling ~~impedes~~may effect the ~~terminal differentiation step in~~ later stages of erythropoiesis to allow ~~additional rounds of erythroid cell replication before cells enter the terminal differentiation phase. The result is~~for a substantial increase in ~~mature erythrocytes released into circulation.~~hemoglobin and hematocrit. Since this proposed mechanism is likely different from that of known anemia agents, ACE-011 may provide a different clinical profile in the treatment of chemotherapy-induced anemia (CIA).

– – – – – – – – – – –

Activin ~~Biology~~Receptor Signaling

The activins (A-E) are a group of proteins that ~~form dimers and heterodimers. All~~ are part of the TGF-~~Beta~~β protein superfamily. ~~The first described activin, activin A, was initially identified as a gonadal 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~~Activin A was ~~also~~initially described as ~~an~~ erythroid differentiation factor (EDF), ~~a~~affecting the maturation and differentiation of ~~red blood cells~~RBCs (Murata, 1988). The mechanism(s) by which ~~a~~Activin A influences erythropoiesis remains under investigation and, in fact, there are data from ~~studies~~ in vitro and in ~~animals~~vivo studies that support erythropoiesis-stimulatory (Shiozaki, 1992; Shiozaki, 1989) and erythropoiesis-inhibitory effects (Nakao, 1991).

~~At the cellular level, the activins bind initially to the~~ The high-affinity ~~Type II~~ActRIIA receptor~~.~~ binds to a number of ligands in the TGF- β superfamily including activins A and B, myostatin and other GDFs as well as a number of the bone morphogenetic protein (BMP) family. The ligand-bound ActRIIA then recruits the low-affinity ~~T~~type I receptor (ActRIA or activin-like kinase [ALK-4~~). The~~]) and then the receptor heterocomplex, through its cytoplasmic protein kinase activity, ~~then~~ activates the Smad signaling cascade to eventually influence nuclear transcriptional factors (Chen, 2002; Mathews, 1994). The competitive binding of activins in the blood and tissues by the ~~ACE-011~~sotatercept 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 also been attributed to erythroid differentiation and has been reported to have proerythrocytic effects and to induce terminal differentiation of RBCs. Inhibition of activin may lead to increases in proliferation of the erythroid lineage. Based on its pharmacologic effects, ACE-011 is being developed for the treatment of bone loss associated with various disease states (e.g., osteoporosis and treatment of osteolytic lesions in patients with multiple myeloma), as well as the treatment of anemia associated with a variety of disorders, such as chemotherapy-induced anemia.~~

Rationale:

Revisions made based on current understanding about ACE-011 mechanism of action.

2.3. Section 2: STUDY OBJECTIVES (Page 25)

Revised Text:

2.3. Exploratory Objectives

- To evaluate treatment-related biomarkers
- To evaluate the change in precursors in the bone marrow ~~precursors~~and blood

Rationale:

Administrative change.

2.4. Section 3: STUDY ENDPOINTS (Page 26)

Revised Text:

3.3. Exploratory Endpoint(s)

- Change in bone mineral density (BMD)
- Changes in serum bone specific alkaline phosphatase (BSAP) and urinary N-telopeptide (uNTX) and other soluble or cellular biomarkers that may be altered in response to ACE-011
- Measurement of erythroid pre-cursors in bone marrow ~~including burst forming units (BFU-E) and erythroid colony forming units (CFU-E)~~and blood using flow cytometry
- Measurement of gene expression profiles in mononuclear cells isolated from bone marrow
- Concentrations of ACE-011 in serum

Rationale:

Administrative change.

2.5. Section 4: OVERALL STUDY DESIGN (Pages 26-28)

Revised Text:

4.1. Study Design

This is a phase 2, open-label, pharmacodynamic study to measure the change in red blood cell mass and plasma volume following one 35 mg SC dose of ACE-011 in subjects with solid tumors. No fewer than 10 subjects will be enrolled into the study.

ACE-011 (35 mg SC dose) will be administered to each subject who will be their own internal control with a pre-ACE-011 and post-ACE-011 RBC/PV test. The measures for analysis of the RBC and hematopoietic effect are lab-related and nuclear scan-related and therefore not subject to biased results. Subjects may receive up to a total of three doses of ACE-011 during the study. (Study Day 1, 43, and 85).

~~At the time of enrollment into the study (Day 1) through Day 28 of the Treatment Period, subjects must not be receiving any other concurrent cytotoxic chemotherapy for their cancer. Once both RBC/PV tests have been completed, subjects can initiate chemotherapy as directed by the Investigator. Subjects can then continue to receive up to two additional doses of ACE-011 at Day 43 and Day 85.~~

Rationale:

Language removed from protocol requiring no concurrent cytotoxic chemotherapy at the time of enrollment (Day 1) through Day 28 of the Treatment Period. This will allow all metastatic solid tumor patients (whether or not receiving chemotherapy) to be evaluated for inclusion in the study.

Revised Text:

4.1.1. ACE-011 Dose Modification Rules

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Table 2: Dose Reduction and Modification Guidelines

NCI Toxicity Grade	Event	Action
	For Hemoglobin ≥ 11 g/dL	
	Hgb ≥ 2 g/dL increase **sustained** for a 28-day period from last dose	• Dose delay[1] • Hold dose for one treatment visit • Re-evaluate Hgb & BP prior to resuming treatment • ~~Resume dosing~~If Hgb < 11 g/dL and hypertension < SBP 150 mmHg and < DBP 100 mmHg at the next scheduled visit, resume dosing – one level dose reduction (See Table 3)
	Hgb ≥ 3 g/dL increase **sustained** for a 28-day period from last dose	• Dose delay[1] • Hold dose for one treatment visit • Re-evaluate Hgb & BP prior to resuming treatment • ~~Resume dosing~~If Hgb < 11 g/dL and hypertension < SBP 150 mmHg and < DBP 100 mmHg at the next scheduled visit, resume dosing – two level dose reduction (See Table 3)

Rationale:

Based on review / recommendation received from FDA on 22FEB12 regarding protocol Amendment #1 (Final: 18APR11), for Amendment #3, in-text Table 2 updated to include clarification language regarding hemoglobin and blood pressure levels required in order to resume dosing at next scheduled visit, along with appropriate dose level reduction.

2.6. Section 5. TABLE OF EVENTS (Page 34)

Revised Text:

Table 4: ACE-011 RBC/PV Table of Events (Continued)

Assessments	Screening Period	Treatment (Tx) Period												Tx DC	Follow-Up Period		Study DC
	D-28 to D-1	D1 [a] (±1d)	D3 (±1d)	D7 (±1d)	D14 (±2d)	D21 (±2d)	D29 (±2d)	D43[a] (±3d)	D57 (±3d)	D71 (±3d)	D85[a] (±3d)	D99 (±3d)	D113 (±3d)	D127 (±3d)	D155 (±7d)	D183 (±7d)	D211 (±7d)
– – – – – – – – – – – –																	
Biomarkers in blood and urine [j]	X	-	-	-X	-	-	X	-	X	-	~~X~~-	-	X	X	X	-	X

Rationale:

The current protocol includes the first biomarker sample collected at the Screening Visit (prior to dosing with ACE-011). The next sample to be collected is at Day 29 (28 days post first dose of ACE-011). The Table of Events is being updated in order to get a post-dose sample as early as possible during the first cycle of the Treatment Period since it is now believed that ACE-011 acts rapidly to mobilize erythroblast populations. Given the current schedule of 28 days post-dose, this early activity might be missed if a sample is not collected earlier in the cycle. Biomarker samples will continue to be collected at a total of eight time points throughout the study; however, the Day 85 sample has been replaced by the Day 7 sample.

2.7. Section 7: STUDY POPULATION (Page 42)

Revised Text:

7.3. Exclusion Criteria

– – – – – – – – – – – –

~~3. Receiving cytotoxic chemotherapy treatment for metastatic cancer (currently or within 21 days of study Day 1). Concurrent trastuzumab (Herceptin®), erlotinib (Tarceva®), leuprolide acetate (Lupron®) and / or hormonal treatments for metastatic cancer are permitted.~~

Rationale:

Exclusion criterion removed from protocol requiring no concurrent cytotoxic chemotherapy at the time of enrollment (Day 1) through Day 28 of the Treatment Period. This will allow all metastatic solid tumor patients (whether or not receiving chemotherapy) to be evaluated for inclusion in the study.

2.8. Section 8: DESCRIPTION OF STUDY TREATMENTS (Page 44)

Revised Text:

8.2. Treatment Administration and Schedule

– – – – – – – – – – –

8.2.2. Selection and Timing of Dosing for Each Patient

– – – – – – – – – – –

~~At the time of enrollment into the study (Day 1) through Day 28 of the Treatment Period, subjects must not be receiving any other concurrent cytotoxic chemotherapy for their cancer. Once both RBC/PV tests have been completed, subjects can initiate chemotherapy as directed by the Investigator. Subjects can then continue to receive up to two additional doses of ACE-011 at Day 43 and Day 85.~~

Rationale:

Language removed from protocol requiring no concurrent cytotoxic chemotherapy at the time of enrollment (Day 1) through Day 28 of the Treatment Period. This will allow all metastatic solid tumor patients (whether or not receiving chemotherapy) to be evaluated for inclusion in the study.

2.9. Section 10: STATISTICAL ANALYSES (Page 48)

Revised Text:

10.3. Sample Size and Power Considerations

No fewer than ten subjects will be enrolled. Assuming standard deviation of 5.5 mL/kg for the intra-patient difference in erythrocyte mass (Lim, 1989), this sample size will have ~~about~~at least 90% power to detect 5.9 mL/kg pre- and post-ACE-011 therapy at one sided 5% significance level based on a paired t-test.

Rationale:

Administrative change.

A PHASE 2, OPEN-LABEL, PHARMACODYNAMIC STUDY TO EVALUATE THE EFFECT OF SOTATERCEPT (ACE-011) ON RED BLOOD CELL MASS AND PLASMA VOLUME IN SUBJECTS WITH SOLID TUMORS

INVESTIGATIONAL PRODUCT (IP):	**SOTATERCEPT (ACE-011)**
PROTOCOL NUMBER:	**ACE-011-ST-001**
DATE FINAL:	**01 FEBRUARY 2010**
AMENDMENT No. 1 DATE FINAL:	**18 APRIL 2011**
AMENDMENT No. 2 DATE FINAL:	**15 NOVEMBER 2011**
AMENDMENT No. 3 DATE FINAL:	**05 MARCH 2012**
EudraCT NUMBER:	**Not Applicable**
CELGENE IND NUMBER:	**103362**
SPONSOR NAME / ADDRESS	Celgene Corporation 86 Morris Avenue Summit, NJ 07901

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

Back-up 24 Hour Global Emergency Contact Call Center: +1-877-501-7738

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

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Printed Name of Celgene Therapeutic Area Head and Title

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SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Site Principal Investigator	**dd mmm yyyy**
Printed Name of Site Principal Investigator **Institution Name:**_____ By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Celgene representatives, the Declaration of Helsinki, ICH Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

PROTOCOL SUMMARY

Study Title

A phase 2, open-label, pharmacodynamic study to evaluate the effect of sotatercept (ACE-011) on red blood cell mass and plasma volume in subjects with solid tumors.

Indication

Solid tumor malignancies

Objectives

The primary objective is:

- To measure red blood cell mass (RBC) change and plasma volume (PV) following one dose of ACE-011 in cancer subjects with solid tumors

The secondary objectives are:

- To measure plasma volume change following one dose of ACE-011 in cancer subjects with solid tumors
- To evaluate the potential change in hematopoietic parameters
- To evaluate the safety and tolerability of ACE-011

The exploratory objectives are:

- To evaluate treatment-related biomarkers
- To evaluate the change in precursors in the bone marrow and blood
- To measure gene expression levels in hematopoiesis
- To evaluate pharmacokinetics of ACE-011

Study Design

This is a mechanism of action (MOA) study of ACE-011 as a supportive care agent. The primary objective is to measure the change in red blood cell mass (RBC) and plasma volume (PV) following one 35 mg dose of ACE-011 in subjects with solid tumors. No fewer than ten subjects will be enrolled and treated.

ACE-011 (35 mg subcutaneous [SC] dose) will be administered to each subject who will be their own internal control with a pre-ACE-011 and post-ACE-011 RBC/PV test. The measures for analysis of the RBC and hematopoietic effect are lab-related and nuclear scan-related and therefore not subject to biased results. Subjects may receive up to a total of three doses of ACE-011 during the study (Study Day 1, 43, and 85).

The effect of ACE-011 will be analyzed based on all treated subjects. Descriptive statistics will be provided for RBC mass and plasma volume pre- and post-ACE-011 therapy. The pre- and post-difference will be compared based on a paired t-test. In addition, descriptive statistics will be provided for secondary endpoints including bone or disease progression, bone mineral density, and bone biomarkers.

An internal Data Monitoring Committee (DMC) will review summaries of the hematopoietic endpoints including RBC and PV 29 days post-dose of the last subject being enrolled.

Study Population

The study population includes subjects with a histologically confirmed diagnosis of a solid tumor malignancy documented by cytology or biopsy, with a presence of metastatic disease. All subjects must have a baseline hemoglobin value between ≥ 8.0 to < 11.0 g/dL (≥ 80 to < 110 g/L). Additionally, subjects must not have received any treatment with erythropoiesis-stimulating agents (ESA) within 28 days of study entry and cannot be administered during the time between the pre-dose RBC / PV test and the post-dose RBC / PV test. Intravenous (IV) iron replacement therapy for iron deficiency anemia is also not allowed during the study.

All subjects who qualify for enrollment into the study will enter the Treatment Period and receive their first subcutaneous 35 mg dose of ACE-011 on study Day 1. A unique subject identification number will be manually assigned by the site staff to each subject entering the Treatment Period.

Length of Study

Each subject will be on the study for approximately eight months (including the Screening Period, the Treatment Period, and the Follow-Up Period).

The Treatment Period is approximately four months (up to 3 doses of ACE-011 to be administered every 42 days through study Day 126) with a post-treatment Follow-Up Period of three months from the subjects' last dose of ACE-011 (through study Day 210). Subjects who discontinue from the Treatment Period early will still continue to the Follow-Up Period for three months (84 days) from their last dose of ACE-011.

Study Treatments

Each 35 mg dose of ACE-011 will be administered as a subcutaneous injection given in the upper arm or thigh.

Subjects will be enrolled and receive their first dose of ACE-011 on study Day 1. Up to two additional doses of ACE-011 will be administered every 42 days during the Treatment Period (Day 43 and Day 85).

Subjects discontinued after Day 28 of the Treatment Period, having completed their second RBC mass and PV test, will not need to be replaced unless their hemoglobin did not increase after the ACE-011 dose. Subjects discontinued for any cause prior to Day 28 or before their second RBC/PV test is completed will need to be replaced.

Overview of Efficacy (Pharmacodynamic) Assessments

- Red blood cell mass / plasma volume

Overview of Safety Assessments

- Complete physical examination including vital signs
- Clinical laboratory evaluations (serum chemistry, hematology, absolute reticulocyte count)
- Serum iron, total iron binding capacity (TIBC), transferrin and serum ferritin

- Serum erythropoietin
- Vitamin B12 and serum folate levels
- Thyroid function evaluation
- Pregnancy testing (serum or urine beta-human chorionic gonadotropin levels [β-HCG] for females of childbearing potential [FCBP] only)
- Electrocardiogram (ECG)
- Anti-ACE-011 antibody assessment
- Concomitant medications and procedures
- Adverse events

Overview of Exploratory Assessments

- Bone mineral density (BMD) (dual energy X-ray absorptiometry [DXA] scan to evaluate overall bone health in subjects with known bone metastases)
- Bone marrow aspirate (BMA) (optional)
- Bone biomarkers (anabolic bone biomarkers in blood and urine will be evaluated)
- Pharmacokinetics

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1. INTRODUCTION

The purpose of this study is to evaluate the effect of sotatercept (ACE-011) on red blood cell (RBC) mass and plasma volume (PV) in cancer subjects with solid tumors.

ACE-011 (ActRIIA-IgG1) is a recombinant human fusion protein consisting of the extracellular domain (ECD) of human activin receptor IIA (ActRIIA) linked to the human IgG1 Fc domain, which includes the heavy chain hinge and constant domains, CH2 and CH3.

The chemical structure of ACE-011 is composed of a disulfide-linked, glycosylated, dimeric protein. ACE-011 competes with the activin receptor IIA that binds a number of TGF-β superfamily ligands including activin, myostatin (growth differentiation factor [GDF]-8), and GDF-11, preventing the biological activities of these ligands.

In both single and multiple-dose phase 1 studies of ACE-011 in postmenopausal women, dose- and time-dependent increases in hemoglobin (Hgb), hematocrit (HCT), and RBC levels were observed following ACE-011 treatment and remained elevated over the course of study.

Please refer to the Investigator Brochure for further information.

While the mechanism(s) underlying the stimulation effect of ACE-011 on erythropoiesis are not yet fully understood, it is hypothesized that a blockade of ActRIIA receptor signaling may effect the later stages of erythropoiesis to allow for a substantial increase in hemoglobin and hematocrit. Since this proposed mechanism is likely different from that of known anemia agents, ACE-011 may provide a different clinical profile in the treatment of chemotherapy-induced anemia (CIA).

This study will provide information on the pharmacodynamic (PD) properties regarding the ability of ACE-011 to increase hemoglobin in subjects with CIA.

Activin Receptor Signaling

The activins (A-E) are a group of proteins that are part of the TGF-β protein superfamily. 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). Activin A was initially described as erythroid differentiation factor (EDF), effecting the maturation and differentiation of RBCs (Murata, 1988). The mechanism(s) by which Activin A influences erythropoiesis remains under investigation and, in fact, there are data from in vitro and in vivo studies that support erythropoiesis-stimulatory (Shiozaki, 1992; Shiozaki, 1989) and erythropoiesis-inhibitory effects (Nakao, 1991).

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

ACE-011 is the soluble and tissue related ligand trap composed of the extracellular domain of the activin receptor ActRIIA. The extracellular domain 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 ACE-011; however, in order to reduce the potential immunogenicity in mice of the fully human molecule, ACE-011, and to maximize the opportunity to maintain exposures in chronic mouse models, a murine surrogate molecule was constructed by exchanging the human immunoglobulin Fc sequence portion of ACE-011 with its murine IgG2a homologue. The resultant construct is referred to as RAP-011 (ActRIIA-mIgG2aFc), and is described in the pharmacology studies below.

Pharmacology Studies

RAP-011 was evaluated in a broad 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 intraperitoneal injection twice per week for 3 months resulted in a 16%-26% increase in RBC counts compared to control animals. Rats treated with ACE-011 at doses of 0.3, 3, and 30 mg/kg once per week for 3 months showed RBC count increases of 6-15% over control animals. Finally, in cynomolgus monkeys treated with 10, 30 or 50 mg/kg of ACE-011 twice per month for 3 months, there was a 21%-24% increase in RBC counts compared to control animals. In this study, the RBC count increase was apparent as early as 2 weeks following the initial dose of 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.

Toxicology

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 as well as 0.03 and 0.1 mg/kg subcutaneously (SC) and phase 1b multiple doses of 0.1 to 2.0 mg/kg (monthly, SC). Weekly dosing in animals was designed to provide continuous, but fluctuating serum concentrations of ACE-011, which would mimick a one-month dosing interval in humans.

ACE-011 dosing in preclinical animal toxicology studies resulted in expected pharmacodynamic effects of inhibition of FSH by the activin signaling pathway, such as effects on male gonadal tissues (testicular degeneration, decrease sperm counts and motility). In addition, the adrenal cortical lesions (necrosis or mineralization) observed in rats may be the result of interference of activin signaling on the developing adrenal gland. The pancreatic findings (zymogen granule depletion and atrophy of pancreatic acini) were only observed in the 1-month rat study by the IV route of administration and were not associated with any clinical signs of pancreatic

insufficiency (abnormal stool, weight loss, etc.). Glomerular lesions (glomerulonephritis) were observed in both rats and monkeys in the 3-month SC studies that were presumed to be due to anti-drug antibody deposition. This presumption is supported by a robust anti-drug antibody response in rats (58% of animals positive for anti-ACE-011 antibodies). In monkeys, due to the high plasma concentrations of ACE-011 interfering with the immunogenicity assay, the true incidence of anti-drug antibodies could not be documented. In a chronic monkey study, the kidney lesions had changed to be more tubular in nature (tubulointerstitial nephritis) and may be due to off-target inhibition of BMP-7 in a setting of the exceedingly high concentrations of ACE-011. A 9-month monkey study is ongoing to evaluate the effects of lower concentrations of ACE-011.

Initial studies utilized IV dosing to identify target organs while longer-term studies (3 months in rats; 3 and 6 months in monkeys) utilized SC dosing to mimic the intended dosing regimen for patients. The expected pharmacologic effect, increased RBCs, Hgb, HCT and reticulocytes, was observed in all studies, presumably based on the ability of ACE-011 to inhibit activin. A second expected pharmacologic effect of ACE-011, based on inhibition of activin, observed was the reversible reduction in sperm production and testicular tubular damage in rats. Since male cynomolgus monkeys were sexually immature in these studies, it was not possible to monitor this effect in this species.

An adverse effect of ACE-011 was only observed on the adrenal gland and was only seen in rats, which was more pronounced in female rats. This toxicological observation may not be relevant for predicting effects in humans since adrenal toxicity was not seen in cynomolgus monkeys. Dose-limiting toxicity and no observable adverse effect levels (NOAELs) were primarily based on renal toxicity in both rats and monkeys. There was some indication that kidney toxicity was an indirect effect, based on the formation of antibody/antigen complexes, but since these studies were not designed to investigate toxicological mechanisms, a definitive cause of renal impairment and renal damage was not determined. Development of antibodies to ACE-011 was noted in all of these studies, which is an expected immune reaction in rats and monkeys dosed with a human protein.

The NOAELs from the 3-month SC studies were 3 and 30 mg/kg in rats and monkeys, respectively. Since the kidney findings were observed at all dose levels, a NOAEL was not identified in the 6-month monkey study.

Summary of Clinical Experience

A011-01: A Phase 1a Study in Healthy Postmenopausal Women

ACE-011 was first studied in a randomized, phase 1a, single dose, dose escalation study in healthy, post-menopausal females (Ruckle, 2009). 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 of ACE-011 was linear for all IV and SC doses. 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 $t_{1/2}$ 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, ACE-011 was completely absorbed, and the mean $t_{1/2}$ was approximately 30 days, with no apparent dependence on dose.

The most commonly occurring treatment-emergent 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 majority of treatment-emergent AEs were mild in severity and were judged to be unrelated to 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 ACE-011 was well tolerated in healthy, post-menopausal 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.

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

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 pharmacodynamics of 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 subcutaneously. 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 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 Hgb and HCT levels. 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 magnetic resonance imaging (MRI), fundoscopy, and ECG performed were reported as normal and headache symptoms resolved following therapeutic 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 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 pharmacodynamic effect at the 1.0 mg/kg dose level. In total, 31 subjects were enrolled and

treated. Dose levels of 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 ACE-011. Due to early discontinuation of study drug, subjects randomized to active treatment in Cohort 2 received 3 doses of ACE-011, and subjects randomized to active treatment in Cohort 3 received 2 doses of 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, HCT, and RBC values were observed (see Table 1 below for changes in Hgb levels):

Table 1: A011-02: A Phase 1b Study in Healthy Postmenopausal Women: Hemoglobin Evaluation

Evaluation Time Point	Mean Change from Baseline (g/dL)			
	Placebo N=7[a]	ACE-011 0.1 mg/kg N=8	ACE-011 0.3 mg/kg N=8	ACE-011 1.0 mg/kg N=8
Baseline Mean, pre-Dose 1	13.20	13.11	13.30	12.71
Day 8	0.17	0.68	0.85	1.21
Day 15	-0.27	0.43	0.44	1.75
Day 29	0.27	0.61	1.21	2.68[b]
Day 36	0.56	0.64	1.89	2.96
Day 43	-0.02	0.89	1.21	2.85
Day 57	0.27	1.28	1.64[b]	2.09
Day 64	0.53	1.11	2.49	2.21
Day 71	-0.10	1.34	2.09	1.66
Day 85	0.38	1.18[b]	2.55	1.86
Day 92	0.00[c]	1.04	1.60[c]	3.80[c]
Day 99	-0.20	1.21	3.20[c]	1.28[c]
Day 113	-0.02	1.30	1.29	1.04
Day 141	0.30	0.95	0.34	2.30
Day 169	0.20[c]	0.06		2.00[c]

a The number of placebo subjects with data decreases over time as a result of the early 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; five subjects with data on Days 71 and 113; four subjects with data on Day 64; three subjects with data on Day 141; two subjects with data on Day 99; and one subject with data on Days 92 and 169.

b Number of doses administered per treatment group: 0.1 mg/kg 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

No severe or 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 count. 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.

Headaches were common in all treatment groups with no dose response evident; most were mild.

Paresthesia and dizziness were reported more frequently in the ACE-011 groups, though the events were 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.

Pharmacokinetic (PK) results confirmed that ACE-011 is linear following the first SC doses of all three dose levels tested, 0.1, 0.3, and 1.0 mg/kg. The terminal half life ($t_{1/2}$) of ACE-011 following the last dose in all three dose groups was identical, with mean $t_{1/2}$ 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, and the mean $t_{1/2}$ ranged from 20.92 to 23.34 days in all 3 dose levels, with no apparent dependence on dose.

Bone mineral density (BMD) 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.

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

Study A011-04 was a phase 2a, multi-center, randomized, multiple-dose study to evaluate the safety, tolerability and efficacy of ACE-011 in subjects with osteolytic lesions of multiple myeloma (MM). Safety evaluations included AEs, clinical laboratory tests, standard 12-lead electrocardiogram, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status and physical examinations. Additionally, the study included the assessment of biochemical markers of bone formation and resorption, skeletal related events (SREs), BMD by DXA, and bone pain by visual analog scale (VAS).

In this study, subjects were randomized in a 4:1 ratio to one of three dose levels of ACE-011 (0.1, 0.3 and 0.5 mg/kg) or placebo, to be administered to subjects every 28 days by subcutaneous injection, for up to four doses over a 3-month period. The test article 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.

A total of 30 subjects were randomized and treated with ACE-011 or placebo.

One (1) subject died on PPD due to sudden death (including progression of disease). Relevant prior medical history included PPD The subject was taking prophylactically PPD The subject had received the first dose of ACE-011/placebo and started cycle 1 MPT on PPD The last study dose was administered on PPD . On PPD the subject developed grade 2 blood pressure increase, which resolved with the subject's blood pressure medication. The following day PPD the subject's blood pressure was reported to have returned to baseline. The subject then died on PPD , 18 days after last study dose, due to the described sudden death. No autopsy was performed. The Investigator assessed event causality as possibly related to ACE-011/placebo and probably related to MPT.

One SAE of atrial fibrillation with syncope was reported in a PPD subject receiving 0.5 mg/kg of ACE-011, resulting in study discontinuation. This was in a subject with prior history of PPD . On further review this subject's inclusion into the study was a protocol violation. The Investigator assessed event causality as unrelated to ACE-011/placebo and possibly related to MPT.

One SAE of prolonged hospitalization due to pneumonia, that was considered not related to ACE-011, was reported in a PPD subject enrolled in the study. On PPD four days after the first dose of ACE-011/placebo and the initial doses of melphalan, prednisolone and thalidomide (MPT), the subject presented with elevated temperatures up to 39ºC, cough and fatigue. Chest x-ray revealed a pneumonic infiltration in the lower lobe of the left lung resulting in prolonged hospitalization. Treatment included moxifloxacin, doripenem, meropenem and fluconazole with resolution of the event.

The Investigator considered the event of pneumonia unrelated to ACE-011 and possibly related to MPT.

An SAE of leg pain was reported in a PPD and was found to have a pathological fracture of the right upper femoral bone approximately 2.5 months after last dose of ACE-011/placebo, approximately 5 weeks after last dose of melphalan-prednisolone and one day after the last dose of thalidomide. Radiologic evaluations demonstrated progressive bone tissue destruction at presentation. The subject was casted, and then underwent coxal bandaging. The event resolved with sequelae. The Investigator considered the events of pain in the right leg and pathological fracture of the upper third of the right femur unrelated to ACE-011/placebo and unrelated to thalidomide (MPT).

The A011-04 study has been completed and final analysis of the data and completion of the clinical study report are ongoing.

Potential Risks for Human Use

Nonclinical studies to determine the safety of 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 activin 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, Hgb, HCT) 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 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 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 ~1.3-fold greater than the projected serum exposure in humans at the maximum proposed human dose of 61 mg every 6 weeks. 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 ACE-011 should continue to be closely monitored.
- In the 9-month monkey study, treatment-related findings in the choroid plexus included: perivascular 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.
- 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), as well as triglycerides, were observed sporadically in rats and monkeys treated with 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 ACE-011 treatment is uncertain; however, these endpoints will continue to be monitored in the clinic.
- Pregnancy and Lactation
  - Due to the potential for effects on hormones in the pituitary, including FSH, in addition to possible direct effects on fetus, there may be potential effects on the

fetus. Delays in fetal development (decreased fetal weights and delays in ossification) were observed at doses ≥ 15 mg/kg (15-fold greater on a mg/kg basis than the maximum proposed human dose of 60 mg every 6 weeks assuming a 60 kg person). In addition, at 50 mg/kg (100-fold 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 lumber 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 (~5-fold greater than the maximum proposed human dose of 60 mg every 6 weeks assuming a 60 kg person) based on reduced fetal weights and associated delays in ossification. Although the risks for embryofetal development effects are considered relatively low given the large safety margins, precautions should still be taken to protect females of childbearing potential. Nonclinical studies on breast milk have not been done.

  - If ACE-011 is taken during pregnancy, a teratogenic effect in humans cannot be ruled out. Therefore, all 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 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_{28d}) in rats at the NOAEL was estimated to be ~ 8,000 µg·hr/mL based on the single-dose IV pharmacokinetic study in rats (Report TR148), ~ 2-fold greater than the serum exposure observed in humans at the maximum proposed dose of 60 mg every 6 weeks (estimated AUC_{28d} ~ 4548 µg·hr/mL).
  - In summary, in view of the potential risks ACE-011 treatment has on fertility, ACE-011 is targeted toward patient groups for whom the potential benefits outweigh the perceived risks.

Because of the potential risks ACE-011 treatment has on fertility, ACE-011 was first studied in healthy postmenopausal women 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 multidose study in the two higher dose groups remaining below baseline at study end. FSH will continue to be evaluated in ongoing studies. No abnormal effects of ACE-011 on growth hormone, ACTH, TSH or kidney toxicities were observed.

Based on the safety data from the two completed phase 1 studies, single doses of ACE-011 up to 3.0 mg/kg IV and multiple doses of ACE-011 up to 0.3 mg SC were generally well tolerated in healthy postmenopausal women. Consistent with observations from nonclinical safety studies, many of the observed pharmacodynamic effects in the phase 1 clinical studies could be attributed to the expected biologic activity of activin inhibition, i.e., dose-dependent decrease in circulating levels of FSH, and transient, reversible effects on RBC parameters. In Study A011-02, one subject experienced persistent, progressive hypertension and headaches approximately 1 week following her second dose of 1.0 mg/kg ACE-011 SC that were attributed to a rapid and significant rise in Hgb levels. The hypertension was reported as an SAE.

In regards to the above safety concerns, appropriate vitals, hematologic, clinical chemistry and endocrine testing will be closely monitored in this clinical study. There may be an effect of delayed wound healing; thus subjects with major surgeries within 30 days prior to study initiation will be excluded. As with all biologics there is the potential for anti-drug antibodies that can be associated with increased drug clearance and hypersensitivity reactions. Although no current evidence of neutralizing anti-drug antibodies formation was seen in two completed phase 1 clinical trials, anti-drug antibody formation will be monitored in this clinical study.

Please refer to the Investigator Brochure for further detailed information on the available pharmacology, toxicology, drug metabolism, clinical studies and AE profile of ACE-011.

2. STUDY OBJECTIVES

2.1. Primary Objective

- To measure red blood cell mass change and plasma volume following one dose of ACE-011 in cancer subjects with solid tumors

2.2. Secondary Objectives

- To measure plasma volume change following one dose of ACE-011 in cancer subjects with solid tumors
- To evaluate the potential change in hematopoietic parameters
- To evaluate the safety and tolerability of ACE-011

2.3. Exploratory Objectives

- To evaluate treatment-related biomarkers
- To evaluate the change in precursors in the bone marrow and blood
- To measure gene expression levels in hematopoiesis
- To evaluate pharmacokinetics of ACE-011

Data from exploratory objectives may not be included in the Clinical Study Report.

3. STUDY ENDPOINTS

3.1. Primary Endpoint(s)

- Red blood cell mass

3.2. Secondary Endpoint(s)

- Plasma volume
- Absolute reticulocyte increase
- Change in erythropoietin levels with any increase in hemoglobin subtypes determined by electrophoresis
- Changes in hemoglobin subtypes determined by hemoglobin electrophoresis
- Safety (type, frequency, and severity [according to the currently active minor version of National Cancer Institute (NCI) Common Terminology for Adverse Events (CTCAE) version 4.0] of adverse events, and relationship to ACE-011)

3.3. Exploratory Endpoint(s)

- Change in bone mineral density (BMD)
- Changes in serum bone specific alkaline phosphatase (BSAP) and urinary N-telopeptide (uNTX) and other soluble or cellular biomarkers that may be altered in response to ACE-011
- Measurement of erythroid pre-cursors in bone marrow and blood using flow cytometry
- Measurement of gene expression profiles in mononuclear cells isolated from bone marrow
- Concentrations of ACE-011 in serum

4. OVERALL STUDY DESIGN

4.1. Study Design

This is a phase 2, open-label, pharmacodynamic study to measure the change in red blood cell mass and plasma volume following one 35 mg SC dose of ACE-011 in subjects with solid tumors. No fewer than 10 subjects will be enrolled into the study.

ACE-011 (35 mg SC dose) will be administered to each subject who will be their own internal control with a pre-ACE-011 and post-ACE-011 RBC/PV test. The measures for analysis of the RBC and hematopoietic effect are lab-related and nuclear scan-related and therefore not subject to biased results. Subjects may receive up to a total of three doses of ACE-011 during the study (Study Day 1, 43, and 85).

4.1.1. ACE-011 Dose Modification Rules

Subjects should have Hgb and blood pressure measured prior to each dose of investigational product (IP). The Investigator must adhere to the following hemoglobin (Hgb) and blood pressure-based dose modification rules (see Table 2) for ACE-011 for the subjects' **second** dose of ACE-011 and beyond.

Table 2: Dose Reduction and Modification Guidelines

NCI Toxicity Grade	Event	Action
	Hypertension: SBP ≥ 150 mmHg DBP ≥ 100 mmHg	• Dose delay[1] • Hold dose until hypertension resolves < SBP 150 mmHg and < DBP 100 mmHg • Resume dosing 7 days or later after previously scheduled treatment visit
≥ Grade 3	Other non-hematological ACE-011 related AEs	• Dose delay[1] • Hold dose until resolves ≤ Grade 2 • Resume dosing 7 days or later after previously scheduled treatment visit
	For Hemoglobin < 11 g/dL	
	Hgb < 2 g/dL increase within a dosing period or a ≥ 2 g/dL increase **not sustained** for a 28-day period since last dosing day	• Continue dosing
	Hgb ≥ 2 g/dL increase **sustained** for a 28-day period from last dose	• Re-evaluate Hgb & BP prior to resuming treatment • Resume dosing – one level dose reduction (See Table 3)
	Hgb ≥ 3 g/dL increase **sustained** for a 28-day period from last dose	• Re-evaluate Hgb & BP prior to resuming treatment • Resume dosing – two level dose reduction (See Table 3)
	For Hemoglobin ≥ 11 g/dL	
	Hgb < 2 g/dL increase within a dosing period or a ≥ 2 g/dL increase **not sustained** for a 28-day period since last dosing day	• Dose delay[1] until Hgb < 11 g/dL and hypertension < SBP 150 mmHg and < DBP 100 mmHg. • Dosing can commence ≥ 7 days after the originally planned ACE-011 dose that was delayed • Subsequent ACE-011 dosing will resume 42 days following this revised treatment dose date
	Hgb ≥ 2 g/dL increase **sustained** for a 28-day period from last dose	• Dose delay[1] • Hold dose for one treatment visit • Re-evaluate Hgb & BP prior to resuming treatment • If Hgb < 11 g/dL and hypertension < SBP 150 mmHg and < DBP 100 mmHg at the next scheduled visit, resume dosing – one level dose reduction (See Table 3)

Table 2: Dose Reduction and Modification Guidelines (Continued)

NCI Toxicity Grade	Event	Action
	Hgb ≥ 3 g/dL increase **sustained** for a 28-day period from last dose	• Dose delay[1] • Hold dose for one treatment visit • Re-evaluate Hgb & BP prior to resuming treatment • If Hgb < 11 g/dL and hypertension < SBP 150 mmHg and < DBP 100 mmHg at the next scheduled visit, resume dosing – two level dose reduction (See Table 3)
	For Hemoglobin > 15 g/dL	
	Hgb is > 15 g/dL, sustained for a 7-day period from last dose	• Discontinue treatment (See Section 8.2.3)

[1] A delayed ACE-011 dose is defined as a dose not administered > 3 days from the planned dosing date due to Hgb ≥ 11 g/dL, hypertension ≥ SBP 150 mmHg and ≥ DBP 100 mmHg and/or ACE-011 related toxicity.

When required, per dose modification rules above, ACE-011 dose(s) during the Treatment Period should be reduced as follows (See Table 3):

Table 3: ACE-011 Dose Reduction Levels

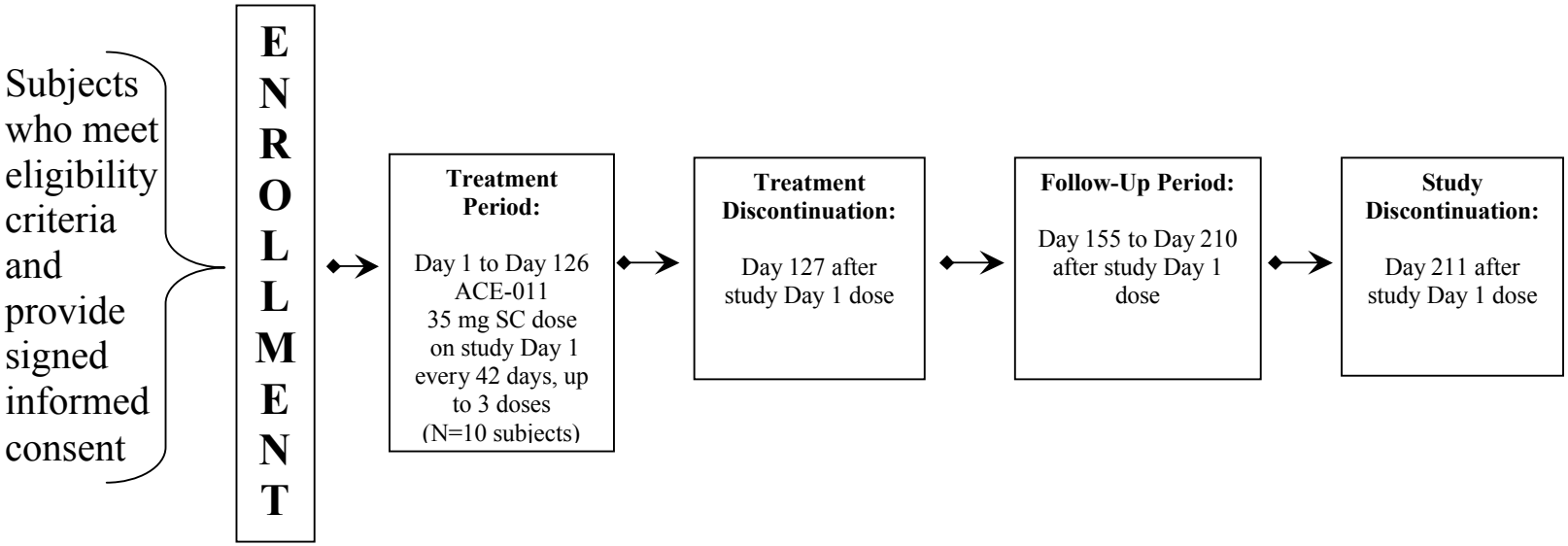
ACE-011 Starting Dose	35.0 mg
Dose Level -1	30.0 mg
Dose Level -2	26.0 mg

If the subject cannot tolerate Dose Level -2, the subject should be discontinued from the study.

Dosing visits are on Day 1 and repeated every 42 days, for up to three doses. Blood pressure and Hgb values must be evaluated prior to dosing at each dosing day for consideration in administration of ACE-011.

The dose level for the initial dose reduction will be maintained unless subsequent dose reductions need to be administered upon evaluation of the dose modification rules listed above. Dose escalations are not permitted at any time during the study.

Figure 1: Study Design



4.2. Study Design Rationale

The A011-01, A011-02, and A011-04 studies have shown that dosing with ACE-011 resulted in the increase in hematopoietic parameters, beginning rapidly and sooner than would be expected from a stimulation of the erythropoietic effect by an ESA. This fact, as well as the fairly rapid and persistent elevation in the relative Hgb, HCT, and RBC counts of the majority of subjects from each dose of ACE-011, suggests an entirely novel mechanism of RBC production. In order to establish that RBCs are produced following ACE-011 therapy, the Sponsor has received expert advice and regulatory authority comment that an RBC mass and plasma volume study should be completed, prior to formulating a registration strategy for this agent. The secondary and exploratory endpoints are designed to elucidate the mechanism of the red blood cell effect in cancer patients with solid tumor malignancies.

4.2.1. Fixed Dose

ACE-011 dose will be fixed at the indicated levels regardless of the subject's body weight. The fixed dosing approach is supported by an exploratory analysis of the relationship between body weight and ACE-011 PK in the previous studies (A011-01, A011-02, and A011-04). In healthy postmenopausal women (Studies A011-01 and A011-02), body weight was estimated to explain less than 2.5% of intersubject variability for the two PK parameters dictating ACE-011 exposure, clearance and central volume of distribution, compared to an overall intersubject variability of 17.4%-25.5% for the two parameters. In MM subjects (Study A011-04), body weight had no apparent effect on ACE-011 exposure. Because the Hgb response is dependent on ACE-011 exposure and because body weight is not a major source for the intersubject variability of ACE-011 exposure, a fixed dosing approach is considered to be appropriate for the current study.

The 35 mg starting dose is equivalent to the 0.5 mg/kg dose for a 70 kg subject. This dose was chosen primarily based on the safety and efficacy data observed in MM subjects (Study A011-04). In MM subjects who received ACE-011 at 0.5 mg/kg every 4 weeks for up to four doses, ACE-011 had an acceptable safety profile and caused significant Hgb response.

4.2.2. Dosing Schedule

The dosing schedule of once every 42 days (6 weeks) is proposed for the current study. This dosing schedule was chosen based on the rapid and prolonged Hgb response to ACE-011 observed in previous clinical studies. The Hgb-increasing effect of ACE-011 was usually evident approximately 1 week after a SC dose and remained detectable through 6-8 weeks.

4.3. Study Duration

To evaluate sequence and study timelines, please see the Table of Events (see Table 4). No fewer than 10 subjects will be enrolled into the study. Each subject will be on the study for approximately 8 months (including the Screening Period, the Treatment Period, and the Follow-Up Period).

The Treatment Period will be up to approximately four months (up to 3 doses of ACE-011 to be administered every 42 days through study Day 126) with a post-treatment Follow-Up Period of three months from the subjects' last dose of ACE-011 (through study Day 210). Subjects who

discontinue from the Treatment Period early will still continue to the Follow-Up Period for three months (84 days) from their last dose of ACE-011.

5. TABLE OF EVENTS

Table 4: ACE-011 RBC/PV Table of Events

Assessments	Screening Period	Treatment (Tx) Period												Tx DC	Follow-Up Period		Study DC
	D-28 to D-1	D1 [a] (±1d)	D3 (±1d)	D7 (±1d)	D14 (±2d)	D21 (±2d)	D29 (±2d)	D43 [a] (±3d)	D57 (±3d)	D71 (±3d)	D85 [a] (±3d)	D99 (±3d)	D113 (±3d)	D127 (±3d)	D155 (±7d)	D183 (±7d)	D211 (±7d)
Informed Consent	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Inclusion / Exclusion Criteria	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Complete Medical History	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Prior Therapies [b]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ECOG Performance Status	X	X	-	-	-	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs / Blood Pressure [c]	X	X	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Weight	X	X	-	-	-	-	X	X	-	-	X	-	X	X	X	X	X
12-Lead Electrocardiogram	X	-	-	-	X	-	X	X	-	-	X	-	-	X	-	-	X
Pregnancy Testing [e]	X (within 3 days prior to Day 1)	-	-	-	-	-	-	X	-	-	X	-	-	X	X	X	X
Hematology [f]	X	X	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Chemistry [g]	X	-	-	-	X	-	X	X	-	-	X	-	-	X	-	-	X
BUN and Creatinine	-	-	-	X[h]	-	-	-	-	-	-	-	-	-	-	-	-	-
Absolute Reticulocyte Count	X	X	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Iron, TIBC, Transferrin and Serum Ferritin	X	-	-	-	-	-	-	-	X	-	-	-	-	X	-	-	X

Table 4: ACE-011 RBC/PV Table of Events (Continued)

Assessments	Screening Period	Treatment (Tx) Period												Tx DC	Follow-Up Period		Study DC
	D-28 to D-1	D1 [a] (±1d)	D3 (±1d)	D7 (±1d)	D14 (±2d)	D21 (±2d)	D29 (±2d)	D43[a] (±3d)	D57 (±3d)	D71 (±3d)	D85[a] (±3d)	D99 (±3d)	D113 (±3d)	D127 (±3d)	D155 (±7d)	D183 (±7d)	D211 (±7d)
Serum Erythropoietin	-	X	-	-	X	-	X	X	-	-	X	-	-	X	X	X	X
Hemoglobin Electrophoresis	-	X	-	X	X	-	X	-	-	-	-	-	-	-	-	-	-
B12 and Serum Folate	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
FSH and LH – Males / Females	X	X	-	-	X	-	X	X	X	-	X	X	-	X	-	-	X
TSH	X	X	-	-	-	-	-	X	-	-	X	-	-	X	-	-	X
RBC Mass / Plasma Volume	X	-	-	-	X (at one additional time point; must be between D14 and D28)		-	-	-	-	-	-	-	-	-	-	-
Bone Marrow Aspirate (BMA) (optional for consented subjects)	X	-	-	-	-	X	-	-	-	-	-	-	-	-	-	-	-
Bone Mineral Density DXA Scan [i]	X	-	-	-	-	-	-	-	X	-	-	-	X	-	X	-	-
Biomarkers in blood and urine [j]	X	-	-	X	-	-	X	-	X	-	-	-	X	X	X	-	X
Pharmacokinetics [k]	-	X	X[d]	X	X	X	X	X	X	-	X	X	-	X	-	-	X
Anti-ACE-011 antibody test [l]	-	X	-	-	-	-	-	X	-	-	X	-	-	-	-	-	X
Adverse Events	X	X	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Procedures	X	X	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Administer ACE-011	-	X	-	-	-	-	-	X	-	-	X	-	-	-	-	-	-

a. All D1, D43, and D85 assessments are to be done prior to ACE-011 administration.
b. All prior cancer and medical diagnosis, radiotherapy, surgeries, and chemotherapies and approximate dates of therapies must be recorded.
c. Vital signs (including heart rate, seated blood pressure, and temperature) will be measured at Screening, at all subsequent visits during the Treatment and Follow-Up Periods, and at Study DC (Discontinuation) visit. Investigators are to report any clinically significant abnormal findings as adverse events.
d. D3 visit is optional; however, these tests are strongly suggested for all subjects on study.

e. Females of childbearing potential (FCBP): A female of childbearing potential is a sexually mature woman who has not undergone a hysterectomy or who has not been postmenopausal for at least 24 consecutive months (i.e. who has had menses at some time in the preceding 24 months). A medically supervised pregnancy test (which must be negative) with a minimum sensitivity of 25 mIU/mL must be performed no more than 3 days from the start of ACE-011 administration (D1). Furthermore, subjects must be on effective contraception for at least 28 days prior to D1 and throughout the remainder of the study including the Follow-up Period. For all additional subsequent doses, a pregnancy test must be performed within 3 days prior to administrations of ACE-011 as indicated above. Subjects must agree to use highly effective methods of birth control during study participation and for at least 112 days following the last dose of ACE-011. Subjects must be counseled concerning measures to be used to prevent pregnancy and potential toxicities prior to the first dose of ACE-011. Pregnancy tests will be performed according to the above schedule during study participation. For FCBP, a final pregnancy test must be performed at least 112 days following the last dose of ACE-011.

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

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

h. At D7, only BUN and creatinine to confirm no plasma volume contraction.

i. Optional dual energy X-ray absorptiometry (DXA) scan to evaluate overall bone health in subjects with known bone metastases.

j. BSAP, uNTX, and other ACE-011 soluble and cellular biomarkers. Both blood and urine samples will be collected on the days indicated above. The urine sample should not be from the first morning void.

k. PK sample will be collected at each study visit indicated above (a total of 12 visits, one sample per visit), including D1 (prior to ACE-011 administration), D3 (optional), D7, D14, D21, D29, D43 (prior to ACE-011 administration), D57, D85 (prior to ACE-011 administration), D99, D127, and D211.

l. Samples for anti-ACE-011 antibody testing should be collected prior to ACE-011 administration on D1, D43, and D85. If a subject has a positive anti-ACE-011 antibody result at the Study DC visit, the subject may be asked to return to the clinical site for additional monthly follow-up, for up to 12 months after their last dose of ACE-011 for a repeat anti-ACE-011 antibody test.

6. PROCEDURES

Screening Period (Day -28 to Day -1)

Potentially protocol-eligible subjects will enter the Screening Period 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 (4 weeks). The assessments and procedures that will be performed during this period are outlined in the Table of Events (see Table 4) and include but are not limited to:

- Informed consent
- Assessment of inclusion / exclusion criteria
- Complete medical history
- ECOG performance status
- Vital signs including height, weight, heart rate, seated systolic and diastolic blood pressure, and temperature
- 12-lead electrocardiogram (ECG)
- Medically supervised pregnancy test (which must be negative) with a minimum sensitivity of 25 mIU/mL for FCBP to be assessed within 3 days of Day 1 (pre-dose)
- Serum chemistry, hematology, absolute reticulocyte count
- Serum iron, total iron binding capacity (TIBC), transferrin and serum ferritin
- Vitamin B12 and serum folate levels
- Follicle stimulating hormone (FSH) and luteinizing hormone (LH) – both males and females
- Thyroid stimulating hormone (TSH)
- Red blood cell mass / plasma volume
- Bone marrow aspirate (optional)
- Bone imaging DXA scan (only for subjects with known bone metastases)
- Biomarkers (blood and urine)
- Evaluation of adverse events
- Documentation of concomitant medications / procedures

Treatment Period (Day 1 to Day 126)

Results from screening evaluations must be reviewed prior to enrollment to confirm subject eligibility. Subjects satisfying all inclusion and exclusion criteria will be enrolled into the Treatment Period. A subject will be considered enrolled once a multi-digit subject identification number has been manually assigned by the site. After assignment of the subject identification number and the inclusion/exclusion criteria have been met, subjects will receive the first subcutaneous 35 mg dose of ACE-011 on study Day 1.

The Treatment Period will not last more than 126 days (18 weeks). The assessments and procedures that will be performed during this period are outlined in the Table of Events (see Table 4) and include but are not limited to:

- ECOG performance status
- Vital signs including weight, heart rate, seated systolic and diastolic blood pressure, and temperature
- 12-lead electrocardiogram (ECG)
- Medically supervised pregnancy test with a minimum sensitivity of 25 mIU/mL for FCBP
- Serum chemistry, hematology, absolute reticulocyte count
- BUN and creatinine (Day 7 only)
- Serum iron, total iron binding capacity (TIBC), transferrin and serum ferritin
- Serum erythropoietin
- Hemoglobin electrophoresis
- Follicle stimulating hormone (FSH) and luteinizing hormone (LH) – both males and females
- Thyroid stimulating hormone (TSH)
- Red blood cell mass / plasma volume (post-dose test must be performed between study Day 14 and Day 28)
- Bone marrow aspirate at Day 21 (optional)
- Bone imaging DXA scan (only for subjects with known bone metastases)
- Biomarkers (blood and urine)
- Pharmacokinetics
- Anti-ACE-011 antibody test (pre-dose on Day 1, Day 43, and Day 85)
- Administration of ACE-011 (Day 1, Day 43, and Day 85)
- Evaluation of adverse events
- Documentation of concomitant medications / procedures

Subjects discontinued after Day 28 of the Treatment Period, having completed their second RBC mass and PV test, will not need to be replaced unless their hemoglobin did not increase after the ACE-011 dose. Subjects discontinued for any cause prior to Day 28 or before their second RBC/PV test is completed will need to be replaced.

Treatment Discontinuation (Day 127)

Subjects who complete the Treatment Period or discontinue from the Treatment Period early will complete the Treatment Discontinuation Visit prior to entering the Follow-Up Period. The assessments and procedures that will be performed during this period are outlined in the Table of Events (see Table 4) and include but are not limited to:

- ECOG performance status
- Vital signs including weight, heart rate, seated systolic and diastolic blood pressure, and temperature
- 12-lead electrocardiogram (ECG)
- Medically supervised pregnancy test with a minimum sensitivity of 25 mIU/mL for FCBP
- Serum chemistry, hematology, absolute reticulocyte count
- Serum iron, total iron binding capacity (TIBC), transferrin and serum ferritin
- Serum erythropoietin
- Follicle stimulating hormone (FSH) and luteinizing hormone (LH) – both males and females
- Thyroid stimulating hormone (TSH)
- Biomarkers (blood and urine)
- Pharmacokinetics
- Evaluation of adverse events
- Documentation of concomitant medications / procedures

Follow-Up Period (Day 155 to Day 210)

Following completion of the Treatment Period, all subjects will be followed for an additional 84 days (12 weeks). The assessments and procedures that will be performed during this period are outlined in the Table of Events (see Table 4) and include but are not limited to:

- ECOG performance status
- Vital signs including weight, heart rate, seated systolic and diastolic blood pressure, and temperature
- Medically supervised pregnancy test which must be negative with a minimum sensitivity of 25 mIU/mL for FCBP
- Serum chemistry, hematology, absolute reticulocyte count
- Serum erythropoietin

- Bone imaging DXA scan (only for subjects with known bone metastases)
- Biomarkers (blood and urine)
- Evaluation of adverse events
- Documentation of concomitant medications / procedures

Additional Procedures

- **Exploratory Bone Mineral Density**

  A dual energy X-ray absorptiometry (DXA) scan will be performed during the Screening Period as well as during the Treatment and Follow-Up Periods (see Table 4) to evaluate overall bone health in subjects with known bone metastases.

- **Exploratory Biomarkers**

  Anabolic bone biomarkers in blood and urine will be evaluated at 8 visits (see Table 4). These biomarkers will include bone specific alkaline phosphatase (BSAP) and urinary N-telopeptide (uNTX). Other ACE-011 soluble and cellular biomarkers may also be evaluated in samples collected from all subjects during the Screening, Treatment, and Follow-Up Periods.

- **Exploratory Pharmacokinetics (PK)**

  Additional blood samples for PK will be taken at up to 12 visits during the Treatment Period (see Table 4) (optional at Day 3; however, these tests are strongly suggested for all subjects on study) for evaluation of serum concentrations of ACE-011 and for exploratory analysis. Collection, handling, and shipping procedures for blood samples are provided in the study reference guide.

Study Discontinuation Visit (Day 211)

Study Discontinuation is the final scheduled visit for this study and should be performed for all enrolled subjects. If a subject discontinues from the study early, the Study Discontinuation Visit procedures should be followed. The assessments and procedures that will be performed during the Study Discontinuation Visit are outlined in the Table of Events (see Table 4) and include but are not limited to:

- ECOG performance status
- Vital signs including weight, heart rate, seated systolic and diastolic blood pressure, and temperature
- 12-lead electrocardiogram (ECG)
- Medically supervised pregnancy test with a minimum sensitivity of 25 mIU/mL for females of childbearing potential (FCBP)
- Serum chemistry, hematology, absolute reticulocyte count
- Serum iron, total iron binding capacity (TIBC), transferrin and serum ferritin
- Serum erythropoietin

- Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) – both males and females
- Thyroid Stimulating Hormone (TSH)
- Biomarkers (blood and urine)
- Pharmacokinetics
- Anti-ACE-011 antibody test
- Evaluation of adverse events
- Documentation of concomitant medications / procedures

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

7. STUDY POPULATION

7.1. Number of Subjects and Sites

This pharmacodynamic study will enroll no fewer than 10 subjects with at least 4 males or females.

7.2. Inclusion Criteria

1. Men and women ≥ 18 years of age.
2. Histologically confirmed diagnosis of a solid tumor malignancy documented by cytology or biopsy.
3. Presence of metastatic disease.
4. Hemoglobin value between ≥ 8.0 to < 11.0 g/dL (≥ 80 to < 110 g/L).
5. ≥ 28 days must have elapsed (prior to pre-dose RBC mass / PV test) since previous treatment with erythropoiesis-stimulating agent (including concurrent treatment with IV iron).
6. ≥ 28 days must have elapsed (prior to Day 1) since the last RBC blood transfusion and receipt of ≤ 2 units of blood in the past 56 days (prior to Day 1).
7. ECOG Performance status of 0 – 1 (Appendix A).
8. Adequate renal (creatinine ≤ 1.5 x ULN or creatinine clearance ≥ 40 mL/min) and hepatic function (bilirubin ≤ 1.5 x ULN; AST/ALT ≤ 2.5 x ULN).
9. Females of childbearing potential participating in the study are to use highly effective methods of birth control for at least 28 days before starting the study, during study participation and for 112 days following the last dose of ACE-011.

   Some highly effective methods of birth control include:

   - Oral contraceptives, intrauterine device, tubal ligation or a partner with vasectomy

   OR

   - Two forms of barrier method birth control, e.g., a latex condom PLUS a diaphragm with spermicide OR a latex condom PLUS a contraceptive sponge with spermicide. If a non-latex condom is used, it cannot be made out of natural (animal) membrane.

   Females of childbearing potential must have a medically supervised pregnancy test (which must be negative) within 3 days prior to the start of ACE-011 administration on Day 1. Subjects must be counseled concerning measures to be used to prevent pregnancy and potential toxicities prior to the first dose of ACE-011. A female of childbearing potential is a sexually mature woman who has not undergone a hysterectomy or bilateral oophorectomy; or who has not been postmenopausal for at least 24 consecutive months (i.e. who has had menses at some time in the preceding 24 months).

10. 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 112 days following the last dose of ACE-011, even if he has undergone a successful vasectomy.
11. Life expectancy of ≥ 6 months.
12. Is willing to adhere to the study visit schedule, understand and comply with all protocol requirements.
13. Understand and sign a written informed consent.

7.3. Exclusion Criteria

1. At the time of screening, subjects who have any grade ≥ 3 toxicity (according to the currently active minor version of NCI CTCAE v4.0 [Appendix B], except for the following disease related toxicities: hematological events- anemia, thrombocytopenia or neutropenia or non hematological events- nausea, vomiting, fatigue, or muscle or bone/joint pain).
2. Prior radiation therapy to > 20% of the whole skeleton. Use of palliative radiation if the area being treated is <15% of body surface area with no pelvic radiation or no more than 10% of the bone marrow reserve is radiated is permitted during patient participation in the study, at the discretion of the investigator.
3. Clinically significant pulmonary, endocrine, neurologic, gastrointestinal, hepatic or genitourinary disease unrelated to underlying hematologic disorder.
4. Patients with heart failure as classified by the New York Heart Association (NYHA) classification of 3 or higher (Appendix C).
5. History of thrombosis, deep vein thrombosis (DVT), pulmonary emboli, or embolic stroke.
6. Untreated CNS metastases (exception: CNS metastases treated with whole brain radiotherapy > 6 months prior to enrollment at study Day 1).
7. Diagnosis of a myeloid malignancy or known history of myelodysplasia.
8. History of second malignancy within 3 years (except excised and cured basal cell carcinoma, squamous cell carcinoma of the skin or cervical carcinoma in situ).
9. Patients with a recent history (within 14 days of Day 1) of administration of systemic (IV or oral) antibiotics. Patients should be free of infection at least 14 days after the last dose of systemic antibiotic treatment (prior to Day 1).
10. Uncontrolled hypertension. If hypertension is considered clinically stable, systolic blood pressure (BP) must be < 150 mmHg and diastolic BP must be < 100 mmHg.
11. Known history of hepatitis C antibody (HCV), hepatitis B surface antigen (HBsAg and HB core Ab), or human immunodeficiency virus (HIV) antibody.
12. Deficiency in iron (serum ferritin < 100 ng/mL [< 224.7 pmol/L]), vitamin B_{12}, or folate.

13. History of anemia as a result of inherited hemoglobinopathy such as sickle cell anemia or thalassemia.
14. History of autoimmune or hereditary hemolysis or gastrointestinal bleeding.
15. Received treatment with another investigational drug or device within 28 days prior to Day 1, or if the half life of the previous product is known, within 5 times the half life prior to dosing, whichever may be longer.
16. Any prior use of ACE-011.
17. Pregnant or lactating females.
18. History of severe allergic or anaphylactic reactions or hypersensitivity to recombinant proteins or excipients in the investigational product (see Investigator Brochure).
19. History of iodinated dye allergy.
20. Major surgery within 30 days prior to Day 1 (subjects must have completely recovered from any previous surgery prior to Day 1).

7.4. Subject Withdrawal Criteria

Subjects will be informed that they have the right to withdraw from the study at any time for any reason without prejudice to their medical care.

Subjects must be withdrawn from the study for any of the following reasons:

- Subject request
- Subject is unwilling or unable to comply with the protocol
- ESA administration during the treatment period
- Disease progression
- Medical reason, such as cancer or unacceptable toxicity, or at the discretion of the Investigator and/or the Medical Monitor(s)

The reasons for withdrawal must be recorded in the subject's case report form (CRF). The Investigator must notify the Medical Monitor immediately when a subject has been discontinued / withdrawn due to an AE (e.g. unacceptable toxicity). All subjects who are withdrawn from the study should complete the tests and evaluations scheduled for Study Discontinuation at the time of withdrawal.

8. DESCRIPTION OF STUDY TREATMENTS

8.1. Description of Investigational Product(s)

Sotatercept (ACE-011) clinical drug product will be provided as a lyophilized powder, Process III.

Process III Clinical Drug Product-Lyophilized Powder:

The clinical drug product consists of ACE-011 in 10 mM citrate buffer, pH 5.8, 8% sucrose, and 0.02% polysorbate 80. It is supplied as a lyophilized powder in labeled, rubber stoppered, 3-mL glass vials. The recommended storage temperature for ACE-011 lyophilized drug product is 2°C to 8°C. Prior to administration, the lyophilized drug product is reconstituted with 1 mL water for injection (WFI). The reconstituted drug product consists of a 50 mg/mL solution of ACE-011. The reconstituted ACE-011, in its original container closure system, may be held for up to 6 hours at 2°C to 8°C.

8.2. Treatment Administration and Schedule

Each dose of ACE-011 will be administered as a subcutaneous injection at the clinical site by the study staff and will be documented in the study source record. Subcutaneous injections will be given in the upper arm or thigh.

8.2.1. Selection of Dose for the Study

ACE-011 administered as a single dose up to 3.0 mg/kg was previously demonstrated to be safe and to have durable effects on markers of bone formation and resorption as well as red blood cells following a single IV administration. A dose-limiting pharmacodynamic effect of ACE-011 with increases in hemoglobin, hematocrit and RBCs was established in healthy post-menopausal women at the 1.0 mg/kg dose level following multiple SC administration. This study will further delineate the hematopoietic profile of ACE-011 in cancer subjects.

8.2.2. Selection and Timing of Dosing for Each Patient

Subjects will be enrolled and receive their first dose of ACE-011 on study Day 1. Up to two additional doses of ACE-011 will be administered every 42 days during the Treatment Period (Day 43 and Day 85). After completion of the Treatment Period, subjects will return to the site for three additional monthly visits (Day 127, Day 155, and Day 183) during the Follow-Up Period, and a Study Discontinuation Visit (Day 211).

Subjects will be discontinued from study participation for reasons listed in Section 12 of the protocol, for unacceptable toxicity, or for disease progression that requires the initiation of another treatment during the first 28 days of the Treatment Period.

8.2.3. Treatment / Study Discontinuation

Refer to Section 12 Discontinuations.

8.3. Method of Treatment Assignment

All subjects who qualify for enrollment into the study will enter the Treatment Period and receive their first subcutaneous 35 mg dose of ACE-011 on study Day 1. A unique subject identification number will be manually assigned by the site staff to each subject entering the Treatment Period.

Subjects discontinued after Day 28 of the Treatment Period, having completed their second RBC mass and PV test, will not need to be replaced unless their hemoglobin did not increase after the ACE-011 dose. Subjects discontinued for any cause prior to Day 28 or before their second RBC/PV test is completed will need to be replaced.

8.4. Packaging and Labeling

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

8.5. Investigational Product Accountability and Disposal

Accountability for ACE-011 is the responsibility of the Investigator. Investigational clinical supplies must be received by a designated person at the clinical site and kept in a secure and temperature-controlled location. The investigational site must maintain accurate records demonstrating dates and amounts of ACE-011 received, to whom it was administered (subject-by-subject accounting), and accounts of any ACE-011 accidentally or deliberately destroyed or returned. Unless otherwise notified, all vials of ACE-011, both used and unused, must be saved for drug accountability. The used vials may be discarded, per the institution's standard practice, after drug accountability has been completed by the monitor. The Investigator must return all unused vials of ACE-011 to the Sponsor at the end of the study, or the ACE-011 may be destroyed at the clinical site with the permission of the Sponsor. For either scenario, the outcome must be documented on the drug accountability log. The Sponsor will provide direction for the outcome of all unused vials.

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

8.6. Investigational Product Compliance

Accurate recording of all IP administration will be made in the appropriate section of the subject's CRF and source documents.

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

9. CONCOMITANT MEDICATIONS AND PROCEDURES

9.1. Permitted Concomitant Medications and Procedures

9.1.1. General concomitant medication usage

During screening, and during the study, subjects may take only stable doses of medications for chronic conditions that are not specifically excluded by the protocol (see Sections 7.2 Inclusion Criteria and 7.3 Exclusion Criteria). The Medical Monitor should be consulted by the Investigator if there are any concerns about what constitutes a stable dose or what is a chronic condition. Concomitant medications will be recorded on the subject's CRF throughout the course of the study.

9.1.2. Concomitant medication for anemia

Concurrent therapy with a new prescription medication related to treatment of anemia during the course of the study must first be discussed with the Medical Monitor prior to administration, unless appropriate medical care necessitates that medication should begin before the Medical Monitor can be consulted.

9.1.2.1. Iron supplementation

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

9.1.2.2. RBC transfusions

Concurrent treatment for chemotherapy-induced anemia with blood transfusions is recommended when hemoglobin value is < 8 g/dL or at the discretion of the Investigator if the hemoglobin value is above 8 g/dL and associated with anemia symptoms such as hemodynamic or pulmonary compromise requiring treatment. If a transfusion is given to a subject during the Screening Period, ACE-011 should be administered no sooner than 28 days from the date of the transfusion. On the day of ACE-011 administration (study Day 1, Day 43, and Day 85), the blood pressure and other vital signs will also be assessed to ensure that the subject is still eligible for participation in the study.

9.2. Prohibited Concomitant Medications and Procedures

Erythropoiesis-stimulating agents (ESAs) cannot be administered during the time between the pre-dose RBC / PV test and the post-dose RBC / PV test. Twenty-one days after the second dose of ACE-011 during the Treatment Period, if there is no hemoglobin response (< 1 g/dL rise in Hgb) and the use of ESAs is indicated, the subject should be considered a treatment failure and discontinued from the study. If treatment with ESAs is required in the opinion of the Investigator, the ESA label instructions are to be followed.

Intravenous (IV) iron replacement therapy for iron deficiency anemia is not allowed during the study.

No concurrent treatments with any other investigational agent are allowed.

9.3. Required Concomitant Medications and Procedures

Not applicable.

10. STATISTICAL ANALYSES

10.1. Overview

This is a mechanism of action (MOA) study of ACE-011 as a supportive care agent. The primary objective is to measure the change in red blood cell mass and plasma volume following one 35 mg dose of ACE-011 in subjects with solid tumors. No fewer than ten subjects will be enrolled and treated.

10.2. Study Population Definitions

All analyses will be based on the treated population which is defined as all subjects who take at least one dose of study medication.

10.3. Sample Size and Power Considerations

No fewer than ten subjects will be enrolled. Assuming standard deviation of 5.5 mL/kg for the intra-patient difference in erythrocyte mass (Lim, 1989), this sample size will have at least 90% power to detect 5.9 mL/kg pre- and post-ACE-011 therapy at one sided 5% significance level based on a paired t-test.

10.4. Background and Demographic Characteristics

Subjects' age, height, weight, and baseline characteristics will be summarized using descriptive statistics, while gender, race and other categorical variables will be provided using frequency tabulations. Medical history data will be summarized using frequency tabulations by system organ class and preferred term.

10.5. Subject Disposition

Subject disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent for both treatment and follow-up phases. A summary of subjects enrolled will be provided. Protocol deviations will be summarized using frequency tabulations.

10.6. Efficacy Analysis

The effect of ACE-011 will be analyzed based on the treated dataset. Descriptive statistics will be provided for RBC mass and plasma volume pre- and post-ACE-011 therapy. The pre- and post- difference will be compared based on a paired t-test. In addition, descriptive statistics will be provided for secondary endpoints including bone or disease progression, bone mineral density, and bone biomarkers.

10.7. Safety Analysis

Safety analyses will be based on the treated dataset. ACE-011 exposure will be summarized. Adverse events, vital sign measurements, clinical laboratory information, ECG interpretations, and concomitant medications will be tabulated and summarized by tumor type. All toxicities

will be summarized by relative and absolute frequency, severity grade (according to the currently active minor version of NCI CTCAE version 4.0), and relationship to treatment. Serious adverse events (SAE) will be listed separately. Safety information obtained during the Follow-up period during each segment will be incorporated into these analyses. Graphical displays will be provided where useful in the interpretation of results.

10.8. Interim Analysis

An internal Data Monitoring Committee (DMC) will review summaries of the hematopoietic endpoints including RBC and PV 29 days post-dose of the last subject being enrolled.

10.9. Other Topics

Not Applicable.

11. ADVERSE EVENTS

11.1. Monitoring, Recording and Reporting of Adverse Events

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

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

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

All AEs (regardless of relationship to IP) will be recorded by the Investigator from the time the subject signs informed consent until at least 42 days after the last dose of IP, up to a maximum of 112 days post-last dose of IP or until the subject begins a new regimen of chemotherapy. Adverse events and serious adverse events (SAEs) will be recorded on the AE page of the CRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. After 112 days post-last dose of IP or once the subject begins a new regimen of chemotherapy, only SAEs assessed as related to study treatment are to be reported.

11.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

11.2.1. Seriousness

A serious adverse event (SAE) is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (i.e., in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);

- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

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

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

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

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

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

11.2.2. Severity / Intensity

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

The severity of AEs will be graded based upon the subject's symptoms according to the currently active minor version of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0);
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

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

Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required

Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required

Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible

Grade 4 = Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

Grade 5 = Death – the event results in death

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

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

11.2.3. Causality

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

Not suspected:	The temporal relationship of the adverse event to IP administration makes **a causal relationship unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	The temporal relationship of the adverse event to IP administration makes **a causal relationship possible**, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

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

11.2.4. Duration

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

11.2.5. Action Taken

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

11.2.6. Outcome

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

11.3. Abnormal Laboratory Values

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

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

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

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

11.4. Pregnancy

11.4.1. Females of Childbearing Potential:

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

The female subject may be referred to her obstetrician-gynecologist or another appropriate healthcare professional for further evaluation.

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

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

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

11.4.2. Male Subjects

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

11.5. Reporting of Serious Adverse Events

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

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent until at least 42 days after the last dose of IP, up to a maximum of 112 days post last dose of IP or until the subject begins a new regimen of chemotherapy), and those made known to the Investigator at anytime thereafter that are suspected of being related to IP. Serious adverse events occurring prior to treatment will be captured.

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

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

11.5.1. Safety Queries

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

11.6. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to ACE-011 based on the Investigator Brochure.

Celgene or its authorized representative shall notify the Investigator of the following information

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

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

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

Celgene Drug Safety Contact Information:

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

12. DISCONTINUATIONS

Treatment Discontinuation

Subjects will be discontinued from study treatment due to the following:

- Adverse Event(s)
  - Hypertension ≥ Grade 3 – defined as Stage 2 hypertension (SBP ≥ 160 mm Hg and DBP ≥ 100 mmHg); medical intervention indicated; initiation of more than one drug or more intensive therapy than previously required or medically significant hypertension that cannot be adequately controlled with antihypertensive therapy
  - Any AE > Grade 2 assessed to be related to ACE-011 therapy
  - Any persistent AE > Grade 1 considered to be related to ACE-011 treatment and causing a subject to miss three months ACE-011 therapy
  - Any thromboembolic event > Grade 2
  - Elevated Hgb > 15.0 g/dL (sustained for a 7-day period, confirmed by laboratory assessment)
- Lack of ACE-011 therapeutic effect, defined as < 1.0 g/dL increase in Hgb following two doses of ACE-011
- Withdrawal of consent
- Progression of disease
- Death
- Lost to follow-up
- Protocol violation

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

Study Discontinuation

The following events **are** considered sufficient reasons for discontinuing a subject from the study:

- Completed study, per protocol
- Withdrawal of consent
- Death
- Lost to follow-up

The following events **may be** considered sufficient reasons for discontinuing a subject from the study:

- Adverse events(s)

- Progression of disease
- Protocol violation

The reason for discontinuation should be recorded in the CRF and in the source documents. The Investigator must notify the Medical Monitor immediately when a subject has been discontinued/ withdrawn due to an AE (any unacceptable toxicity). All subjects who are withdrawn from the study should complete the tests and evaluations scheduled for Study Discontinuation at the time of withdrawal.

13. EMERGENCY PROCEDURES

13.1. Emergency Contact

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

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

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

13.2. Emergency Identification of Investigational Products

This is an open-label study; therefore, IP will be identified on the package labeling.

14. REGULATORY CONSIDERATIONS

14.1. Good Clinical Practice

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

14.2. Investigator Responsibilities

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

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

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

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

14.3. Subject Information and Informed Consent

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

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

14.4. Confidentiality

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

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

14.5. Protocol Amendments

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

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

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

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

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should also be revised.

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

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

14.7. Ongoing Information for Institutional Review Board / Ethics Committee

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

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

14.8. Closure of the Study

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

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

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

15. DATA HANDLING AND RECORDKEEPING

15.1. Data/Documents

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

15.2. Data Management

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

15.3. Record Retention

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

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

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

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

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

16. QUALITY CONTROL AND QUALITY ASSURANCE

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

16.1. Study Monitoring and Source Data Verification

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

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

16.2. Audits and Inspections

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

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

17. PUBLICATIONS

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

18. REFERENCES

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19. APPENDICES

Appendix A: ECOG Performance Status Scale

The ECOG scale (Oken, 1982) is used to assess a patient's quality of life in an evaluation by a health professional of the daily activities and how the activities are affected by the disease of the patient.

Table 5: ECOG Performance Status Scale

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

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

Currently active minor version of NCI CTCAE, Version 4.0:

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

Appendix C: New York Heart Association - Classification of Heart Failure

Table 6: New York Heart Association - Classification of Heart Failure

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

Appendix D: Measurement of Red Blood Cell Mass and Plasma Volume

Principle of Procedure

Polycythemia is a hematologic disorder characterized by an absolute increase in red cell volume due to an absolute erythrocytosis. *Primary polycythemia* originates in the bone marrow (polycythemia vera/myeloproliferative syndrome). *Secondary polycythemia* is caused by an increase in the production of erythropoietin caused by renal or liver tumors, or high altitude, smoking, heart or lung diseases that result in hypoxia. Both primary and secondary are due to an absolute increase in red cell volume or an absolute erythrocytosis. Some patients have a relative erythrocytosis, i.e., an elevated hematocrit due to reduced blood plasma, caused by fluid loss e.g., burns, dehydration, etc., so-called stress polycythemia.

The determination of red blood cell volume and plasma volume in these patients is an important tool for differentiating absolute from relative polycythemia. Both the determination of red cell volume and plasma volume are by isotope dilution techniques. Due to the possibility of a relative erythrocytosis, the plasma volume should not be calculated from the determined value of red cell volume and the venous hematocrit (corrected to the whole body hematocrit). Plasma volume must be determined independently using a second isotopic label. ^{125}I-HSA is used to label plasma volume. ^{125}I-HSA rapidly reaches equilibrium and begins immediately to leave the vascular space. Therefore, it is necessary to take specimens at 10, 20 and 30 minutes and graphically back extrapolate to time zero to obtain the correct plasma volume.

The label for the red blood cell determination is ^{51}CrO4. Red blood cells labeled with ^{51}CrO4 do not rapidly elute the label, therefore this is the label of choice. The larger the volume into which the label is distributed, the lower the counts will be in samples taken once equilibrium has been reached. Two consecutive samples with count rates that do not vary significantly are taken as evidence of attaining equilibrium. In a normal individual, equilibrium is reached in about 10 minutes. The population of patients referred for polycythemia; however, likely include patients with splenomegaly and much longer times are required for equilibrium to occur. Samples for red cell volume determination are therefore taken at 30, 60 and 90 minutes.

Procedure

This testing will be performed by a separate laboratory from the study site. Subjects participating in the study will travel to this external laboratory on days where RBC/PV sampling will be done (see Table 4).